BRÈVE HISTOIRE DE LA MÉDECINE RÉGÉNÉRATIVE

FACTEURS DE CROISSANCE

PLASMA RICHE EN PLAQUETTES SANGUINES AUTOLOGUES

CELLULES SOUCHES MÉSENCHYMATEUSES AUTOLOGUES

GROUPE DE RECHERCHE INTERNATIONAL SUR LES INJECTIONS DE PLAQUETTES

Médecine Régénérative en Pathologie Musculosquelettique

DOCTEUR PHILIPPE ADAM

ACADEMIE DU LANGUEDOC

14 JUIN 2022

La Médecine Régénérative (ou Régénératrice) est
« un domaine interdisciplinaire
de recherche et *d'applications cliniques*
axé sur *la réparation, le remplacement ou la régénération de cellules*, de tissus ou d'organes
pour restaurer une fonction altérée du corps humain »

Elle représente *l'Ingénierie Tissulaire*
et pour cela utilise en particulier
Les facteurs de croissance plaquettaires
et les cellules souches mésenchymateuses

I - LES FACTEURS DE CROISSANCE (Growth Factors)

Quelques Définitions

Les Origines

Les Facteurs de Croissance Plaquettaires

(PRP, Platelet-Rich Plasma)

Naturellement présents dans l'organisme, les ***facteurs de croissance sont des substances (peptide, protéine…) qui régulent le nombre de nos cellules*** *en augmentant ou en diminuant leur multiplication en fonction des besoins*

Ce sont des ***messagers chimiques diffusibles émis par des cellules pour agir sur d'autres cellules, i****ls déclenchent une* ***cascade d'évènements*** *transmembranaires et intra-cellulaires*

Ils ont ***leur cible cellulaire***
2 exemples de FC synthétisés : ***l'EPO*** *(érythropoïétine), qui stimule la production de globules rouges par la moelle osseuse, et les* ***facteurs granulocytaires****, qui aident à produire plus de globules blancs*

Nous ne développerons que les facteurs de croissance ***d'origine plaquettaire***
Après un rappel historique

Un exemple de FCP (GF):

Le PDGF (Platelet-Derived Growth Factor

Il est nécessaire à la ***division des fibroblastes (ténocyte pour le tendon)***

Il possède des ***récepteurs sur la membrane plasmique des fibroblastes***

Lorsqu'il s'associe à son récepteur ***il stimule la division des cellules +++****(réparation tendineuse) et leur attraction ou déplacement* ***(chimiotactisme)+++***

Le facteur de croissance nerveuse est une protéine présente chez les animaux vertébrés. Il a été découvert dans les années 1950 par Rita Levi-Montalcini et Viktor Hamburger et compte parmi les nombreux facteurs neurotrophiques. Le NGF appartient au groupe des neurotrophines ; il stimule la prolifération et la différenciation des cellules d'origine ectodermique et mésodermique et a été mis en évidence dans une grande variété de tissus. Les mutations du NGF-Gen peuvent entraîner une neuropathie héréditaire (HSAN5).

In Vitro Experiments on the Effects of Mouse Sarcomas 180 and 37 on the Spinal and Sympathetic Ganglia of the Chick Embryo

Rita Levi-Montalcini, Hertha Meyer, and Viktor Hamburger

DOI: Published January 1954

Article | Info & Metrics | PDF

Summary

Small fragments of mouse Sarcomas 180 and 37 were placed at a distance of 1–2 mm. from spinal or sympathetic ganglia of a chick embryo in a hanging-drop tissue culture. Under this condition the ganglion produces precociously, within 24 hours, an excessive number of nerve fibers which grow very straight radially in all directions, forming a dense "halo" around the ganglion. Their density decreases, and their length increases, with increasing distance from the sarcoma. In addition, the migration of spindle cells from the ganglia is inhibited by the sarcomas. Mouse Sarcoma 1 has a similar, but milder, effect. Mouse adenocarcinoma dbrB and mouse neuroblastoma C1300 do not stimulate nerve growth. Control experiments with heart tissue from chick embryos were entirely negative, but heart tissue of fetal mice was found to have a mild stimulating effect. However, in the latter instance, the growth pattern is very different from that found in the presence of sarcomas and very similar to that found in normal, isolated ganglia. Sarcomas have no effect on spinal cord fibers.

It is concluded that the mouse sarcomas tested produce a diffusible agent which strongly promotes the nerve fiber outgrowth of ganglia. The results obtained *in vitro* are compared to previous results obtained by intra-embryonic transplantation of the same sarcomas, and the conclusion is reached that the *in vitro* and the *in vivo* effects on the spinal and sympathetic ganglia are due to the same agent.

UN
AGENT DIFFUSIBLE...

RITA LEVI-MONTALCINI
Publié avec Hamburger
1954

Le premier facteur de croissance nerveux

NGF
Nerve Growth Factor
(Groupe des Neurotrophines)

Current Neuropharmacology, 2018, *16*, 1455-1465

REVIEW ARTICLE

Nerve Growth Factor: Early Studies and Recent Clinical Trials

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ARTICLE HISTORY

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Abstract: Since its discovery, nerve growth factor (NGF) has long occupied a critical role in developmental and adult neurobiology for its many important regulatory functions on the survival, growth and differentiation of nerve cells in the peripheral and central nervous system. NGF is the first discovered member of a family of neurotrophic factors, collectively indicated as neurotrophins, (which include brain-derived neurotrophic factor, neurotrophin-3 and neurotrophin 4/5). NGF was discovered for its action on the survival and differentiation of selected populations of peripheral neurons. Since then, an enormous number of basic and human studies were undertaken to explore the role of purified NGF to prevent the death of NGF-receptive cells. These studies revealed that NGF possesses important therapeutic properties, after topical administration, on human cutaneous pressure ulcer, corneal ulcers, glaucoma, retinal maculopathy, Retinitis Pigmentosa and in pediatric optic gliomas and brain traumas. The aim of this review is to present our previous, recent and ongoing clinical studies on the therapeutic properties of NGF.

Keywords: Nerve growth factor (NGF), nerve cells, cutaneous cells, visual cells, cancer cells, brain traumas.

1. INTRODUCTION

1.1. The NGF Discovery and Early Studies

The nerve growth factor (NGF) is the first discovered member of a family of neurotrophic factors, collectively indicated as neurotrophins, which include brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin 4/5 [1]. These factors share significant structural homologies and derive from a common ancestor gene [2]. Pioneering studies, started in the early 1950's by R. Levi-Montalcini on laboratory animals and isolated cells, were focused on the biological action of NGF [3]. These studies have demonstrated the protective action of NGF not only in the survival of degenerating peripheral nerve cells, but also in the regulation of neurotransmitters and neuropeptides synthesis of sympathetic and sensory nerve cells [4, 5]. *In vivo* down-regulation of NGF, through the administration of NGF-antibodies or by peripheral nerve lesion causes a marked decrease in Substance P (SP) and Calcitonin-Gene Related Peptide (CGRP) synthesis [6, 7]. Indeed, both SP and CGRP gene expression are regulated by NGF [8], and their depletion, subsequent to NGF down-regulation, is parallel to the impairment in sensory perceptions, *i.e.* those described in diabetic neuropathy [9]. Exogenous NGF administration influences neuronal plasticity that allows the adult nervous system to modify its structure and functions in response to stimuli [10]. Moreover, it was also demonstrated that the constitutive synthesis of NGF in adult tissues correlates with peripheral nervous system (PNS) neurons phenotypic features, such as innervation density, cell body size, axonal terminal sprouting, dendritic growth, induction and/or inhibition of neuropeptides and neurotransmitters or transmitter-producing enzymes [11-14].

NGF exerts its action on the growth and survival of peripheral sensory and sympathetic neurons and on a number of brain neurons, particularly basal forebrain cholinergic neurons (BFCN) that are among the major NGF-target cells within the central nervous system (CNS) [4, 15, 16]. NGF, initially believed to act only on the growth and differentiation of peripheral sympathetic and sensory neurons, was found to interact with a number of other target cells within the nervous system as well as extra-neuronal targets (Table **1**), such as mast cells, T and B lymphocytes, granulocytes, monocytes, keratinocytes, endothelial cells, hormones-secretory cells in the reproductive system [5, 17-20]. The NGF action on cells belonging to the immune and endocrine systems, suggests that the neurotrophin exert a modulatory role on neuro-immuno-endocrine mechanisms of vital importance in the regulation of homeostatic processes [21]. Accordingly, it has been shown that circulating and brain NGF levels undergo significant variations after exposure to stressful events, both in animal models and in humans [22].

In the 1970's, the existence of a NGF precursor

Second facteur de croissance découvert Epidermal Growth Factor (EGF) Années 50 également

The Nobel Prize in Physiology or Medicine 1986

Stanley Cohen
Rita Levi-Montalcini

Share this

Stanley Cohen
Facts

Photo from the Nobel Foundation archive.

Stanley Cohen
The Nobel Prize in Physiology or Medicine 1986

Born: 17 November 1922, Brooklyn, NY, USA

Died: 5 February 2020, Nashville, TN, USA

Affiliation at the time of the award: Vanderbilt University School of Medicine, Nashville, TN, USA

Prize motivation: "for their discoveries of growth factors."

Prize share: 1/2

Work

Human beings develop from a single cell that divides to form new cells. These new cells then also further divide and multiply. Little by little, different types of cells with different functions are formed. After Rita Levi Montalcini discovered a substance that promotes growth of the nervous system, in the mid-1950s Stanley Cohen discovered another growth factor that promotes growth of cells in the skin and cornea. The discovery of what are now known as growth factors has provided a deeper understanding of medical problems like deformities, senile dementia, delayed wound healing, and tumor diseases.

This paper is
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Origins of Growth Factors: NGF and EGF

Published, JBC Papers in Press, August 12, 2008, DOI 10.1074/jbc.X800008200

Stanley Cohen
From the Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-0146

Growing up on the streets of Brooklyn, I remember being interested in how worked: taking apart an old telephone and the gears of my new 4-speed bicy most enjoyable. As a biology major at Brooklyn College in 1945, I was fascir embryology. How does an egg turn into a chicken or a frog or a person? N insight into the problem was the thought that it was necessary to understand the chemic tions inside the egg and embryo and not simply observe biological structures. I, therefore, a double major in chemistry and biology (also with the hope of earning a living as a lab technician). My first job after graduating was working nights as a bacteriologist in a milk p ing plant. One of my professors at Brooklyn College wrote asking whether I was interested to graduate school. The college had been sending one student a year to the Biology Depa at Oberlin to work as a laboratory assistant while studying for a master's degree. I Oberlin offered to pay my tuition plus some $300 a semester for living expenses, I jur the chance. School and science were both interesting and fun. Upon graduating, I co my education toward a Ph.D. working as an assistant in the Biochemistry Departmen University of Michigan under Howard B. Lewis. My research involved studying the Kre cycle in the common earthworms that I collected from the university campus. I had be at Oberlin that the yellow cells surrounding the gut in the worm corresponded to th malian liver. I decided to check whether the enzymatic reactions in worms were sir those in mammals. They were (1).

My first "real job" was in the Pediatrics Department at the University of Colorado s creatine metabolism in premature infants under Harry Gordon. I think he hired me becaus impressed by my ability to stomach tube earthworms. After several years, I decided I ne learn the then new technique of using radioisotopes in metabolic studies, and I obta American Cancer Society fellowship to work in the Radiology Department of Washingt versity under Martin Kamen where I combined this new knowledge with my interest in e ogy. Although fertilized frog eggs and early embryos are impermeable to small mo (amino acids, phosphates, etc.), sufficient amounts of $C^{14}O_2$ were metabolized by inta and embryos to permit the identification of the radioactive compounds present at stages of development (2).

Upon completion of my fellowship, Dr. Kamen recommended me for a position in the Department of Washington University in the laboratory of Viktor Hamburger and Ri Montalcini. This move was critical in determining the direction of my research for t 40-some odd years: the isolation, structure, and function of the first of the "growth factors growth factor (NGF) and epidermal growth factor (EGF).

Nerve Growth Factor

The original neuroembryological experiments started more than half a century ag laboratories of Drs. Viktor Hamburger and Rita Levi-Montalcini. They had discovered a

Cohen Stanley
Médecine, 1986
Etats-Unis

Levi-Montalcini Rita
Médecine, 1986
Italie

L'attribution du ***prix Nobel de Médecine 1986***

Rita Levi Montalcini et Stanley Cohen

a récompensé la découverte dans les années 50 des 2 premiers facteurs de croissance

« Que le corps fasse ce qu'il veut Je ne suis pas mon corps Je suis mon esprit Mon corps se ride mais pas le cerveau »

Le second NGF découvert au cerveau (groupe neurotrophines)
Brain-Derived Neurotrophic Factor (Barde 1982)
Puis NT-3 (Maisonpierre 1982) et NT-4/5 (Hallbook, Ip)
Découverte récente du BDNF ***dans les plaquettes+++***
Ils ne sont pas uniquement présents dans leurs cellules ou tissus cibles

Le BDNF, une molécule qui a le pouvoir de régénérer le cerveau

Le BDNF améliore la mémoire et augmente la plasticité du cerveau

Dans certaines pathologies, la mémoire peut s'altérer au fur et à mesure du temps, et peu à peu, conduire la personne vers un état de démence. Les maladies neuro-dégénératives impliquent presque toujours une dégénérescence neuronale importante au niveau du noyau de Meynert. L'émergence de ces nouvelles affections peut être directement corrélée à l'allongement de l'espérance de vie, et représentent ainsi un problème majeur de santé publique.

La « stratégie neurotrophique » est définie par Christopher Henderson, directeur de recherche au CNRS et à l'INSERM comme : « L'emploi de facteurs neurotrophiques pour aider les neurones à résister au processus pathologique, même lorsque celui-ci n'implique aucune altération du fonctionnement normal des facteurs eux-mêmes » [1]. Les facteurs neurotrophiques (NGF, IGF-1, CNTF, NT-3…) sont des facteurs de croissance de nature protéique. Un bon nombre d'études ont montré qu'ils étaient des médiateurs importants de la plasticité structurale et fonctionnelle du cerveau [2][3]. Outre leur rôle trophique, ils régulent la transmission synaptique, la synaptogénèse, et permettraient même l'inhibition de l'apoptose [1] [2] [3].

La grande majorité des recherches menées en « stratégie neurotrophique » portent sur la neurotrophine BDNF (Brain-Derived Neurotrophic Factor), car elle est la plus abondante de notre système nerveux. On la retrouve avec son récepteur TrkB (Tropomyosine-related kinase B) dans les régions neuronales hautement plastiques. Ses facultés de maintien des fonctions neuronales ont été démontrées dans une étude des chercheurs A. H. Nagahara et David A. Merrill [4].

Cette équipe de recherche a testé les effets du BDNF sur des primates et rongeurs en fin de vie ainsi que sur des modèles animaux modifiés génétiquement pour développer la maladie d'Alzheimer. Les résultats obtenus étaient très encourageants quant à la potentielle utilisation du BDNF dans le traitement de la maladie d'Alzheimer, ou simplement pour favoriser l'apprentissage et la mémoire chez les personnes âgés.

Les pouvoirs étonnants du BDNF sur les cerveaux de modèles animaux

Chez les rats et primates âgés, la transfusion de BDNF a amélioré la régulation de l'expression génique au niveau neuronal et a restauré les signalisations cellulaires. Le BDNF a agi comme un neuroprotecteur en compensant la perte synaptique par une neurogénèse augmentée au niveau du cortex et de l'hippocampe. Chez les animaux transgéniques, le BDNF a véritablement inversé l'atrophie neuronale. L'amélioration des déficiences cognitives était flagrante autant chez les animaux âgés que chez ceux atteints de la maladie d'Alzheimer.

Ces découvertes indiquent que le BDNF exerce un effet protecteur des circuits neuronaux impliqués dans la maladie d'Alzheimer, (même s'il agit à travers des mécanismes indépendants de « la cascade amyloïde »). La stratégie neurotrophique exploitant le potentiel de BDNF mérite une exploration plus poussée pour tenter une application thérapeutique contre les maladies neurodégénératives ou tout simplement pour supplémenter le déclin cognitif rencontré avec l'âge [4].

Sources :

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[3] Faigle, R., & Song, H. (2013). Signaling mechanisms regulating adult neural stem cells and neurogenesis. Biochimica et Biophysica Acta (BBA)-General Subjects, 1830(2), 2435-2448.

[4] Nagahara, A. H., Merrill, D. A., Coppola, G., Tsukada, S., Schroeder, B. E., Shaked, G. M., … & Rockenstein, E. (2009). Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. Nature medicine, 15(3), 331.

UN FACTEUR DE CROISSANCE DEPENDANT DES PLAQUETTES Qui STIMULE LA PROLIFERATION DES CELLULES endothéliales

1973 Russell ROSS+++

A Platelet-Dependent Serum Factor That Stimulates the Proliferation of Arterial Smooth Muscle Cells *In Vitro*

(primate/cell culture/atherosclerosis)

RUSSELL ROSS*, JOHN GLOMSET†, BEVERLY KARIYA*, AND LAURENCE HARKER‡

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Communicated by Sidney Udenfriend, November 21, 1973

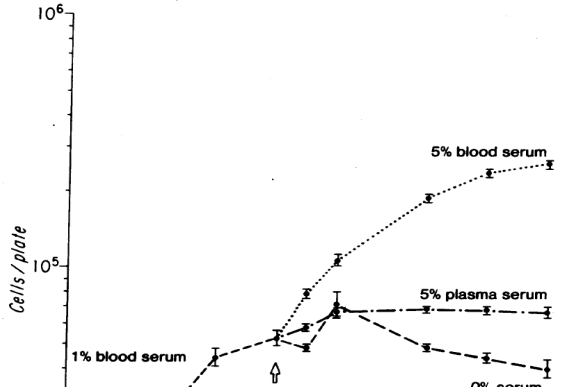
ABSTRACT **Dialyzed serum from clotted monkey blood ("blood serum") promotes the proliferation of monkey arterial smooth muscle cells in culture, but dialyzed serum prepared from recalcified platelet-poor plasma ("plasma serum") is much less effective. Addition of platelets and calcium to platelet-poor plasma increases the activity of plasma serum to the same level achieved with blood serum. Furthermore, addition to plasma serum of a platelet-free supernatant prepared by exposing purified platelets to thrombin also stimulates the proliferation of smooth muscle cells. Thus, much of the growth-promoting activity of dialyzed serum is directly or indirectly derived from platelets. This finding has important implications for the response of arteries to localized injury and provides a key to further understanding of the role of factors derived from blood serum in promoting cell proliferation *in vitro*.**

We have been studying the growth of arterial smooth muscle cells (SMC) in culture as part of an attempt to determine why these cells accumulate focally in atherosclerosis (1). Since our working hypothesis has been that atherosclerosis is an exacerbated arterial response to local endothelial injury, we have been interested in the fact that SMC, like most other diploid, nontransformed cells, do not proliferate in culture except in the presence of blood serum. We have been attempting to identify the serum factors involved, in order ultimately to test the possibility that endothelial injury increases their concentration in the subendothelial space and thereby promotes SMC proliferation in the intima. We have already found (1, 2) that serum lipoproteins are necessary for optimal cell growth in culture, and now wish to report studies of a nondialyzable serum component that is probably not a lipoprotein and that appears to be derived from platelets.

equal numbers in 35-mm Falcon plastic petri dishes. The reproducibility of cell plating was confirmed in each experiment. The medium was changed three times per week. For the first 7 days the medium contained 1% pooled monkey blood serum. Thereafter, the 1% serum was replaced with the different serum fractions to be tested. Each fraction was added in an amount that corresponded to that provided by 5% monkey blood serum, and subsequent cell proliferation was compared with that obtained in medium containing 5% blood serum and 0% serum.

RESULTS

In initial experiments nondialyzable components were found to be responsible for most if not all of the effect of serum on SMC proliferation. To increase the supply of these com-



Platelets clearly play a complex role in stimulating the response of tissues to injury (19, 20), but their potential role in stimulating the proliferation of subendothelial cells has not previously been recognized. For example, in a recent discussion (1) of the role of subendothelial SMC in atherosclerosis, we suggested that "local injury to the endothelium may increase the concentration of plasma proteins in the vicinity of medial smooth muscle cells and in response to some of these proteins the cells migrate into the intima and proliferate." It is now apparent that this concept must be specifically modified to include concepts developed by others concerning the adherence of platelets to focal areas of injured endothelium (19, 20), the release of specific platelet factors (10, 11) into the subendothelial space, and the proliferative response of SMC to the platelet-derived factor(s) demonstrated in the present investigation.

A CE JOUR
BEAUCOUP PLUS D'APPLICATIONS THERAPEUTIQUES AVEC LE PRP

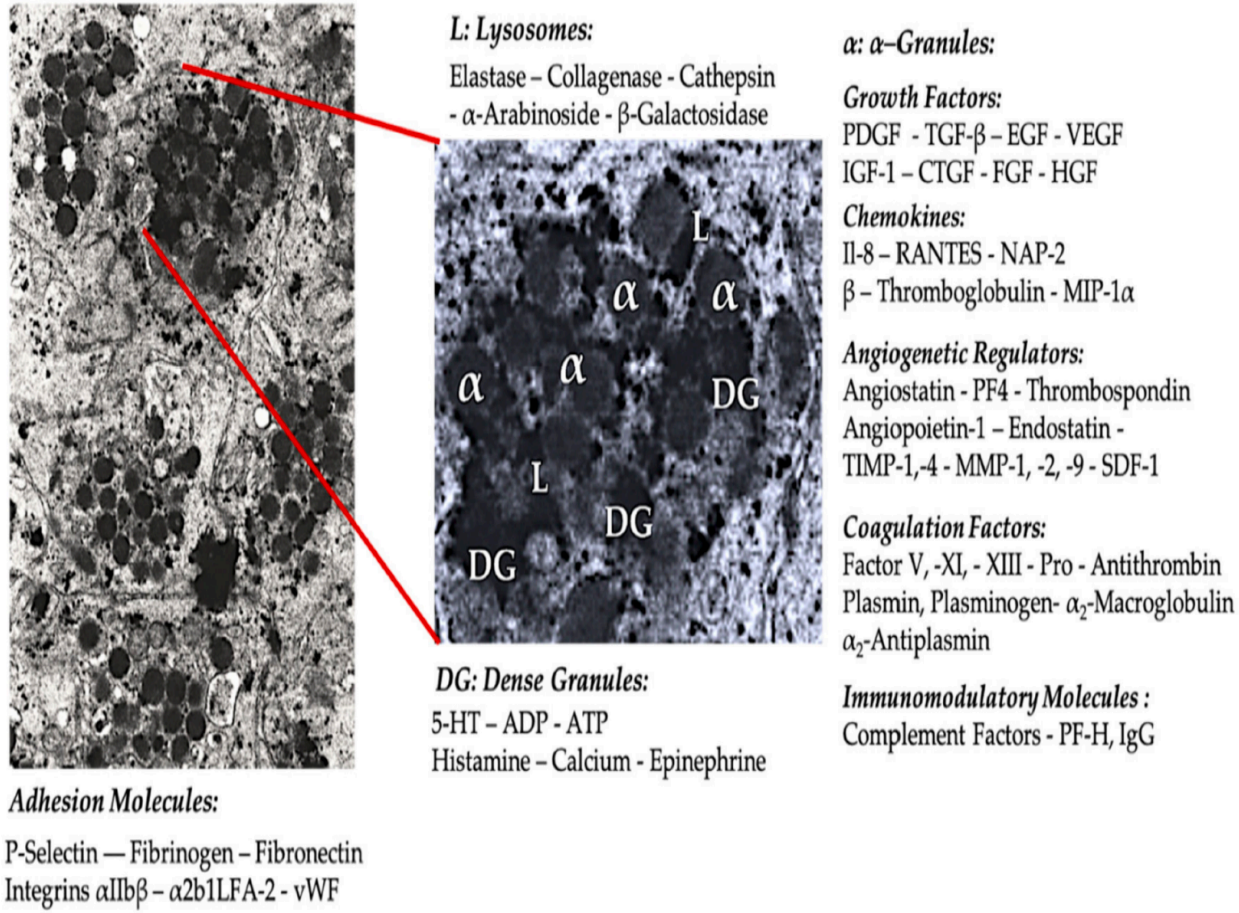
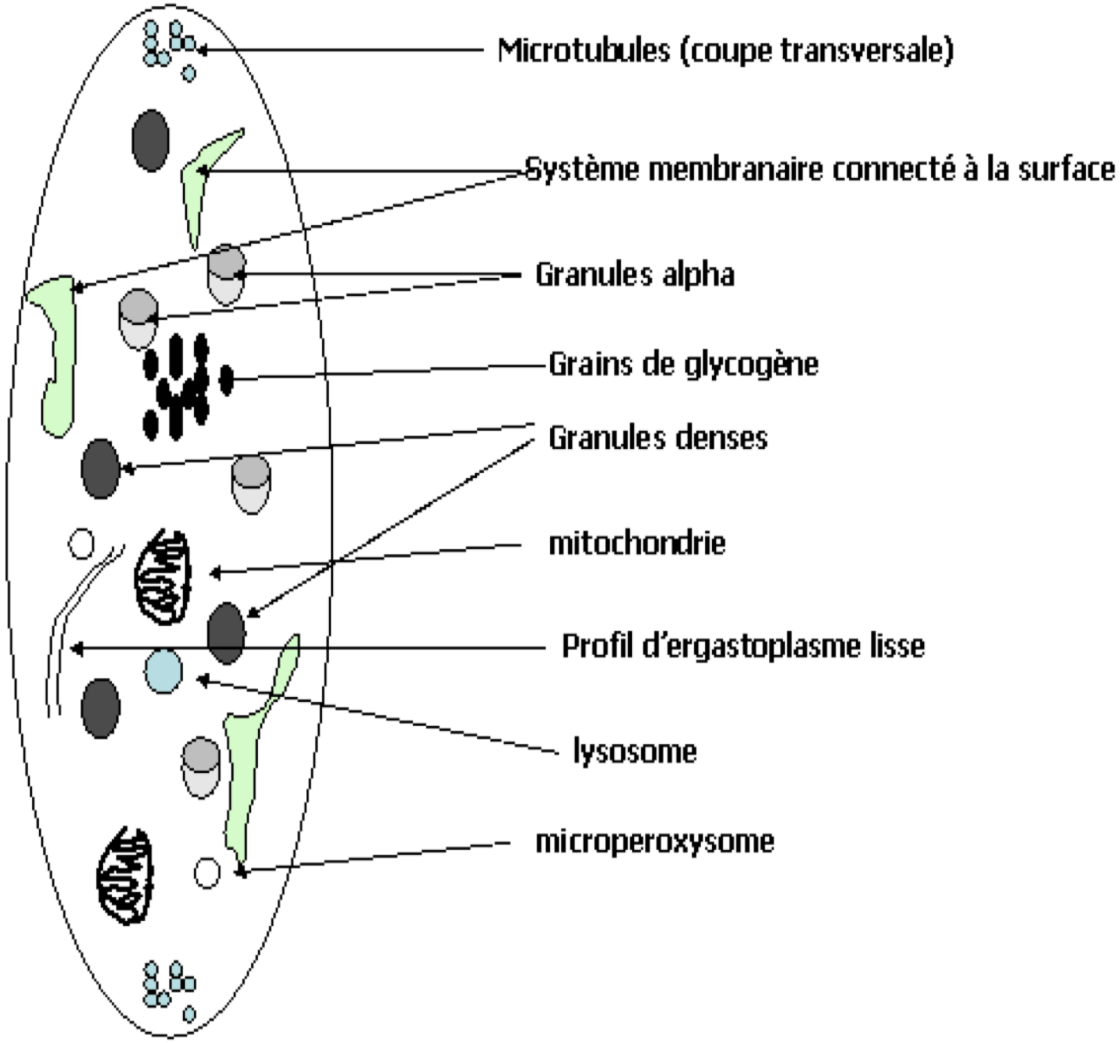


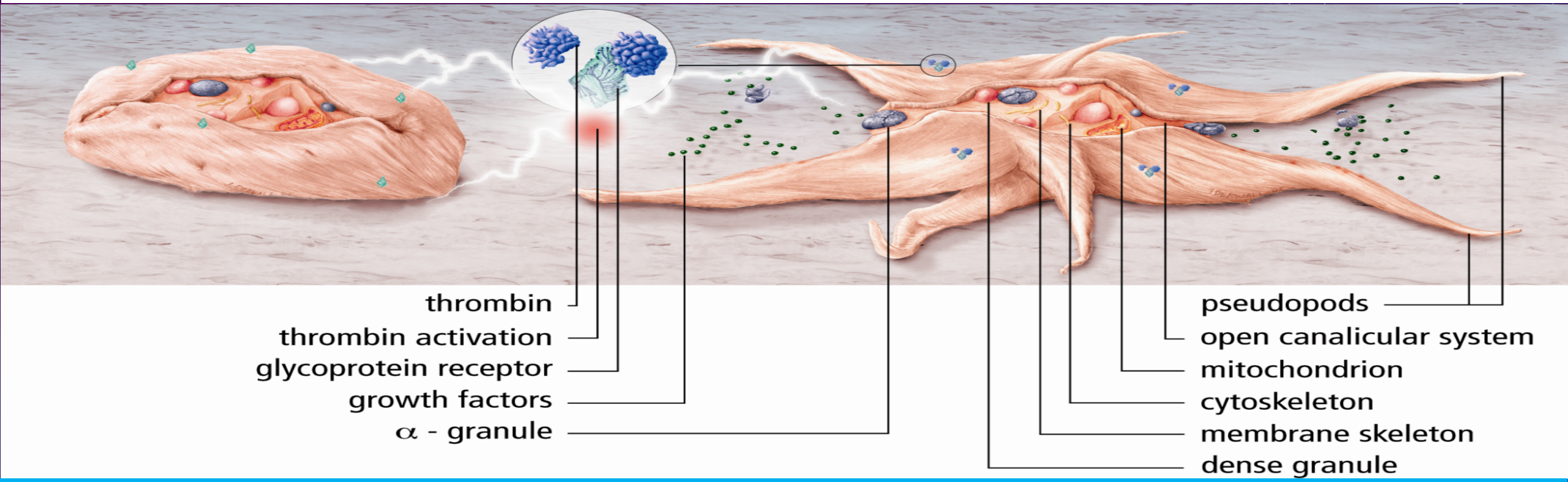
Figure 2. Electron microscopic picture of a cluster of platelets from a PRP vial and a extrapolation of a single platelet (original magnification × 10,000) (from volunteer PE), representing the most familiar cellular constituents of α-granules (α), dense granules (DG), and lysosomes (L), including some platelet surface adhesion molecules. Adapted and modified from Everts et al. [61].



Représentation schématique d'une plaquette sanguine

Les Facteurs de Croissance Plaquettaires libérés par les granules alpha+++

PLAQUETTE AU REPOS *PLAQUETTE ACTIVÉE*



Les Plaquettes sont des entités vivantes et fonctionnelles impliquées dans ***l'hémostase et la cicatrisation****, elles sont utilisées après* ***élimination par centrifugation des hématies (GR) et en général des polynucléaires neutrophiles (GB)***

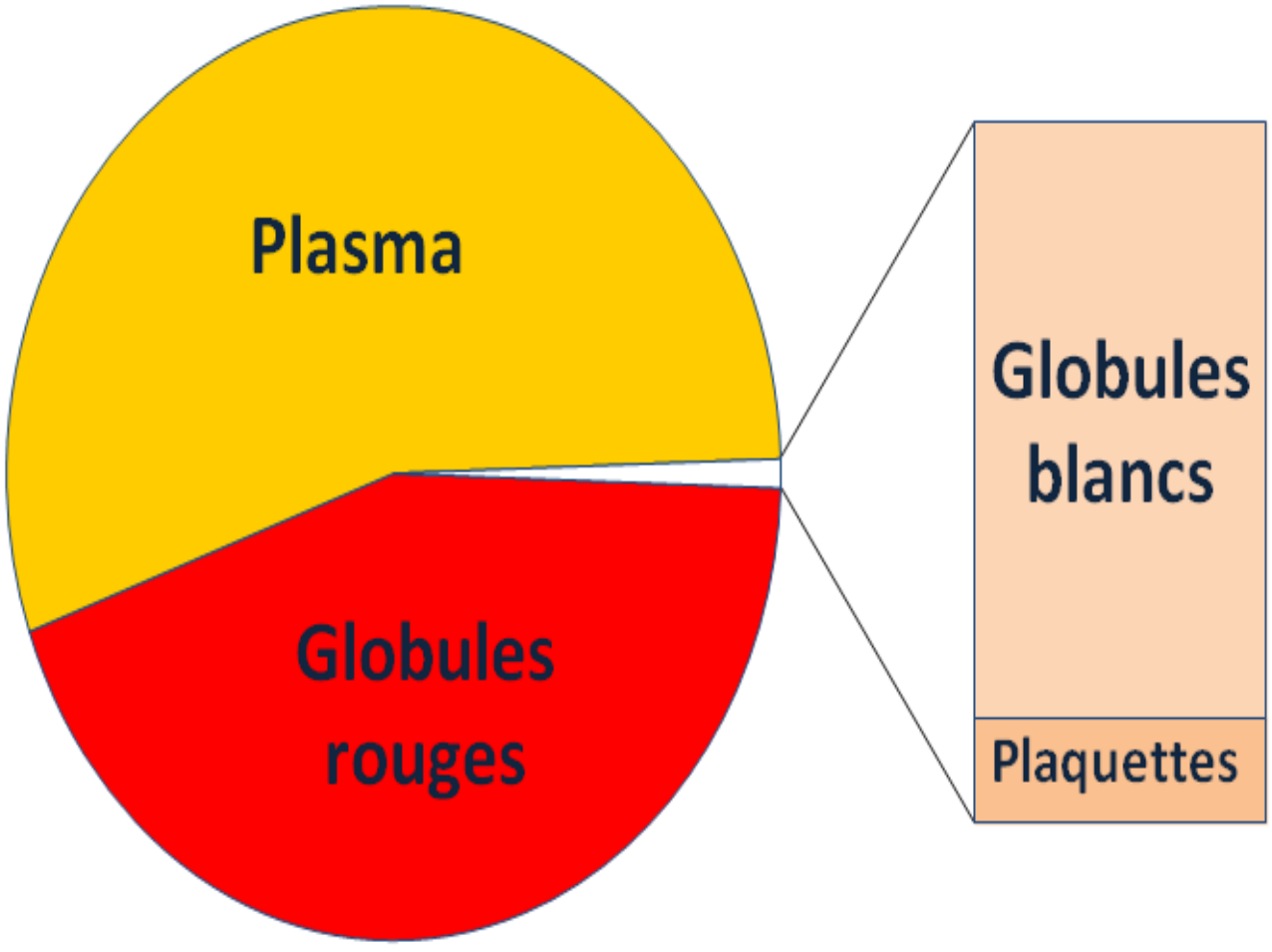
Elles sécrètent, de façon contrôlée des doses de facteurs de croissance spécifiques pour chaque étape du processus de guérison qui sera accéléré + antalgique + anti-inflammatoire

Plasma du patient (autologue) enrichi en plaquettes

obtenu par centrifugation

du sang du patient

Concentration optimale sub-physiologique (1,6-2 fois)



1/PLASMA

55% du volume sanguin

- Protéines plasmatiques (globulines, albumine, ***fibrinogène***)
- Nutriments
- Vitamines
- Hormones
- Electrolytes
- ***Facteurs de croissance (IGF)***

2/Eléments cellulaires

45% du volume sanguin

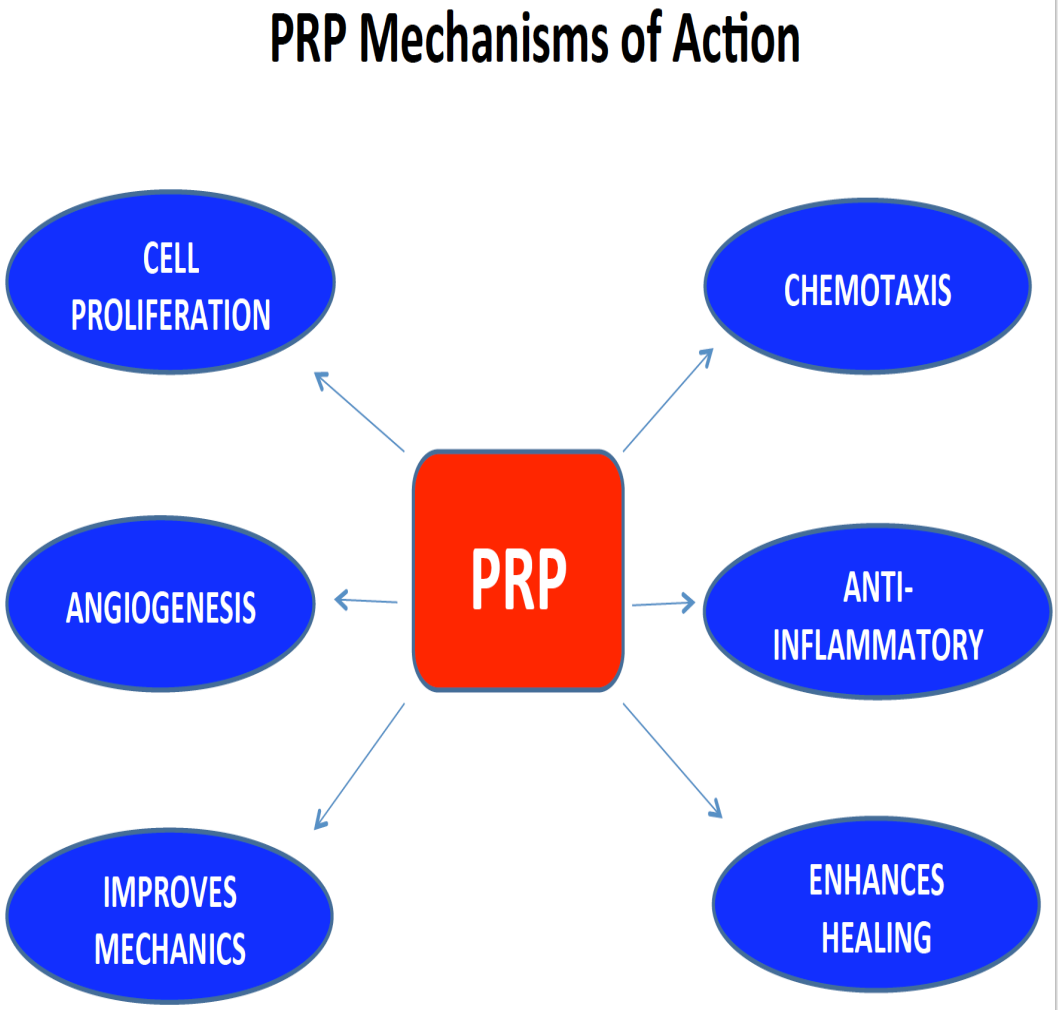
- Globules rouges (44%)
- Globules blancs(1%)
- ***Plaquettes (0.15%)***

PROPRIETES DES FACTEURS DE CROISSANCE PLAQUETTAIRES

Activation cellulaire, Chimiotactisme, Collagène, Vascularisation…

TABLE 1. Growth Factors and Cellular Effects.

Growth Factor	Cellular Effects
PDGF *Platelet Derived Growth Factor*	Macrophage activation and angiogenesis Fibroblast chemotaxis and proliferative activity Enhances collagen synthesis Enhances the proliferation of bone cells
IGF-I *Insulin-like Growth Factor-I*	Chemotactic for myoblast and fibroblasts and stimulates protein synthesis Mediator in growth ad repair of skeletal muscle Enhances bone formation by proliferation and differentiation of osteoblasts
TGF-β *Transforming Growth Factor-β*	Enhances the proliferative activity of fibroblasts Stimulates biosynthesis of type I collagen and fibronectin Induces deposition of bone matrix Inhibits osteoclast formation and bone resorption Regulation in balance between fibrosis and myocyte regeneration.
PDEGF *Platelet Derived Endothelial Growth Factor*	Promotes wound healing by stimulating the proliferation of keratinocytes and dermal fibroblasts
PDAF *Platelet Derived Angiogenic Factor*	Induces vascularization by stimulating vascular endothelial cells
EGF *Endothelial Growth Factor*	Cellular proliferation Differentiation of epithelial cells
VEGF *Vascular Endothelial Growth Factor*	Angiogenesis Migration and mitosis of endothelial cells Creation of blood vessel lumen Creation of fenestrations Chemotactic for macrophages and granulocytes Vasodilation (indirectly by release of nitrous oxide)
HGF *Hepatocyte Growth Factor*	Stimulates of hepatocyte proliferation and liver tissue regeneration Angiogenesis Mitogen for endothelial cells Antifibrotic



PROPRIETES DES FACTEURS DE CROISSANCE PLAQUETTAIRES

Exemple de la réparation tendineuse (plusieurs semaines, mois…)

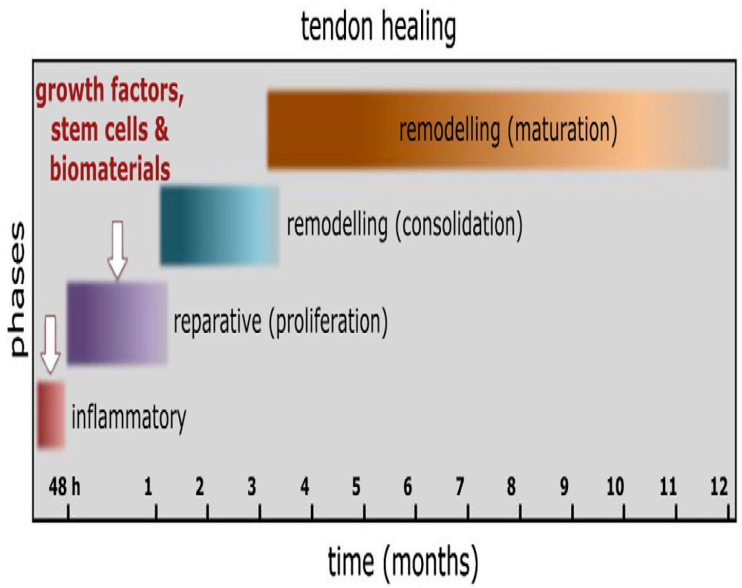
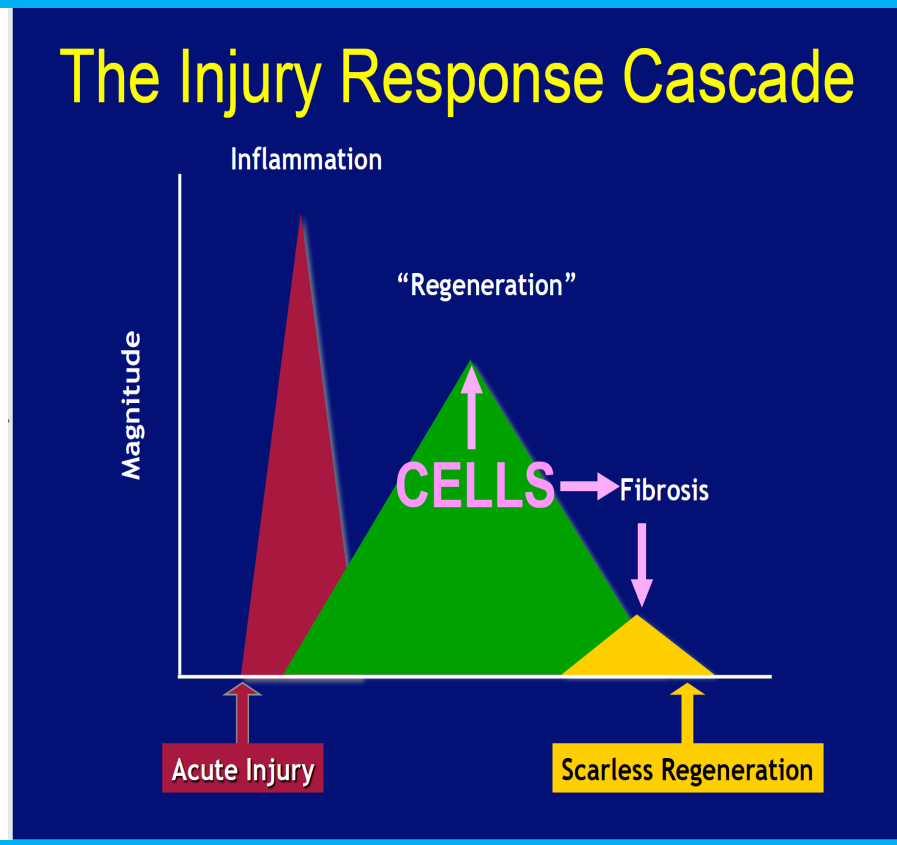


Fig. 2. The tendon repair process in humans. The healing of ruptured tendons passes through three main phases containing distinctive cell and molecular cascades. These phases overlap and their duration depends upon the location and severity of the tendon injury. Currently, the tendon research field is actively exploring the use of growth factors, genes, stem cells and biomaterials, alone or in various combinations, for enhancing tendon healing. Mostly, the appropriate times of application are in the first two stages (indicated by white arrows), and depend on the type of growth factors, genes, stem cells or biomaterials implemented. Based on [47].



AMA (agence mondiale antidopage) 2011

L'usage du Plasma Riche en Plaquettes n'est pas du dopage

AUTOLOGUE (pas d'un animal, pas d'un autre humain, pas de synthèse)

Ce n'est pas de l'EPO !

HISTOIRE DE L'UTILISATION CLINIQUE
DES FACTEURS DE CROISSANCE PLAQUETTAIRES

*DÉBUTS DE LA **BIO-MEDECINE REGENERATIVE***
ODONTO-STOMATOLOGIE
MÉDECINE DU SPORT, ORTHOPÉDIE
MÉDECINE VÉTÉRINAIRE
***VIEILLISSEMENT** (PEAU, TENDONS, CARTILAGE, GÉNITAL)*

ANNEES 90 : pionniers en maxillo-facial, dentistes, stomatos (colle biologique)

Ann Surg. 1986 Sep;204(3):322-30.

Classification and treatment of chronic nonhealing wounds. Successful treatment with autologous platelet-derived wound healing factors (PDWHF).

Knighton DR, Ciresi KF, Fiegel VD, Austin LL, Butler EL.

Abstract

Previous animal data showed that platelets contain growth factors that stimulate capillary endothelial migration (angiogenesis), fibroblast proliferation and migration, and collagen synthesis. This study utilized autologous platelet-derived wound healing factors (PDWHF) to treat 49 patients with chronic nonhealing cutaneous ulcers. Patients were classified on the basis of 20 clinical and wound status parameters to generate a wound severity index. Forty-nine patients--58% diabetic (20% with renal transplants); 16% with trauma, vasculitis, etc.; 14% with decubitus ulcers; and 6% each with venous stasis or arterial insufficiency--with a total of 95 wounds had received conventional wound care for an average of 198 weeks (range: 1-1820 weeks). After informed consent was obtained, patients received autologous PDWHF. Mean 100% healing time for all patients was 10.6 weeks. There was no abnormal tissue formation, keloid, or hypertrophic scarring. A multivariant analysis showed a direct correlation to 100% healing with initial wound size and the initiation of PDWHF therapy. This is the first clinical demonstration that locally acting growth factors promote healing of chronic cutaneous ulcers.

Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998 Jun;85(6):638-46.

Platelet-rich plasma: Growth factor enhancement for bone grafts.

Marx RE[1], Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR.

Author information

Abstract

Platelet-rich plasma is an autologous source of platelet-derived growth factor and transforming growth factor beta that is obtained by sequestering and concentrating platelets by gradient density centrifugation. This technique produced a concentration of human platelets of 338% and identified platelet-derived growth factor and transforming growth factor beta within them. Monoclonal antibody assessment of cancellous cellular marrow grafts demonstrated cells that were capable of responding to the growth factors by bearing cell membrane receptors. The additional amounts of these growth factors obtained by adding platelet-rich plasma to grafts evidenced a radiographic maturation rate 1.62 to 2.16 times that of grafts without platelet-rich plasma. As assessed by histomorphometry, there was also a greater bone density in grafts in which platelet-rich plasma was added (74.0% +/- 11%) than in grafts in which platelet-rich plasma was not added (55.1% +/- 8%; p = 0.005).

PMID: 9638695 DOI: 10.1016/s1079-2104(98)90029-4

[Indexed for MEDLINE]

J Oral Maxillofac Surg. 1997 Nov;55(11):1294-9.

Platelet gel: an autologous alternative to fibrin glue with applications in oral and maxillofacial surgery.

Whitman DH[1], Berry RL, Green DM.

Author information

Abstract

The preparation and use of platelet gel, an autologous formulation of fibrin glue, are described. The unique features of this biologic sealant are that it is derived from autologous blood collected in the immediate preoperative period by the anesthesiologist, it contains a high concentration of platelets, and it can be used in patients who are not candidates for blood bank donation. Platelet gel has been used successfully in the area of reconstructive oral and maxillofacial surgery in conjunction with ablative surgery of the maxillofacial region, mandibular reconstruction, surgical repair of alveolar clefts and associated oral-antral/ oral-nasal fistulas, and adjunctive procedures related to the placement of osseointegrated implants.

PMID: 9371122 DOI: 10.1016/s0278-2391(97)90187-7

Int J Oral Maxillofac Implants. 1999 Jul-Aug;14(4):529-35.

Plasma rich in growth factors: preliminary results of use in the preparation of future sites for implants.

Anitua E[1].

Author information

Abstract

This article presents preliminary clinical evidence of the beneficial effect of the use of plasma rich in growth factors of autologous origin. The plasma is obtained from the individual patient by plasmapheresis. The macroscopic and microscopic results obtained with bone regeneration using this technique, which uses no membrane or barrier, can be observed. The incorporation of these concepts can introduce several advantages, including the enhancement and acceleration of bone regeneration and more rapid and predictable soft tissue healing.

PMID: 10453668

ANNEES 2000 : débuts du cosmétique « skin », tendons

Format: Abstract

Int J Oral Maxillofac Implants. 1999 Jul-Aug;14(4):529-35.

Plasma rich in growth factors: preliminary results of use in the preparation of future sites for implants.

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Abstract

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Send to

Plast Reconstr Surg. 2001 Jan;107(1):229-37; discussion 238-9.

The use of autologous platelet-rich plasma (platelet gel) and autologous platelet-poor plasma (fibrin glue) in cosmetic surgery.

Man D[1], Plosker H, Winland-Brown JE.

Author information

Abstract

The purpose of this study was to evaluate a new technique of harvesting and preparing autologous platelet gel and autologous fibrin glue (body glue) and to evaluate their effectiveness in stopping capillary bleeding in the surgical flaps of patients undergoing cosmetic surgery. A convenience sample of 20 patients ranging from 25 to 76 years of age undergoing cosmetic surgery involving the creation of a surgical flap were included in the study. The types of surgical procedures included face lifts, breast augmentations, breast reductions, and neck lifts. Platelet-poor and platelet-rich plasma were prepared during the procedure from autologous blood using a compact, tabletop, automated autologous platelet concentrate system (SmartPReP, Harvest Autologous Hemobiologics, Norwell, Mass.). The platelet-poor and platelet-rich plasma were combined with a thrombin-calcium chloride solution to produce autologous fibrin glue and autologous platelet gel, respectively. Capillary bed bleeding was present in all cases and effectively sealed within 3 minutes following the application of platelet gel and fibrin glue. The technique for making the solution and for evaluating its effectiveness in achieving and maintaining hemostasis during cosmetic surgical procedures is described. Autologous platelet gel and fibrin glue prepared by the automated concentrate system are compared with autotransfusor-prepared platelet gel and Tisseel (Baxter Healthcare Corp.), a commercially prepared fibrin sealant preparation.

PMID: 11176628 DOI: 10.1097/00006534-200101000-00037

Wound Repair/Cosmetic Surgery
Healing Enhancement of Skin Graft Donor Sites with Platelet-Rich Plasma

Presented at the
82ND ANNUAL AMERICAN ACADEMY OF ORAL AND MAXILLOFACIAL SURGERY MEETING
September 22, 2000, San Francisco, CA

Kevin Monteleone, DDS, R, Marx, DDS, R. Ghurani
University of Miami School of Medicine, Miami, FL

Introduction

Split-thickness skin grafts are frequently used in oral and maxillofacial preprosthetic surgeries as well as several types of mucosal neck surface deficiencies, such as may be seen in tumor and trauma wounds. As a variable of size and depths, healing is noted to be slow, associated with discomfort, and eventuates into a scar. Platelet-rich plasma (PRP) has been documented to accelerate and enhance bone graft healing and maturity. However, no definitive data in humans have yet shown a similar effect on soft tissue healing.

Purpose

The purpose of this study was to assess the potential of PRP to accelerate the soft tissue wound healing and epithelialization of a split thickness skin graft donor site.

Materials and Methods

This study consisted of 20 patients who required split-thickness skin grafts in excess of 10x10 cm. Each patient underwent 2 side-by-side split-thickness graft harvests measuring about 5x7 cm. One donor area was treated with topical bovine thrombin covered with an occlusive Opsite dressing. The adjacent second donor area was treated with 6 mL of a platelet concentrate containing greater than 1 million platelets per mm^3, obtained from the Platelet Concentrate Collection System (3i Corp.) and an occlusive Opsite dressing (Figures 1 and 2).

Wound assessments were conducted by direct observation, a patient pain evaluation scale, and photographic morphometry at 7 days, 14 days, 20 days, and 30 days. Histopathology specimens were obtained at variable times with special patient consents.

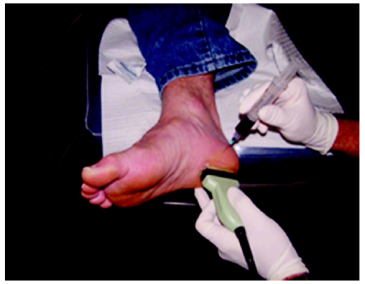
FEATURES

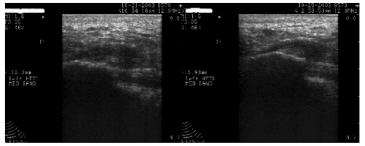
Growth Factors For Chronic Plantar Fasciitis?

November 03, 2004
Volume 17 - Issue 11 - November 2004
Pages: 36 - 42

By Stephen L. Barrett, DPM, CWS, and Susan E. Erredge, DPM, CWS

Plantar fasciitis/heel pain syndrome is the most common condition treated by podiatric foot and ankle specialists in the United States.1 However, the true etiology of plantar fasciitis is still unknown and has been attributed to many different etiological factors. Even the term "plantar fasciitis" is a misnomer as the plantar fascia is really a tendonous aponeurosis and not a fascial layer.2 It is entirely possible that our whole paradigm for treating plantar fasciitis is based on a false foundation, especially in light of the histological findings of Lemont, et. al., regarding specimens of





Am J Sports Med. 2006 Nov;34(11):1774-8. Epub 2006 May 30.

Treatment of chronic elbow tendinosis with buffered platelet-rich plasma.

Mishra A[1], Pavelko T.

Author information

Abstract

BACKGROUND: Elbow epicondylar tendinosis is a common problem that usually resolves with nonoperative treatments. When these measures fail, however, patients are interested in an alternative to surgical intervention.

HYPOTHESIS: Treatment of chronic severe elbow tendinosis with buffered platelet-rich plasma will reduce pain and increase function in patients considering surgery for their problem.

STUDY DESIGN: Cohort study; Level of evidence, 2.

METHODS: One hundred forty patients with elbow epicondylar pain were evaluated in this study. All these patients were initially given a standardized physical therapy protocol and a variety of other nonoperative treatments. Twenty of these patients had significant persistent pain for a mean of 15 months (mean, 82 of 100; range, 60-100 of 100 on a visual analog pain scale), despite these interventions. All patients were considering surgery. This cohort of patients who had failed nonoperative treatment was then given either a single percutaneous injection of platelet-rich plasma (active group, n = 15) or bupivacaine (control group, n = 5).

RESULTS: Eight weeks after the treatment, the platelet-rich plasma patients noted 60% improvement in their visual analog pain scores versus 16% improvement in control patients (P =.001). Sixty percent (3 of 5) of the control subjects withdrew or sought other treatments after the 8-week period, preventing further direct analysis. Therefore, only the patients treated with platelet-rich plasma were available for continued evaluation. At 6 months, the patients treated with platelet-rich plasma noted 81% improvement in their visual analog pain scores (P =.0001). At final follow-up (mean, 25.6 months; range, 12-38 months), the platelet-rich plasma patients reported 93% reduction in pain compared with before the treatment (P <.0001).

CONCLUSION: Treatment of patients with chronic elbow tendinosis with buffered platelet-rich plasma reduced pain significantly in this pilot investigation. Further evaluation of this novel treatment is warranted. Finally, platelet-rich plasma should be considered before surgical intervention.

PMID: 16735582 DOI: 10.1177/0363546506288850

Mikel Sánchez >
Juan Azofra >
Beatriz Aizpurua >
Jorge Guadilla >
Nicolás Fiz >
Orlando Pompei >
Ane Miren Bilbao >
Gorka Knörr >

I HAVE AN INJURY

Access to the affected area to learn more about your injury

SHOULDER
ELBOW
HAND
HIP
KNEE
ANKLE
FOOT



Mikel Sánchez

Doctor Mikel Sánchez graduated in **Medical Studies from the University of Bordeaux** (France) and validated his degree to obtain a degree in Medicine and Surgery from the University of the Basque Country in 1979. He took the **specialty in Traumatology and Orthopedic Surgery** at the Santiago Apóstol Hospital in Vitoria-Gasteiz. During this time he was responsible for the facial trauma injuries service at the aforementioned hospital and was also assigned to the rheumatology and neurosurgery services to complement his specialty training. He worked as a specialist for the hospital's traumatology service until 1986. Since 1993 he has worked exclusively in the private sector and in the year 2000, he started work at the La Esperanza Clinic following his appointment as head doctor and as head of the traumatology, orthopedic and arthroscopic surgery service. That year he also set up the **Arthroscopic Surgery Unit** (UCA) within the clinic facilities.

He has pioneered the advance of Arthroscopic Surgery in Europe and in Spain. He is a member of the Leeds-Keio work group, Rheumatism Research Unit, University of Leeds, UK and Department of Orthopedic Surgery, Keio University, Japan. The Leeds-Keio group was an Anglo-Japanese collaborative project whose aim was to promote the development of arthroscopic surgery in Europe and Japan, especially knee and shoulder ligament replacement surgery.

He has worked with renowned names in the field of arthroscopic surgery such as Hideo Matsumoto and Bahaa Botros Seedhom. He has developed surgical instrument prototypes for anterior (ACL) and posterior (PCL) cruciate ligament reconstruction as well as techniques and instruments for treating recurrent shoulder dislocation. This technology and the functional and biological concepts on which it was founded remain in force today. **At international level he was the first doctor to understand the therapeutic potential of PRP and to apply it to the field of traumatology**. He founded the Arthroscopic Surgery Unit (UCA) and the Biological Therapy Unit (UTB).

He has been awarded several prizes for his professional work including the Mapfre Medicine Foundation (2010) “Development of Applied Traumatology” Prize for his “Innovation in the Treatment of Tendon Injuries”; the Gold Medal from the city Vitoria-Gasteiz in 2007 for his work in the world of medicine; the 2003 Basque Country Prize for Sport for his scientific and technical contribution to sports development; the Third National Prize for research into Sports Medicine from the University of Oviedo in 2002 and 2003 for the application of plasma rich in growth factors (PRGF®-Endoret®) and its use in the treatment of tendon injuries.

Mikel Sánchez discovered the impact of PRPs in Sports Medicine and initially intended to use this in the arthroscopic treatment of a knee cartilage avulsion in a young footballer (Sánchez M, 2003). Furthermore, he also innovated in anterior cruciate ligament (ACL) reconstruction surgery, inventing a method for Intra-Operative preparation of bioactive grafts for reconstructive surgery of the anterior cruciate ligament using the tissue engineering paradigm (Spanish Society for Arthroscopic Surgery Prize, 2003). The aim of this surgery is to achieve rapid (transformation of the tendon into ligament) and also to rapidly fasten the ligamentoplasty to the bone (Sánchez M, Arthroscopy 2010).

Currently he is a member of the Basque-Navarrese Society of Orthopedic Surgery and Traumatology (SVNCOT). Likewise, he is also a member of the "International Society of Arthroscopy, Knee surgery and Orthopaedic Sports medicine" (ISAKOS).

In 2006 he created the first Biological Therapy Unit (UTB) in Vitoria-Gasteiz at the USP La Esperanza Clinic facilities to successfully treat, using **Plasma Rich in Growth Factors (PRGF®-Endoret®)**, hundreds of patients and world-famous sportspersons.

Le grand pionnier Européen et Mondial!

MIKEL SANCHEZ

CHIRURGIEN

Meet Dr. Steven Sampson of The Orthohealing Cen

VoyageLA

LOCAL STORIES

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Today we'd like to introduce you to Dr. Steven Sampson.

So, before we jump into specific questions about the business, why don't you give us some details about you and your story.
During my residency in New York City, I was disappointed in the overall focus to treat orthopedic injuries by managing symptoms with cortisone or medications, that gave a false sense of improvement, masked injury and making injuries worse. Following the residency in New York City, I moved to Santa Monica California for an opportunity to work with professional athletes. Early on I learned of a unique approach to healing that maximizes the body's ability to heal itself. Doctors in Spain were treating professional soccer players with their own blood, called Platelet Rich Plasma "PRP."

Immediately a light went on for me after I reviewed the basic science that seemed promising. We treated our 1st patient a US world cup soccer athlete who recovered in half the expected time from an MCL tear (knee ligament tear). The procedure was featured on CBS news nationally and the treatment gained attention. I began to vigorously study and publish literature on PRP becoming an international expert speaking at the United Nations Geneva and around the globe.

As one of the few physicians studying and injecting PRP into painful joints and tendons, I created an annual meeting so doctors can collaborate together & share scientific advances, clinical experience and patient data. This conference (TOBI) The Orthobiologic Institute started with approximately 15 doctors at the Hotel Palomar and now is in its 9th year at the Wynn Las Vegas with nearly 600 doctors and industry leaders from over 40 countries and hundreds live streaming!

2008

Le grand pionnier américain

TOBI = structure Enseignement et Recherche

STEVEN SAMPSON

Ramon Cugat

From Wikipedia, the free encyclopedia

> The topic of this article **may not meet Wikipedia's notability guideline for biographies**. Please help to establish notability by citing reliable secondary sources that are independent of the topic and provide significant coverage of it beyond a mere trivial mention. If notability cannot be established, the article is likely to be merged, redirected, or deleted.
> *Find sources:* "Ramon Cugat" – news · newspapers · books · scholar · JSTOR *(November 2018) (Learn how and when to remove this template message)*

Ramón Cugat Bertomeu (born 25 August, 1950) is a Spanish surgeon specializing in orthopedic surgery, orthopaedic sports medicine, and arthroscopy.[1] Cugat's first venture into sports was as a member of the team of orthopedic surgeons during the 1992 Summer Olympics in Barcelona. Since then, he has been bound to the Catalan Mutual Insurance of Football where he has operated on thousands of players from all categories[2] most often the Association football players of FC Barcelona, among those being Pep Guardiola, Xavi Hernández, Samuel Eto'o, Andrés Iniesta, Carles Puyol, David Silva, David Villa[3], Luis Suárez and Fernando Torres. He has also operated on multiple Manchester City players, including Benjamin Mendy, Ilkay Gundogan, Kevin de Bruyne and Aymeric Laporte. [4]

Ramón Cugat's career expands throughout different countries such as Spain, England and the United States. He is currently co-director of the Department of Orthopaedic Surgery and Traumatology Hospital Quiron Barcelona, Chairman of the Board of the Garcia Cugat Foundation for Biomedical Research and President of the Medical Council at the Catalan Mutual Insurance of Football under the Royal Spanish Football Federation. He is Associate Professor at the Faculty of Medicine of the University of Barcelona.

Contents [hide]

Ramon Cugat

Born	Ramon Cugat Bertomeu August 25, 1950 L'Aldea - Spain
Nationality	Spanish
Occupation	Orthopedic Surgery

Biography [edit]

Life and career [edit]

Ramón Cugat was born in L' Aldea (Tarragona), spain on August 25, 1950 in a farming family. At the age of 15, he moved away from the rural life to Barcelona in 1965, where he was selected to play for the youth team of FC Barcelona until 1971.

In 1969 he enrolled at the Faculty of Medicine of the University of Barcelona and started his venture in sports medicine under the guidance of Dr. Jose Garcia Cugat, founder of the Spanish Arthroscopy Association. By 1975, he had graduated in medicine and surgery and in the next two years he received his doctorate and obtained the title of specialist in orthopedic and trauma surgery. By then, he was also completing his first major in England in 1979. Ramon Cugat learned arthroscopy in England and the United States in the late 70s. He trained at Massachusetts General Hospital under the guidance of Dr. Bertram Zarins and has continued collaboration with him.

Medical Career [edit]

In 1980, Ramon Cugat began his collaboration with Bertram Zarins, Head of Sports Medicine at Massachusetts General Hospital at Harvard University in the United States. He was a founding member of the Spanish Arthroscopy Association created in 1982 and chaired this organization from 1993 to 1995.[5]

In 1990 he returned to spain to be appointed Associate Professor at the Faculty of Medicine at the University of Barcelona. In 1991 he was appointed as orthopaedic surgeon to the American Football Team of Barcelona Dragons, a member of the Barcelona sport organisation. He was appointed a member of the team of orthopedic surgeons during the 1992 Summer Olympics in Barcelona.

From 1992 to 2004 he worked as medical assistant in the Department of Trauma and Orthopedics at the Hospital del Mar in Barcelona directing the Arthroscopic Surgery Unit.

2008

RAMON CUGAT

Chirurgien

Dès les ANNEES 2010 : la grande indication du PRP l'ARTHROSE +++ (KOA)

Aplicación de plasma autólogo rico en factores de crecimiento en cirugía artroscópica

M. Sánchez[(1)], J. Azofra[(1)], B. Aizpurúa[(1)], R. Elorriaga[(1)], E. Anitua[(2)], I. Andía[(3)]

[(1)]Unidad de Cirugía Artroscópica. Clínica USP La Esperanza. Vitoria-Gasteiz.
[(2)]Biotechnology Institute (BTI). Vitoria-Gasteiz.
[(3)]Dpto. Investigación Neuroquímica. Osakidetza-Servicio Vasco de Salud.

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D. Juan Azofra
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Clínica USP La Esperanza
01002 Vitoria-Gasteiz
e-mail: juan.azofra@cle,uspeurope.com

La utilización de plasma autólogo rico en factores de crecimiento (PRGF), tiene como objetivo mejorar la evolución quirúrgica, reforzando y potenciando el proceso de reparación fisiológica, además de permitir una regeneración más rápida y de mayor calidad en los tejidos conjuntivos dañados. Se describe el método de aplicación de PRGF en la cirugía artroscópica de las plastias del ligamento cruzado anterior. Se compara la evolución clínica en 50 plastias realizadas sin PRGF y 50 plastias aplicando PRGF. Cuando se utiliza PRGF, asociado a la cirugía, las complicaciones postoperatorias y los signos inflamatorios son menores, se acelera la cicatrización de las heridas y la integración de la plastia. La utilización de PRGF no implica ningún riesgo ni complicación para el paciente, y los beneficios de su aplicación son considerables.

Palabras clave: Artroscopia de rodilla, reconstrucción del ligamento cruzado anterior, factores de crecimiento.

Use of autologous plasma rich in growth factors in arthroscopic surgery. The application of an autologous plasma rich in growth factors (PRGF), is beneficial in restoring connective tissues through the enhancement and acceleration of the healing process. This is achieved by creating conditions that allowed natural healing to proceed. The procedure for the application of PRGF during the reconstruction of the anterior cruciate ligament (ACL) is described. Clinical outcome following ACL reconstruction, with and without PRGF, was evaluated. Postoperative complications and inflammation are reduced; healing and remodeling rates of the autologous tendon graft are improved with the use of PRGF. It has not got risks and the benefits for the patient are enormous.

Key words: Knee arthroscopy, ACL reconstruction, growth factors.

En la actualidad, los avances en las diferentes especialidades de la medicina se deben al esfuerzo y a la participación de distintas ramas de la ciencia: bioingeniería, informática, química, biología y medicina. De esta colaboración entre disciplinas han

Clin Exp Rheumatol. 2008 Sep-Oct;26(5):910-3.

Intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee OA: a retrospective cohort study.

Sánchez M[1], Anitua E, Azofra J, Aguirre JJ, Andia I.

Author information

Abstract

OBJECTIVE: To obtain preliminary information about the effectiveness of intra-articular injections of an autologous preparation rich in growth factors (PRGF) for knee OA treatment to be explored further in future studies.

METHODS: We have characterized PRGF treatment by platelet count and concentration of relevant growth factors (TGF-Beta1, PDGF-AB, VEGF-A; HGF and IGF-I) involved in healing mechanisms. We have performed an observational retrospective cohort study using hyaluronan injections as a control. Each group included 30 patients with OA of the knee, matched according to age, sex, body mass index and radiographic severity. Both treatments were based on three weekly injections. Clinical outcome was examined using the WOMAC questionnaires prior to treatment and at 5 weeks after treatment.

RESULTS: The observed success rates by week 5 for the pain subscale reached 33.4% for the PRGF group and 10% for the hyaluronan group. The difference was attributed exclusively to the treatment modality, p = 0.004. The percent reductions in the physical function subscale and overall WOMAC at 5 weeks were also associated solely with treatment modality in favour of PRGF, p = 0.043 and p = 0.010 respectively.

CONCLUSIONS: Although these preliminary results need to be evaluated in a randomized clinical trial, they provide useful infomration about the safety of PRGF and open new perspectives on autologous treatments for joint diseases.

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Groupe de Réflexion sur les Injections de PRP

Congrès SFR
9 décembre 2019

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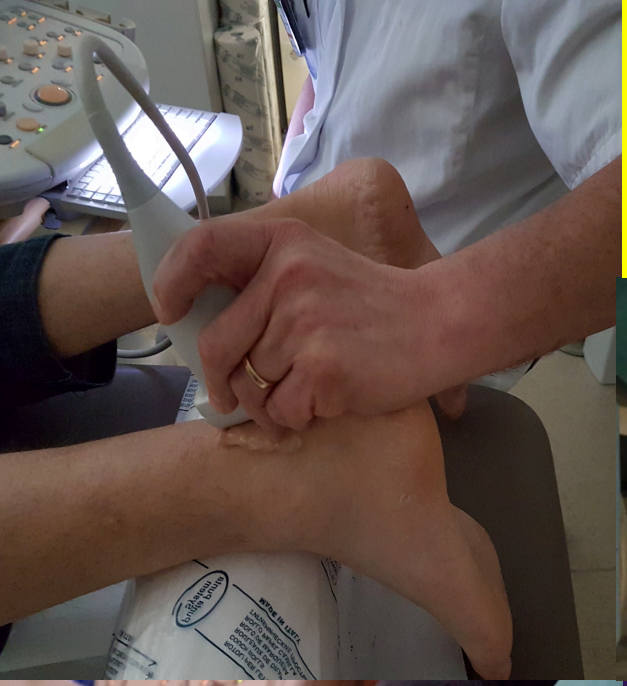
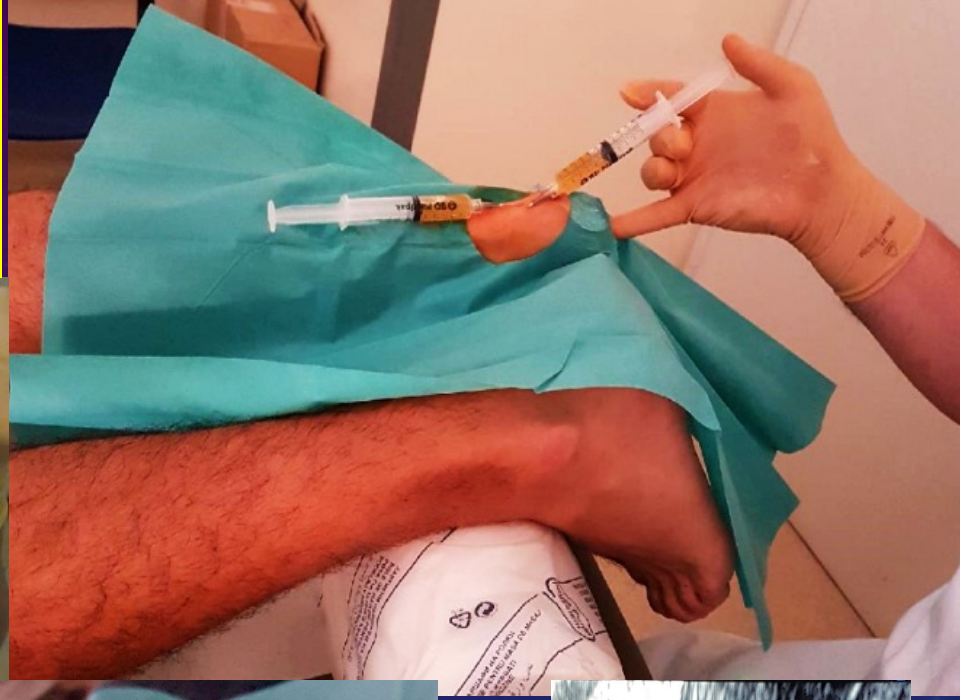
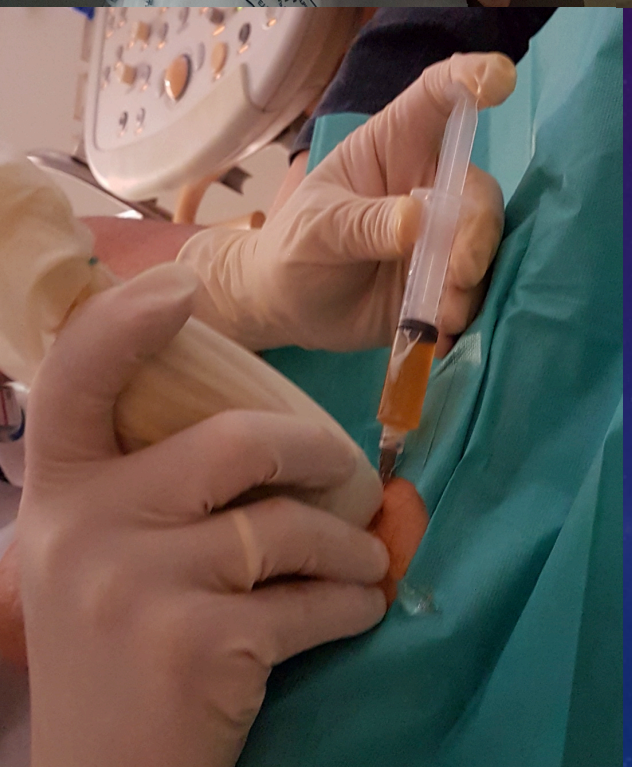
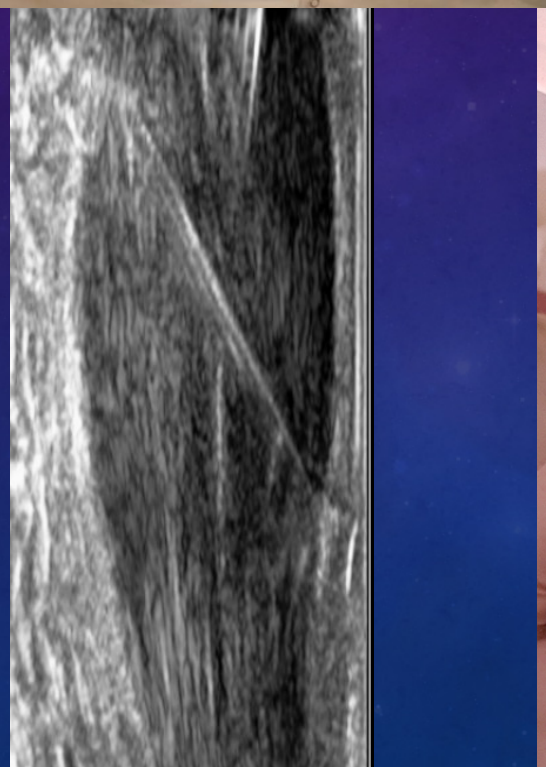
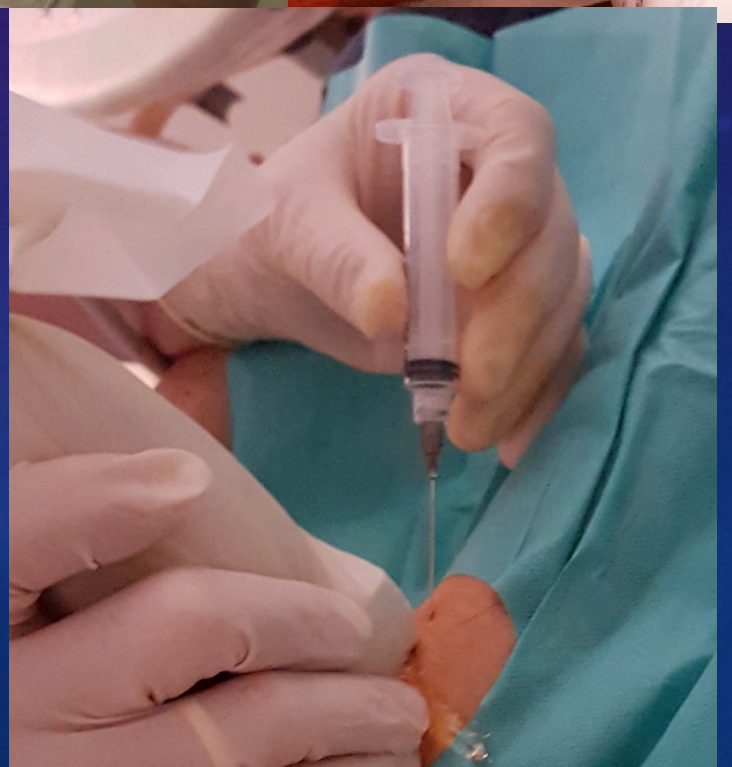
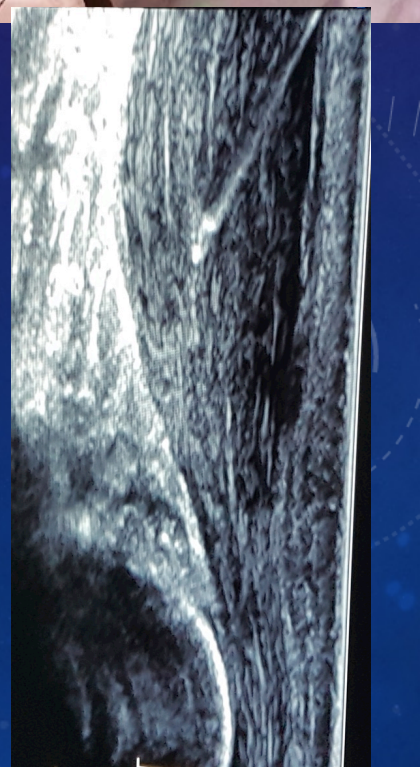










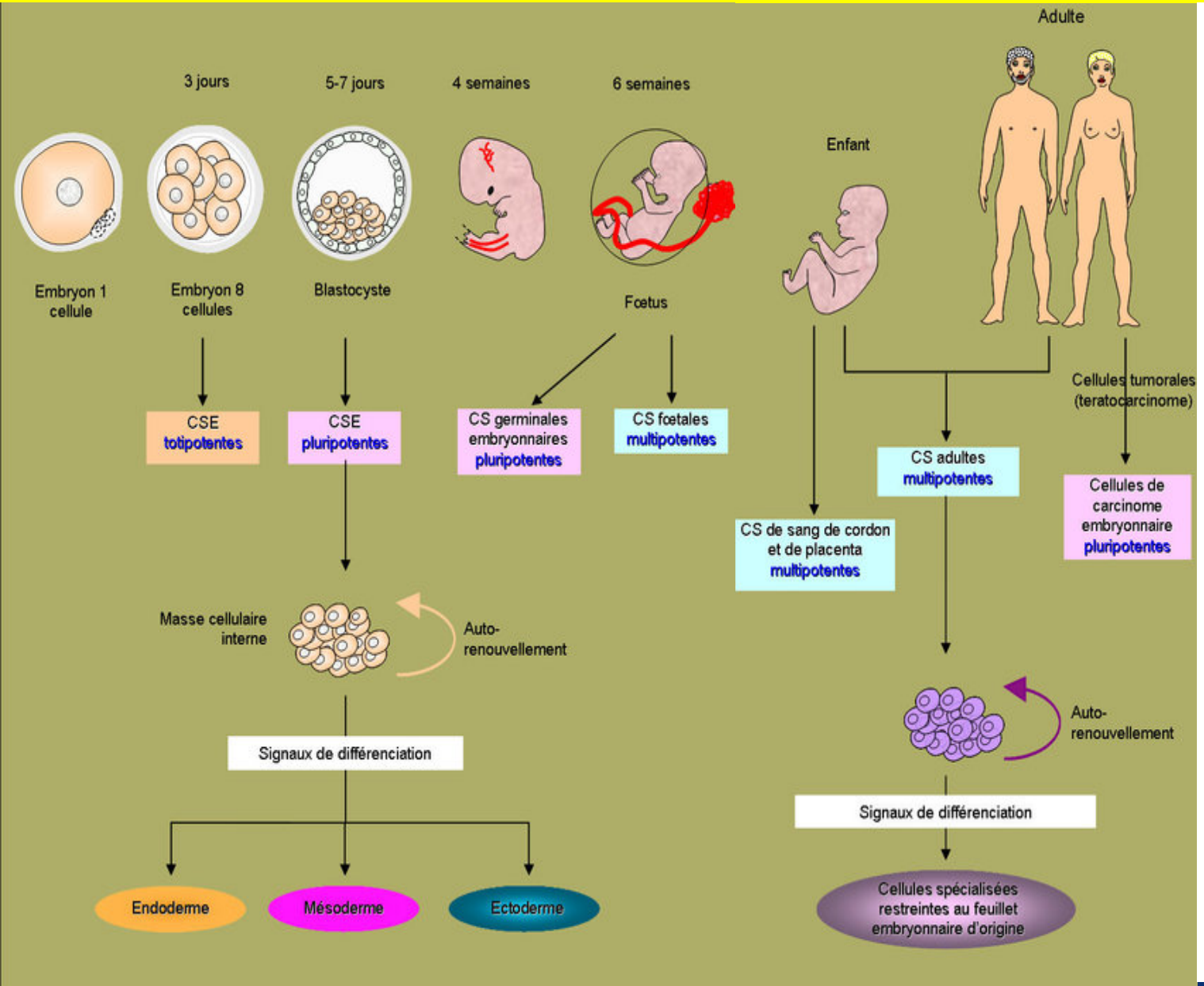


II- LES CELLULES SOUCHES MESENCHYMATEUSES INGENIERIE des TISSUS MSK (fibro-cartilage, cartilage, os)

Dans le cadre de l'objectif ambitieux de réparation du cartilage
la médecine régénérative va rechercher ***les « niches à chondrocyte »***
présentes dans de nombreux ***tissus riches en cellules souches***
(moelle osseuse, tissu adipeux, pulpe dentaire, cordon ombilical)

mais aussi dans les tissus articulaires résidents tels que
le cartilage, la synoviale, le périoste, l'os trabéculaire
et la poche graisseuse infra-patellaire (mais peu abondant)

Le grand laboratoire des Cellules Souches c'est le Corps Humain
Au stade d'embryon puis chez l'enfant et l'adulte



**CS unipotente donne naissance à un seul type de cellule*

****CS multipotente foetale et adulte produit plusieurs types de cellules donc potentiel d'autorenouvellement et de réparation (différentiation en cellules spécialisées)***

**CS totipotente embryonnaire (1ères divisions, jusqu'au 4ème jour) pouvant donner tout type cellulaire*

**CS pluripotente embryonnaire ou IPS*
Les cellules pluripotentes sont les cellules souches qui donnent naissance à tout type de cellules se développant à partir des trois couches germinales embryonnaires, dont l'endoderme, l'ectoderme et le mésoderme

*Les cellules souches mésenchymateuses **adultes** ou cellules stromales mésenchymateuses **multipotentes** utilisées dans l'Ingénierie tissulaire ont été initialement identifiées dans la moelle osseuse mais sont présentes dans tous les tissus

*Elles sont prélevées le + souvent à partir de la moelle osseuse ou du tissu adipeux

Med Sci (Paris) 2011 ; 27 : 289–296

Les cellules souches en ingénierie des tissus ostéoarticulaires et vasculaires

Stem cells for osteoarticular and vascular tissue engineering

Claire Vinatier[2], Laurence Bordenave[4], Jérôme Guicheux[1] et Joëlle Amédée[3*]

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Résumé

Les lésions tissulaires ou les pertes d'organes provoquent des changements structuraux et métaboliques qui peuvent être à l'origine de graves complications. L'ingénierie tissulaire (IT), dont l'objectif thérapeutique est de recréer, régénérer ou restaurer la fonction d'un tissu lésé, est la coalescence de trois éléments : un biomatériau d'origine synthétique ou biologique, dégradable ou non, des cellules réparatrices et des signaux (hypoxie, contraintes mécaniques, morphogènes, etc.). Le cartilage articulaire, l'os et les vaisseaux font partie des tissus pour lesquels l'IT s'est développée considérablement, de la recherche fondamentale jusqu'aux essais cliniques. Si les biomatériaux doivent présenter des propriétés différentes en fonction du tissu à régénérer, la composante cellulaire de l'IT est majoritairement représentée par les cellules souches, au premier rang desquelles les cellules souches mésenchymateuses adultes prélevées à partir de la moelle osseuse ou du tissu adipeux. Ces dernières années, des progrès ont été accomplis dans la compréhension des mécanismes biologiques qui régissent la différenciation des cellules souches et dans le développement de matériaux aux propriétés biologiques et physicochimiques contrôlées. Cependant, de nombreux verrous technologiques et réglementaires devront être levés avant que l'ingénierie tissulaire puisse passer du laboratoire à la clinique et entrer dans l'arsenal thérapeutique de la médecine régénératrice. Cette revue a pour objectif de souligner les progrès récents accomplis dans l'utilisation des cellules souches en ingénierie des tissus ostéoarticulaires et vasculaires.

Med Sci (Paris) 2011 ; 27 : 297–302

Cellules souches mésenchymateuses

Production à usage clinique et contraintes sécuritaires

Mesenchymal stem cells

The challenge of a good therapeutic product

Luc Sensebé* et Philippe Bourin

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Résumé

Les cellules souches mésenchymateuses ou cellules stromales mésenchymateuses multipotentes (CSM) appartiennent à une population cellulaire initialement identifiée dans la moelle osseuse mais présente dans tous les tissus. Par leur potentiel de différenciation, leur production de cytokines, de facteurs trophiques et leurs actions immunosuppressives, les CSM sont un outil thérapeutique tant en médecine régénérative que dans le traitement des pathologies immunitaires et inflammatoires. Actuellement, une centaine d'essais utilisant des CSM sont officiellement répertoriés. Un prérequis pour l'utilisation thérapeutique des CSM est leur conformité avec les standards de « bonnes pratiques de fabrication » (BPF ou *good manufacturing practices*, GMP) assortis de contrôles de sécurité adéquats. Le défi est de passer de procédés de culture utilisés en recherche à des procédés de production correspondant à ces standards et à la réglementation nationale et internationale (européenne et nord-américaine). Ceci nécessite un travail de recherche et développement en liaison directe avec les équipes de recherche et les équipes cliniques qui mettent en place les essais cliniques. C'est cette intégration verticale, assurant des allers-retours permanents entre la recherche, le développement et la clinique, qui permettra les développements pertinents débouchant sur les procédés et les indications définitifs.

Quelles sont les Propriétés des MSCs Progénitrices Multipotentes Adultes ?

1/Régénératives :
Différentiation en cellules spécialisées
(ostéoblastes, adipocytes, chondrocytes, …)

2/Activité paracrine
Anabolique + Anti-Inflammatoire
(facteurs de croissance, cytokines)
Immunorégulation de l'inflammation locale (arthrose)

3/Production d'exosomes (VEC)
Qui renforcent les actions des MSCs

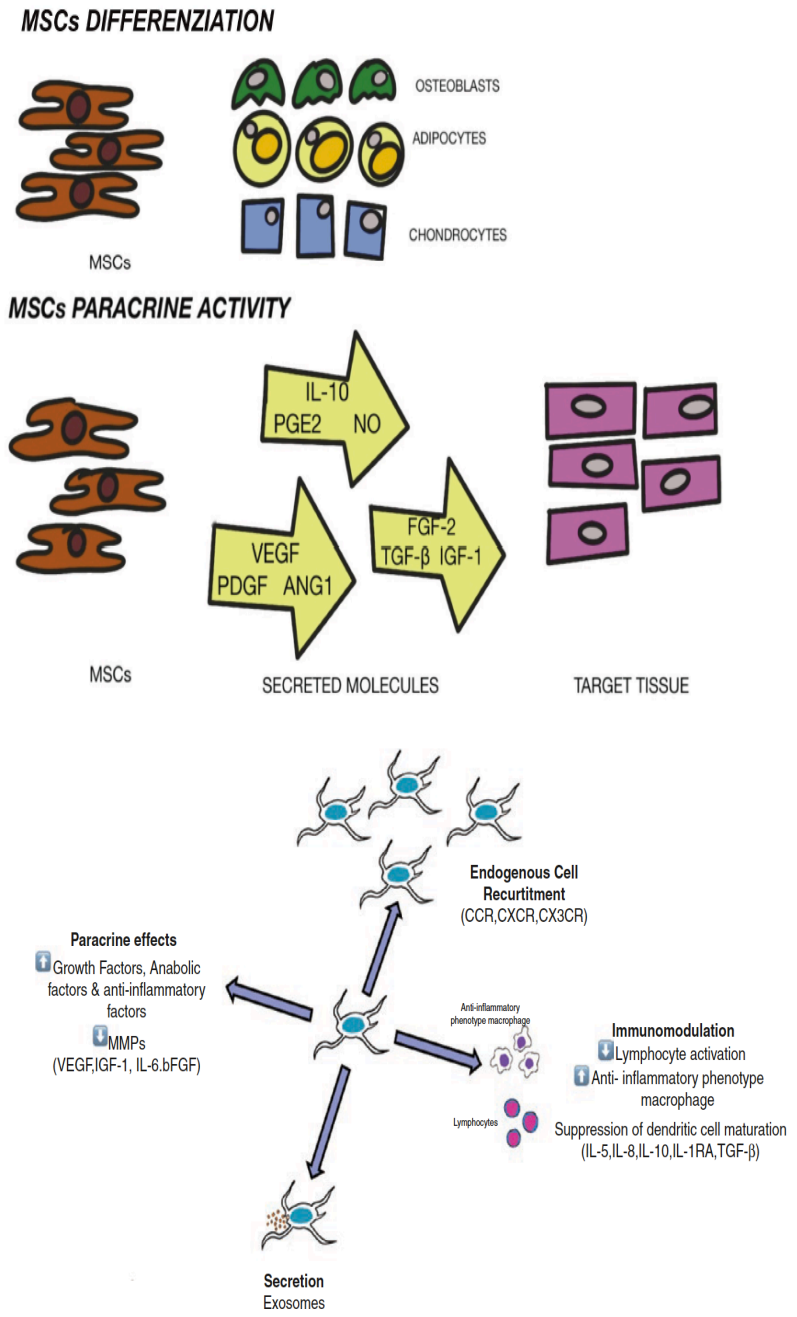


Fig. 20.1 Summarizing the various mechanisms of action of MSCs

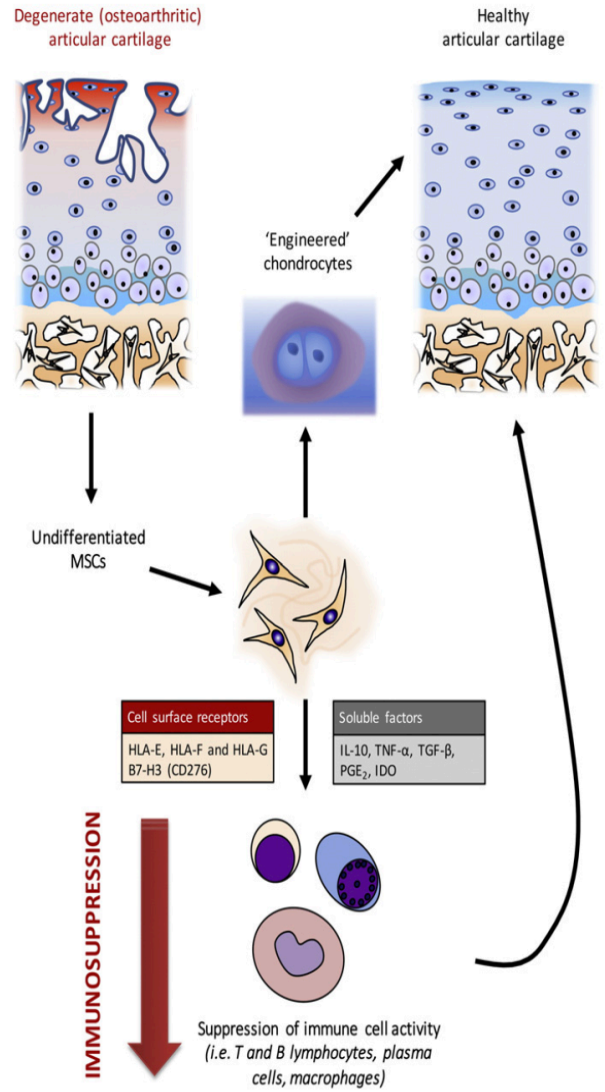


Fig. 1. In addition to their regenerative properties, the immunoregulatory potential of MSCs make them ideal for use as therapeutic agents as they are uniquely positioned to suppress local inflammation and at the same time participate in tissue repair. MSCs isolated from the bone marrow (as shown here) or elsewhere employ diverse molecular mechanisms to modulate the immune system including expression of cell surface receptors (HLA-E, HLA-F and HLA-G non-canonical type I MHC receptors, as well as the co-stimulatory molecule B7-H3 (CD276) that inhibits T cell activation) and the secretion of soluble mediators (IL-10, interleukin-10; TNF-α, tumour necrosis factor-alpha; TFG-β, transforming growth factor-beta; PGE_2, prostaglandin-E_2; IDO, indoleamine-2,3-dioxygenase). Please note that this list is not exhaustive.

L'HISTOIRE DES CELLULES SOUCHES

**CAPLAN (US) PERICYTE (CELLULES VASCULAIRES QUI ENVELOPPENT LES CELLULES ENDOTHÉLIALES)*

**YAMANAKA (JAPON) IPS*

**JORGENSEN (F) ADIPOA*

**HERNIGOU (F) MSC EN ORTHOPÉDIE*

DR ARNOLD CAPLAN PHD: THE FATHER OF MESENCHYMAL STEM CELLS

Mesenchyme stem cell therapy is one of the biggest topics when it comes to regenerative medicine. Dr. Arnold Caplin PhD is the scientist who first discovered mesenchyme stem cells, and he is known as the father of mesenchymal stem cells. Dr. Caplan is a Professor of Biology at Case Western Reserve University, and he is also the Director of the Skeletal Research Center there.

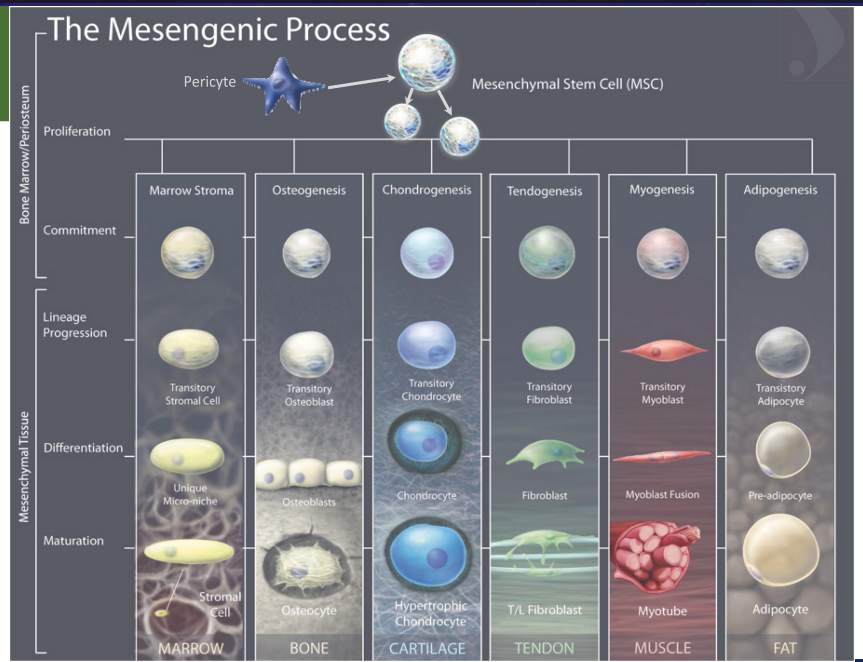
Cell Stem Cell
Previews

All MSCs Are Pericytes?

Arnold I. Caplan[1,*]
[1]Department of Biology, Skeletal Research Center, Case Western Reserve University, Cleveland, OH 44106-7080, USA
*Correspondence: arnold.caplan@case.edu
DOI 10.1016/j.stem.2008.08.008

In this issue of *Cell Stem Cell*, Crisan et al. (2008) document a subpopulation of human perivascular cells that express both pericyte and mesenchymal stem cell (MSC) markers in situ. The isolated population can expand and is clonally multipotent in culture, establishing that MSCs found throughout fetal and adult tissues are members of the pericyte family of cells.

Cell Stem Cell 2011 911-15DOI: (10.1016/j.stem.2011.06.008)



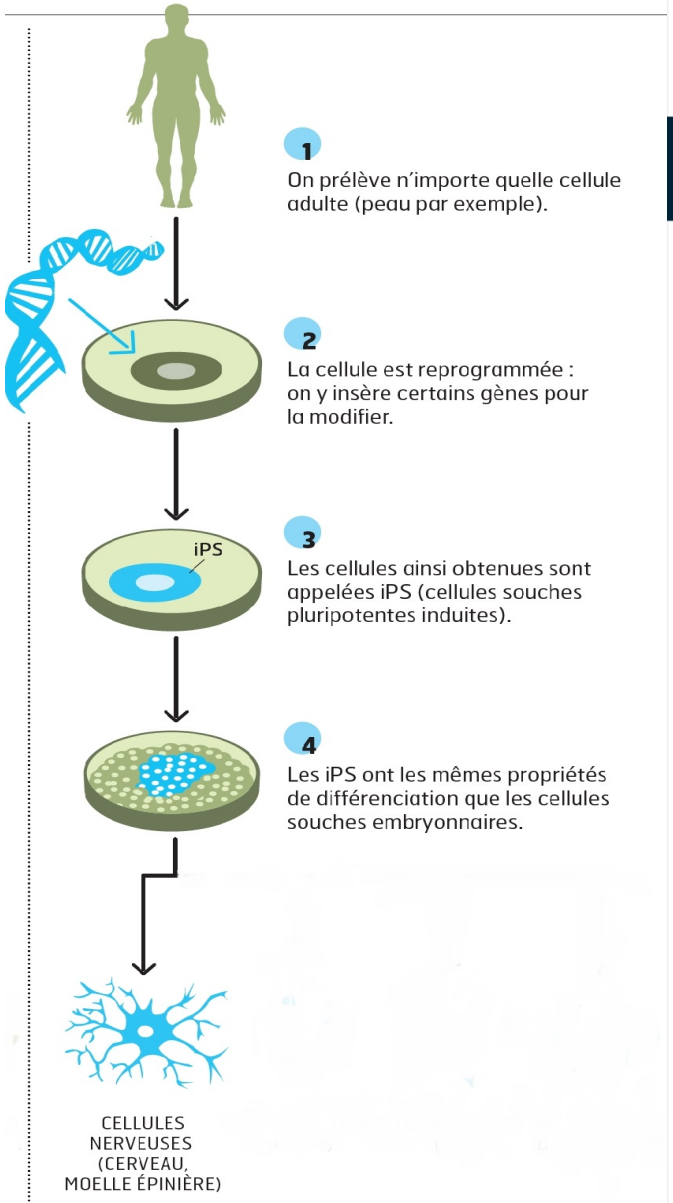
Les MSCs sont elles de la même famille cellulaire que les Péricytes ?

Cellules périvasculaires = un type de MSC qui peuvent devenir multipotentes en culture

IPS (cellule pluripotente induite) produite en laboratoire
YAMANAKA Prix Nobel 2012 *Usage clinique limité à ce jour*

En 2006, Shinya Yamanaka a fait une découverte remarquable : il a trouvé un moyen de produire un nouveau type de cellule souche en laboratoire

*Cette cellule est **pluripotente** – elle peut faire n'importe quelle cellule du corps – on l'appelle une cellule pluripotente induite, ou cellule iPS (de l'anglais « induced pluripotent stem cell »)*
Seules les cellules souches embryonnaires (ES), dérivées, chez l'homme, d'un embryon de 4-5 jours, sont naturellement pluripotentes
La découverte d'Yamanaka veut dire que toutes les cellules du corps, mis à part les spermatozoïdes et les ovules, peuvent maintenant être transformées en cellules souche pluripotentes



EuroStemCell

Dernière mise à jour: 30.11.2016

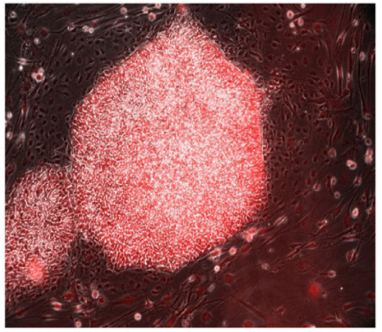
Cellules iPS et reprogrammation: Comment changer n'importe quelle cellule du corps en une cellule souche

Que savons-nous ?

On pensait que les cellules souches embryonnaires étaient la source unique de cellules pluripotentes jusqu'à ce que Kazutoshi Takahashi et Shinya Yamanaka, en 2006, montrent que les cellules de la peau pouvaient être reprogrammées en cellules souches pluripotentes 'induites' (cellules iPS) en ajoutant artificiellement quatre gènes.

Les chercheurs furent enthousiasmés par l'opportunité qu'offraient les cellules iPS pour étudier, traiter et potentiellement guérir certaines maladies. Les cellules iPS évitent aussi plusieurs problèmes moraux liés à l'utilisation des cellules souches embryonnaires.

Ces cellules offrent aux chercheurs un excellent moyen de créer et d'étudier des cellules malades qui ont le même patrimoine génétique que celles des patients.



Colonies de cellules iPS humaines

Image: Johannes Jungverdorben, Reconstructive Neurobiology, Bonn Medical Center

Sur quoi travaillent les chercheurs ?

Les chercheurs travaillent sans relâche pour mieux comprendre comment fonctionne la reprogrammation cellulaire afin de développer de meilleures méthodes de contrôle de la différenciation cellulaire.

On utilise les cellules iPS pour rechercher et développer des traitements pour de nombreuses maladies, comme un moyen pour remplacer les cellules que les maladies ont détruites.

Les erreurs génétiques responsables de maladies varient d'un patient à l'autre. Des traitements sur mesure, utilisant les cellules iPS, pourraient corriger les défauts génétiques spécifiques d'un patient. De plus, les greffes de cellules iPS ne seraient pas rejetées par le système immunitaire du patient, puisque ces cellules sont créées à partir de ses propres cellules.

Quels sont les défis ?

Plusieurs études montrent que les cellules iPS et les cellules souches embryonnaires fonctionnent souvent différemment, sans doute parce que les cellules iPS ne sont pas vraiment reprogrammées 'à 100%'. Les scientifiques cherchent encore à déterminer l'incidence de ces différences sur la recherche et la médecine.

Du fait de défis techniques et de notre compréhension encore limitée des cellules iPS, il est difficile de contrôler les cellules souches et le comportement dans l'organisme des cellules obtenues à partir de cellules iPS.

Bien que des traitements médicaux à base de cellules iPS fabriquées sur mesure semblent attrayants, le développement de tels traitements efficaces et d'un coût abordable reste une tâche très difficile.

Travaux du Pr JORGENSEN (ADIPOA) TRAITEMENT DE L'ARTHROSE DEBUTANTE Du GENOU par injection articulaire de Cellules Souches d'origine Adipeuse (ADSC) Buts : régénérescence du cartilage (chondrocytes), effets anti-inflammatoires

Arthrose : un traitement prometteur à l'étude

CHU Montpellier - mardi 09 octobre 2012. 203339 vu(s)

Professeur Christian Jorgensen, coordonnateur européen du programme ADIPOA - CHU de Montpellier

Avec **7 millions de personnes touchées en France** et plus de **58 millions en Europe**, **l'arthrose** ne bénéficie aujourd'hui d'aucun traitement de fond capable de faire reculer anatomiquement la maladie. La commission européenne a ainsi décidé de financer un programme de recherche sur 4 ans coordonné par le Professeur Christian Jorgensen (CHRU de Montpellier) : le projet ADIPOA, un programme collaboratif pour lequel le CHRU de Montpellier est le coordonnateur européen. 200 chercheurs, originaires de 7 pays s'attellent à valider un nouveau concept de traitement basé sur la thérapie cellulaire : Une "bio-infiltration" de cellules souches adipocytaires (ASC) prélevées dans le tissu adipeux du patient est réalisée au niveau de l'articulation malade pour activer la "régénérescence" du cartilage.

Précisons tout d'abord que la majorité des cellules souches prélevées actuellement le sont dans le tissu adipeux, c'est-à-dire les tissus stockant les graisses. C'est le cas du **projet européen nommé ADIPOA** coordonné par le centre universitaire hospitalier de Montpellier. Les équipes de recherches constituant le programme innovant ADIPOA tentent de valider un nouveau concept de traitement basé sur la thérapie cellulaire. Des injections de cellules souches graisseuses sont ainsi injectées au coeur de l'articulation atteinte dans le but d'activer la régénérescence du cartilage. Ces cellules possèdent de grandes capacités de sécrétion de facteurs de croissance et de stimulation des cellules souches endogènes du cartilage comme les chondrocytes. Elles seront injectées chez les patients souffrant d'une arthrose débutante.

Ce projet, coordonné par le Professeur Christian Jorgensen, fait intervenir 12 partenaires français et étrangers (hôpitaux, laboratoires, universités, entreprises privées) et l'ensemble de ces équipes regroupe plus de 200 chercheurs.

Trois étapes constituent ce programme :

- détermination du profil et du mécanisme d'action des cellules in vitro (en laboratoire,)
- validation chez l'animal atteint d'arthrose,
- validation de l'innocuité et de l'efficacité du traitement chez l'homme.

Le programme lancé en 2012 est toujours en cours d'évaluation alors que la phase 3 a été lancée fin 2020

TECHNIQUE DE PRELEVEMENT DES CELLULES SOUCHES MESENCHYMATEUSES

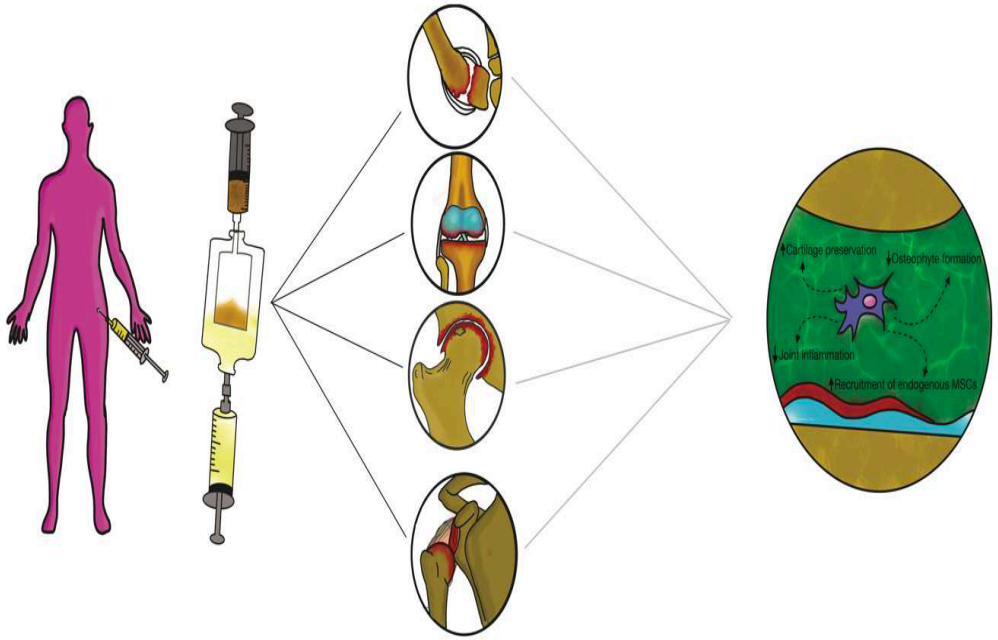


Figure 4. Non-enzymatic procedures have been proposed including mechanical dissociation of adipose tissue using automated closing devices and non-operator-dependent tools.

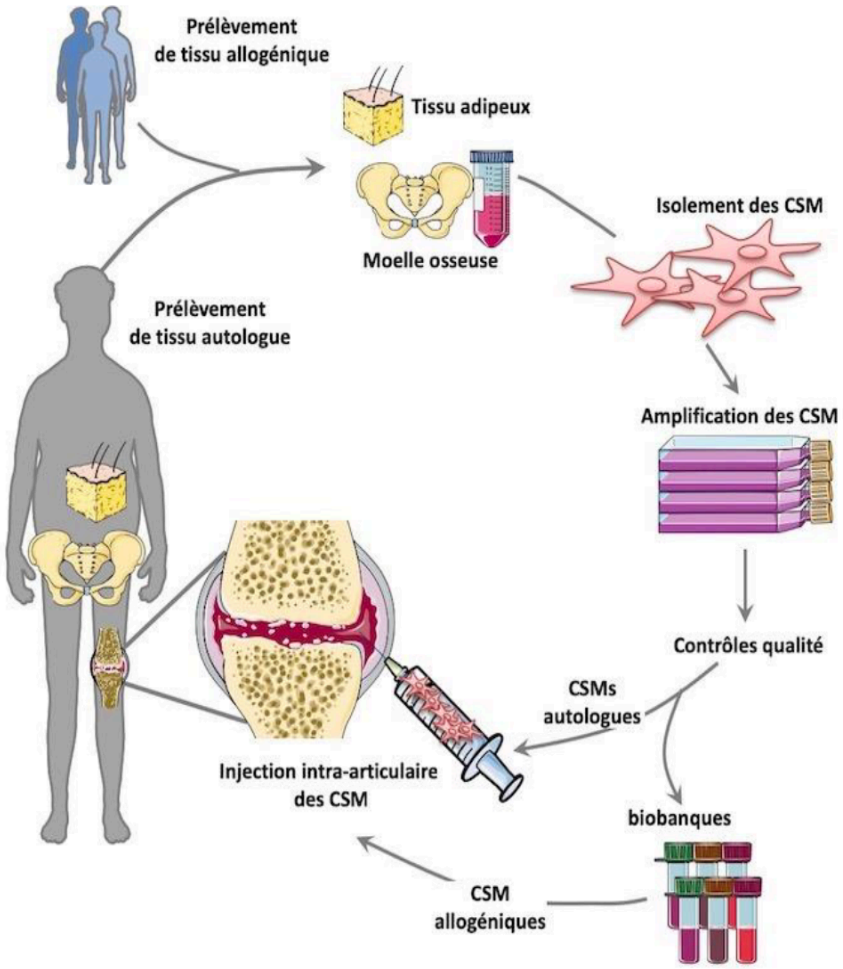


Figure 17. Processus de préparation autologue et allogéniques de CSM pour injection intra-articulaire[87]

1/PONCTION CRÊTE ILIAQUE (MOELLE OSSEUSE) : BONE MARROW MSC

2/LIPOSUCCION (TISSU ADIPEUX RICHE EN MSC, GRAISSE ABDOMINALE, INFRA PATELLAR FAT PAD)

**ADIPOSE TISSUE-DERIVED MSCS (ADSC)*

**ADIPOSE TISSUE-DERIVED STROMAL VASCULAR FRACTION*

LE TISSU ADIPEUX CONTIENT PRÉADIPOCYTES FIBROBLASTES MACROPHAGES CELLULES SANGUINES ET ENDOTHÉLIALES
CONSTITUANT LA FRACTION VASCULAIRE STROMALE DU TISSU ADIPEUX

3/SANG DU CORDON OMBILICAL ET DE LA GELÉE DE WHARTON AUTOUR DU CORDON : CELLULES SOUCHES HÉMATOPOIÉTIQUES DE SANG

Commentaires réglementation PRP vs Stem cells (EMA / FDA)
"Scope of FDA's Regulation of HCT/Ps" (Solange Visher)

Les produits sanguins, **y compris le PRP, ne font pas partie des « HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS» (HCT/Ps) donc **pas de problème réglementaire spécifique +++***

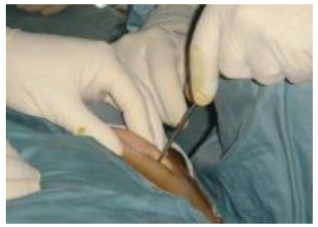
**Que ce soit aux USA ou en Europe, l'injection de cellules souches ne peut se faire que pour une utilisation « homologue » et le prélèvement ne doit « pas subir de modifications majeures (minimally manipulated) »*

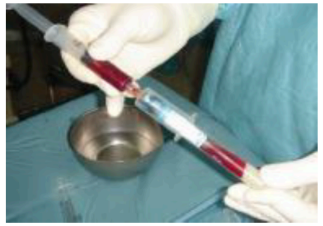
**Plus simplement la graisse ou ses produits dérivés doit être injectée dans l'espace sous cutané pour corriger les volumes, remplacer du tissu mou*
La graisse ne doit pas subir de digestion enzymatique ni perdre sa fonction de tissu structurel ce qui exclurait l'utilisation de la fraction vasculaire stromale
**Les cellules souches de la moelle sont soit utilisées à des fins hématopoïétiques soit pour la reconstruction osseuse*
**Les injections intra-articulaires de ces cellules ne sont donc pas légales, de plus ont elles un sens biologique : en effet les cellules souches qui génèrent le cartilage sont dans l'os sous chondral pas dans l'espace intra-articulaire*

? INJECTION uniquement SOUS-CHONDRALE DES STEM CELLS pour refaire du Cartilage?

Le Kit de prélèvement de moelle osseuse : RegenKit Extracell BMC (Bone Marrow Concentrate = Concentré de Moelle Osseuse) Regen Lab

RegenKit EXTRACELL BMC





Bone Reconstruction Requirements

Diamond concept
Giannoudis 2007

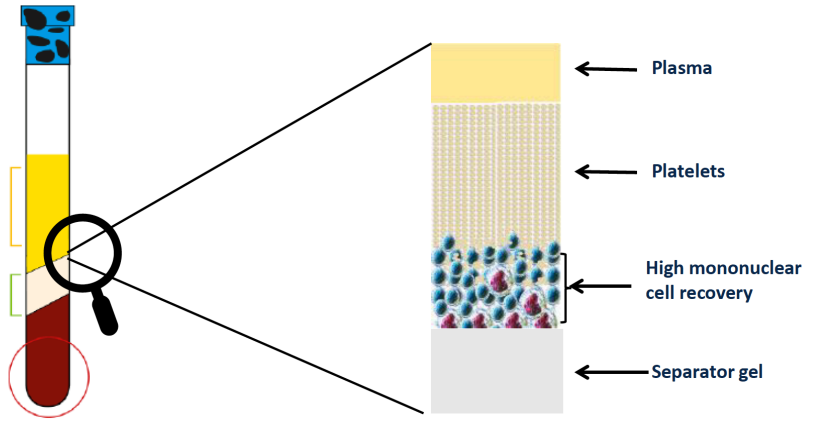
Regenerative Pentagon
Calori 2011

- Mechanical stability
- Good vascular supply
- Cell stimulation
  - Growth factors
  - Hormones
- Stem cells & precursors
- Matrix support
  (bone substitute, bone graft)

PRP

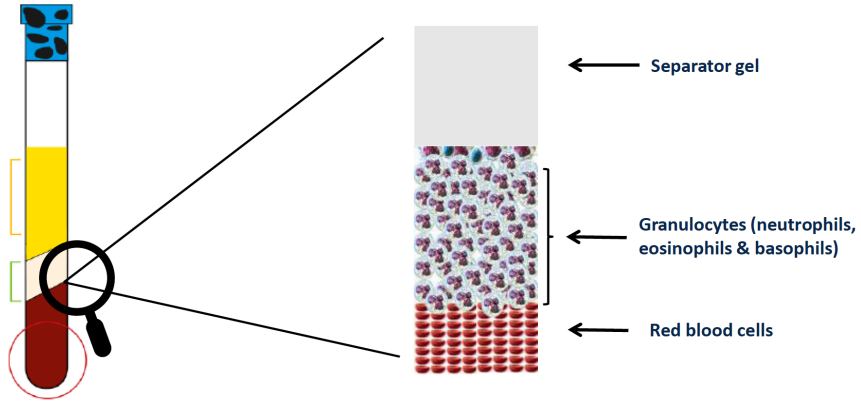
BMC

Bone Marrow stem cell isolation in RegenTHT tube



Most of the mononuclear cells (mature lymphocytes and monocytes and **stem cells**) remain **above the gel**, with platelets and plasma.
NB Bone marrow aspirates contain **low level of platelets**, thus combination of BMC with PRP is often required

Depletion of undesired cells with RegenTHT tube



The large bone marrow nucleated cells and the mature pro-inflammatory white blood cells are trapped below the gel with the red blood cells in the lower part of the device

Angel System Arthrex GmbH : traitement du BMA (bone marrow aspirate) BMC, PPP, PRP, LP PRP, LR PRP

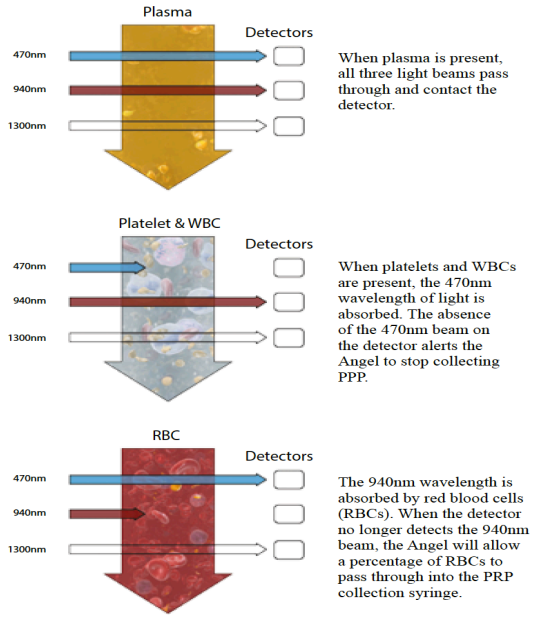
The Arthrex Angel System™ Bone Marrow Concentration

Arthrex, Inc. Research and Development

Purpose

The Arthrex Angel System™ is an advanced blood and bone marrow processing system. The Angel Three Sensor technology allows for customization of different autologous cellular products. The Angel® produces customized cellular product by utilizing three specific wavelengths of light to more precisely separate cell types after centrifugation. **Figure 1** illustrates this process. Additionally, different starting volumes (40-180cc), different delivery volumes, and different hematocrit settings can all be utilized within the Angel System. By controlling the aforementioned variables, a clinician can tailor a specific cellular formulation for individual patients. The first section illustrates the cellular differences between equal volumes of whole blood and bone marrow aspirate. The second section illustrates how the different Angel hematocrit settings can affect bone marrow concentrate cellular concentrations. Also demonstrated is the effect of expanding the final bone marrow concentrate volume with autologous platelet poor plasma.

Figure 1: Three Wavelengths of Light



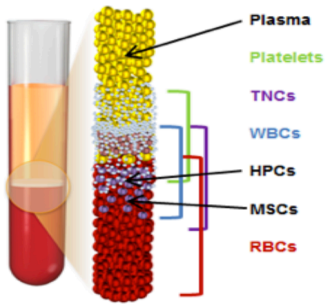
Materials and Methods

Approximately 60 mLs of heparinized human bone marrow aspirate (BMA) from the iliac crest (bilateral aspiration) was obtained (Lonza Group Ltd Walkersville, MD). Nine donors were utilized with a mean age 33 ± 5 years old (range 26 to 41). After a control sample was aliquotted, the 60 mL BMA specimen was processed in the Angel system. Due to BMA volume limitations, only one hematocrit setting (HCT) was used on each donor. BMA was processed from three donors at each of the following Angel hematocrit settings (HCT): 7%, 10%, and 15%. After processing, an aliquot of bone marrow concentrate (BMC) and platelet poor plasma (PPP) were analyzed for specific cell concentrations: red blood cells (RBC), white blood cells (WBC), neutrophils (NE), platelets (PLT), total nucleated cells (TNC), and hematopoetic cells (HPC) using a BMA validated hematological analyzer (Sysmex XE-5000, Sysmex, Lincolnshire, IL). For each HCT setting, cellular concentrations were measured on the raw output and the diluted 7 mL sample. The control BMA was also analyzed for the same cellular concentrations.

Results

Table 1 illustrates the different cellular concentrations in BMA versus whole blood. **Figure 2** depicts the different cellular layers after a sample of BMA has been centrifuged. **Figures 3-8** illustrate the cellular concentrations in the BMA and Angel BMC. "7% BMC" describes the BMC sample after processing 60 mL of BMA at the 7% HCT setting. "7% BMC 7 mL" describes the BMC sample after processing 60 mL of BMA at the 7% HCT setting then expanding with PPP to achieve a final volume of 7 mL. Table 2 shows the raw volume of BMC output for the different HCT settings and the Angel BMC ratios when compared to BMA (ie: [(RBC Concentration of 7% HCT BMC) / (RBC Concentration of BMA)]).

Figure 2: Centrifugal Density Gradient of Bone Marrow Aspirate



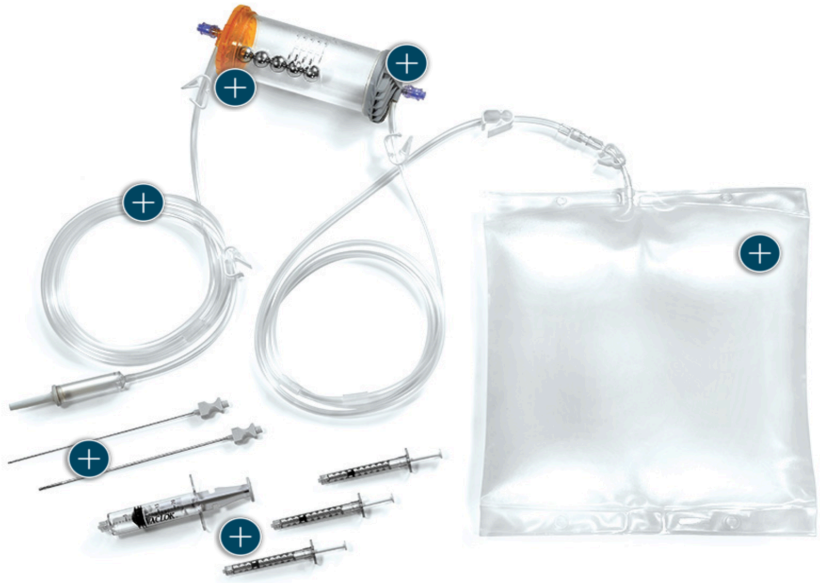
ABS-10066 Arthrex Angel System

Prélèvement de la graisse abdominale : Lipogems System (autologous adipose tissue)

Lipogems-Derived hASCs Can Be Committed to Classical Mesenchymal-Derived Lineages

Lipogems-derived hASCs were cultured under specific conditions for targeted commitments, including osteogenic, chondrogenic, and adipogenic lineages, demonstrating that these cells exhibit the typical developmental potential of hMSCs (Fig. 6). Adipogenic differentiation showed

The Lipogems® system is a sterile single-use medical device intended for the closed-loop processing and transferring of autologous adipose tissue in a single surgical step.



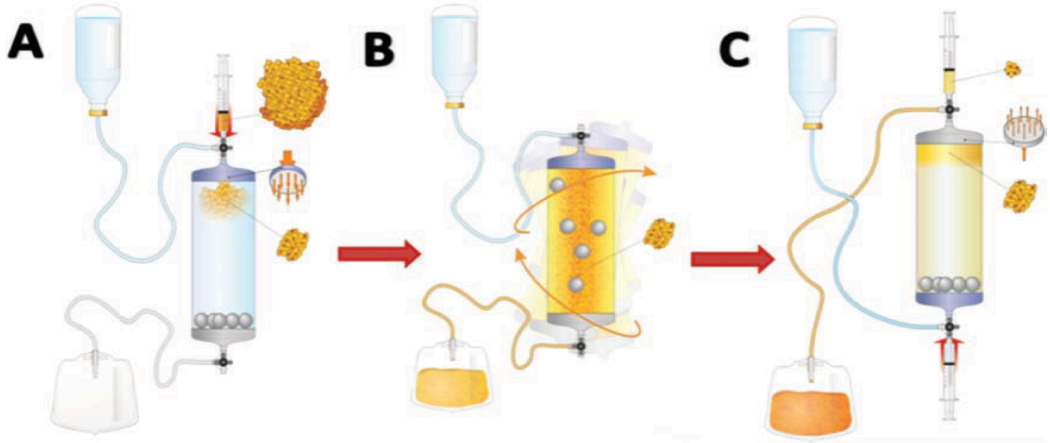


Figure 1. Schematic representation of the Lipogems device. In this completely closed system, the original lipoaspirate is processed by mild mechanical forces without using collagenase or other enzymes/additives. In the Lipogems device, the lipoaspirate is initially subjected to a first cluster reduction (A), obtained by pushing the aspirated fat from the syringe into the device through the large filter (blue end), and allowing the corresponding quantity of saline to exit towards the wasting bag. Stainless steel marbles contained in the device are essential to obtain a temporary emulsion between oil, blood, and saline, which can be washed away against density following the current of saline moved by gravity (B) (for details, see the Materials and Methods section). After this washing step (the flowing solution appears clear and the lipoaspirate yellow), the saline flux is stopped and the device is reversed (gray cap up), leading to the second adipose cluster reduction (C). Such reduction is obtained by pushing the floating adipose clusters through the second cutting hexagonal filter, pushing fluid from below with a 10-ml syringe. The reduced clusters pass in another 10-ml syringe placed above (C).

APPLICATIONS DES MSC

EN THERAPIE CELLULAIRE MSK

1/KNEE DEGENERATIVE ARTHRITIS

(CARTILAGE)

Faculté de Pharmacie
Aix*Marseille Université

THESE

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LE 23 OCTOBRE 2020

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TITRE :

THERAPIE CELLULAIRE ET ARTHROSE DU GENOU :
REVUE DE LA LITTERATURE

JURY :

Président : Professeur Florence SABATIER

Membres : Docteur Jérémy MAGALON

Docteur Hervé COLLADO

Docteur Didier PROST

Prospective Study Comparing Leukocyte-Poor Platelet Rich Plasma Combined with Hyaluronic Acid and Adipose Derived Mesenchymal Stem Cells in Patients with Early Knee Osteoarthritis

Vetri Kumar* M.S., Katarzyna Herman* M.D., Dawid Szwedowski* M.D., Alberto Gobbi M.D.,
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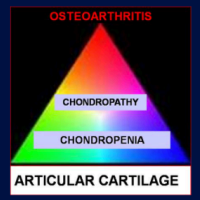
INTRODUCTION

• The benefits of infiltrative therapy using platelet-rich plasma (PRP) and adipose derived mesenchymal stem cells has been well documented, which has increased its use among the orthopaedic surgeons to treat early osteoarthritis (OA). The aim of this study is to evaluate the clinical efficacy of repeated doses of PRP combined with hyaluronic acid (HA) and single dose of adipose derived mesenchymal stem cell (ADMSC) injections.



•The rationale of using PRP combined with Hyaluronic acid has been studied and found that both PRP and HA works synergistically without altering the properties of both product.

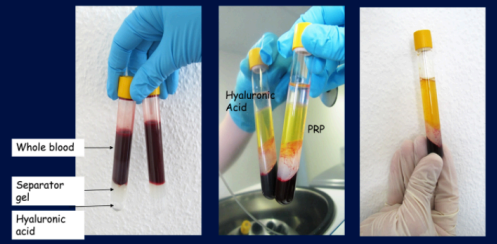
• Adipose derived mesenchymal stem cells (ADMSCs) have been investigated in order to evaluate their potential contribution to the treatment of cartilage defects and osteoarthritis.
•Given the common indications for the use of these two treatment modalities, we aimed to assess if there would be any difference in the outcome obtained in the treatment of early symptomatic OA in a group of patients treated with similar line of conservative intra-articulations injections.

EXCLUSION CRITERIA

• Tricompartmental osteoarthritis, rheumatoid arthritis, or concomitant severe hip osteoarthritis
•Patients with blood diseases, systemic metabolic disorders, immunodeficiency, Hepatitis B or C, HIV positive status, local or systemic infection.
•Ingestion of anti-platelet medications within 7 days prior to the treatment, or intra-articular or oral corticosteroids in the 3 months prior to initiating therapy.

TECHNIQUE

•(PRP with HA) (RegenLab-Cellular Matrix®): 6 ml. of blood was extracted from the ante-cunbital vein and the sample was centrifuged for 5 min. at 3500 R.P.M.

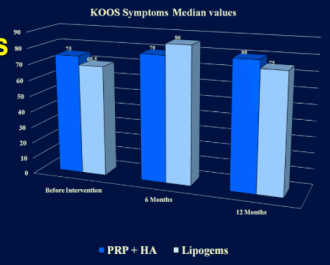


•Injection of (ADMSC) (Lipogems, Italy): Using aseptic precautions, under local anaesthesia, adipose tissue was harvested using abdominal lipoharvest method. The subcutaneous fat was infiltrated with up to 300 ml of tumescent fluid (comprising of 30 ml of 2% lidocaine, 1 ml of 1:1000 adrenaline and 1 ml of 8.4% bicarbonate suspended in a normal saline solution to a total 1000 ml). Following this, up to 60 ml of adipose tissue and tumescent fluid was aspirated through a 4 mm lipoaspirate cannula and collected within a sterile medical grade single use Shippert Tissu-Trans Collection filter (Shippert Medical, CO, USA). The lipoaspirate was transferred directly to an Lipogems device, a closed, full-immersion, low-pressure cylindrical system, to obtain fluid and a uniform product containing many pericytes/MSCs. Throughout the procedure, the processed fat is subjected to only slight mechanical forces, with no detrimental effects on the integrity of the stromal vascular.

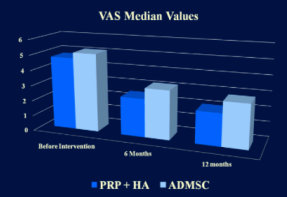
RESULTS

• All patients showed significant improvement in pain relief (VAS P=<0.001) and knee function (KOOS Symptom [S] P=0.003 , Pain [P] P= 0.002 & KOOS Quality Of Life [QOL] P=<0.001 parameter at the end of 12 months.
•The intra-group analysis (PRP + HA vs ADMSC) did not show any statistical significant difference between groups in all outcome scores at 6 months and 12 months follow up period .
• There were no complications associated with either modality of treatment in any of the subjects.

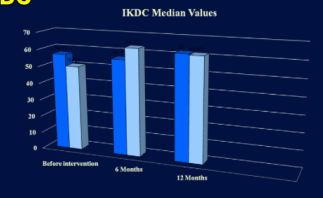
KOOS



VAS



IKDC



Comparaison PRP-HA (Cellular Matrix)
Vs
Adipose Stem Cells
Early Knee Osteoarthritis

Résultats équivalents CM/MSCs+++
Alberto GOBBI

Une des constantes de la littérature est l'association permanente des facteurs de croissance plaquettaire (PRP) et des Stem Cells (cellules souches)

D'où le concept thérapeutique associatif+++ :

**PRP : on peut l'injecter partout*
**MSCs : + invasif + cher « homologous »*
**Acide Hyaluronique*

Résultats équivalents à 1 an

PRP vs Stem Cells Knee Osteoarthritis

"This study did not prove BMC to be superior to PRP, providing guidance to clinicians treating OA"

Donc PRP ou PRP-HA (vite préparés au cabinet et pas cher) donne probablement la même amélioration que des cellules de graisse micro-fragmentée (prélevées au bloc, donc procédure très couteuse)

Original Research

Bone Marrow Aspirate Concentrate Is Equivalent to Platelet-Rich Plasma for the Treatment of Knee Osteoarthritis at 1 Year

A Prospective, Randomized Trial

Adam W. Anz,*† MD, Ryan Hubbard,† MD, Nicole K. Rendos,† PhD, Peter A. Everts,‡ PhD, FRSM, James R. Andrews,† MD, and Joshua G. Hackel,† MD

Investigation performed at the Andrews Research & Education Foundation, Gulf Breeze, Florida, USA

Background: Approximately 47 million people in the United States have been diagnosed with arthritis. Autologous platelet-rich plasma (PRP) injections have been documented to alleviate symptoms related to knee osteoarthritis (OA) in randomized controlled trials, systematic reviews, and meta-analyses. Autologous bone marrow aspirate concentrate (BMC) injections have also emerged as a treatment option for knee OA, with a limited clinical evidence base.

Purpose: To compare the efficacy of BMC to PRP for the treatment of knee OA regarding pain and function at multiple time points up to 12 months after an injection. We hypothesized that BMC will be more effective in improving outcomes in patients with knee OA.

Study Design: Randomized controlled trial; Level of evidence, 2

Methods: A total of 90 participants aged between 18 and 80 years with symptomatic knee OA (Kellgren-Lawrence grades 1-3) were randomized into 2 study groups: PRP and BMC. Both groups completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and subjective International Knee Documentation Committee (IKDC) questionnaires before and 1, 3, 6, 9, and 12 months after a single intra-articular injection of leukocyte-rich PRP or BMC.

Results: There were no statistically significant differences in baseline IKDC or WOMAC scores between the 2 groups. All IKDC and WOMAC scores for both the PRP and BMC groups significantly improved from baseline to 1 month after the injection ($P < .001$). These improvements were sustained for 12 months after the injection, with no difference between PRP and BMC at any time point.

Conclusion: Both PRP and BMC were effective in improving patient-reported outcomes in patients with mild to moderate knee OA for at least 12 months; neither treatment provided a superior clinical benefit. Autologous PRP and BMC showed promising clinical potential as therapeutic agents for the treatment of OA, and while PRP has strong clinical evidence to support its efficacy, BMC has limited support. This study did not prove BMC to be superior to PRP, providing guidance to clinicians treating OA. It is possible that the results were affected by patients knowing that there was no control group.

Registration: NCT03289416 (ClinicalTrials.gov identifier).

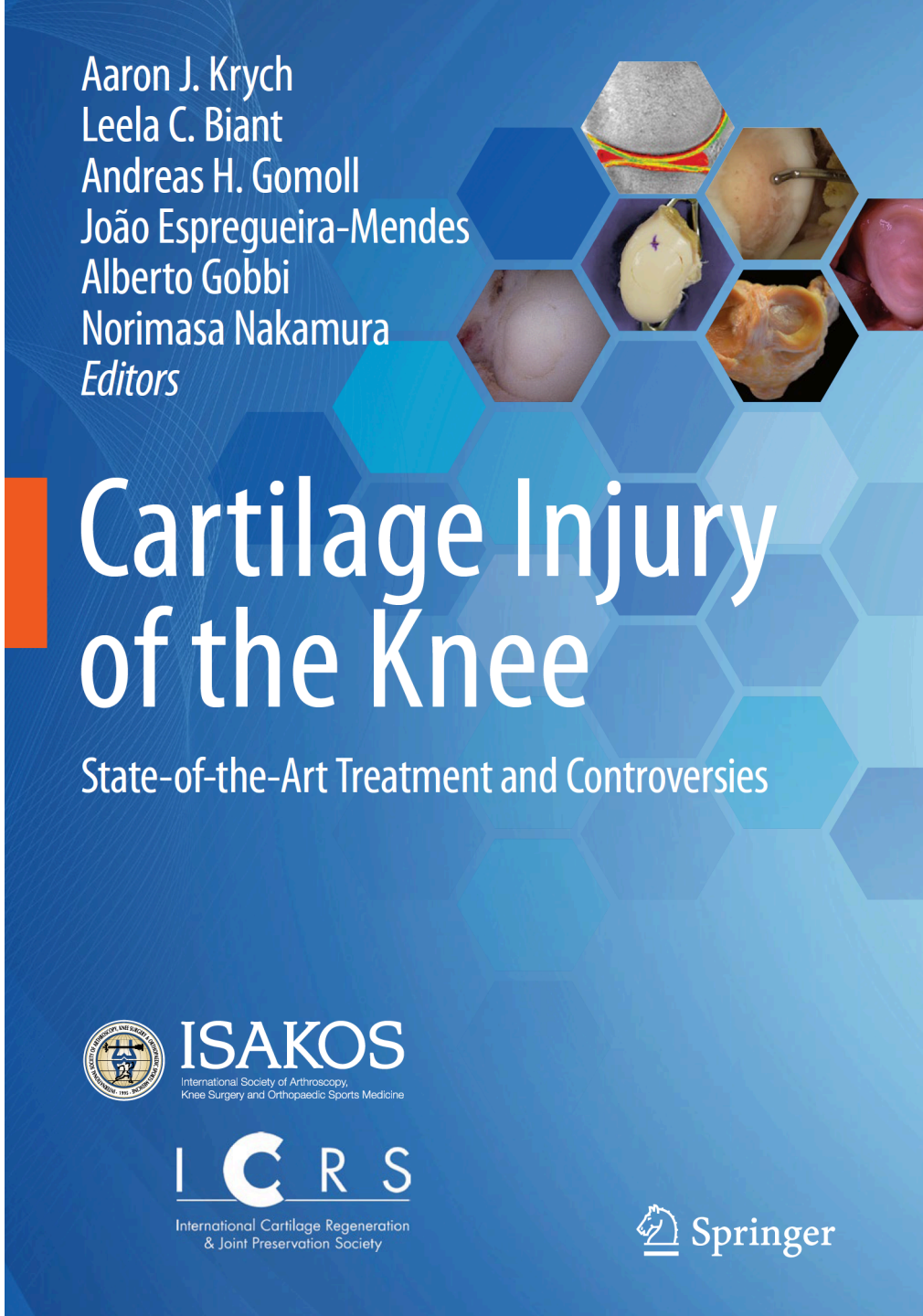
Keywords: platelet-rich plasma; bone marrow aspirate; bone marrow concentrate; regenerative medicine; osteoarthritis

2/CARTILAGE INJURY OF THE KNEE

SCAFFOLD (GREFFON)

+ PRP-MSC « AUGMENTATION »

(MOELLE OSSEUSE)



Greffon chirurgical ou Injection articulaire (« scaffold » ou « free cells »)

Surgical therapy for cartilage loss

Joint replacement is an established surgical technique focused on treating the end-stage of OA. For this reason, more minor surgical procedures have been developed to be used in the case of localized, traumatic or early disease with the aim of regenerating cartilage and rejuvenating the joint. In this section, we examine the evidence for the use of autologous stem cell and cartilage therapies as potential treatment options.

ficient evidence to recommend the use of ACI [10].

The method developed over time to include collagen-covered ACI, and subsequently MACI, with the latter providing benefits including reduced size of the incision, greater surgical consistency, more consistent cell seeding, reduced periosteal hypertrophy and fewer adverse events [11–14].

Indeed, the matrix-applied method did perform significantly better than microfracture in the SUMMIT study

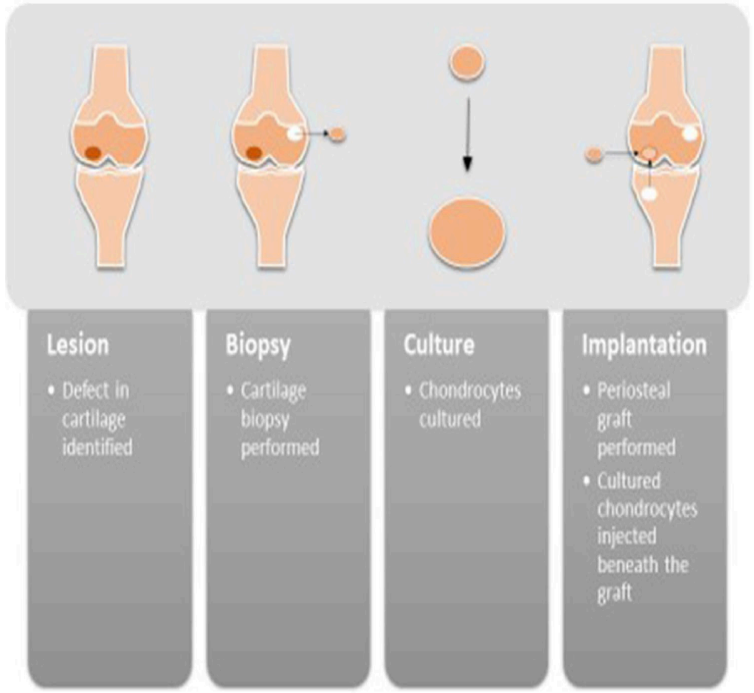
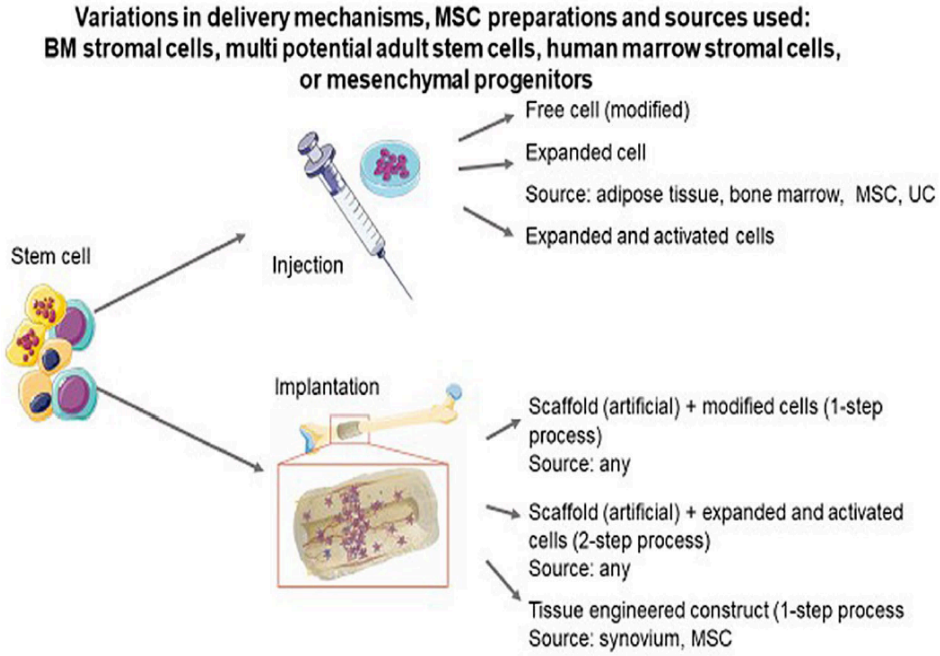


Fig. 1 A schematic demonstrating the process of autologous chondrocyte implantation. A chondral lesion is identified and a biopsy of non-articular cartilage is performed. The biopsy is cultured to amplify the number of chondrocytes. These are then injected under a periosteal flap (which is acquired from the proximal tibia)

Fig. 2 A depiction of the injectable and implantable options for delivery of MSCs and the potential sources of MSCs which are appropriate for each method



La seconde technique, développée par des chercheurs français à l'université de Strasbourg et l'Institut National de la Santé, consiste à insérer un implant bicouche sur l'articulation lésée. La première couche est constituée d'une membrane de nanofibres contenant des facteurs de croissance, alors que la seconde, qui constitue l'essence même du traitement, pourrait-être décrite comme un hydrogel d'alginates et d'acide hyaluronique contenant des cellules souches issues de la moelle osseuse du patient. La revue « Trends in Biotechnology » du 6 juin 2016, a d'ailleurs fait écho à ce nouveau concept bio médical.

3/*RECONSTRUCTION DES GRANDS DÉFECTS TRAUMATIQUES DES OS LONGS (PRP + BMC MOELLE OSSEUSE) PSEUDARTHROSES FRACTURAIRES COMBLEMENT DES KYSTES OSSEUX*

Injury International Journal of the Care of the Injured

FULL LENGTH ARTICLE | VOLUME 47, SUPPLEMENT 1, S47-S51, JANUARY 01, 2016

Stem cell therapy: is there a future for reconstruction of large bone defects?

Yoshinobu Watanabe • Noriko Harada • Kenji Sato • Satoshi Abe • Katsuyuki Yamanaka • Takashi Matushita

DOI: https://doi.org/10.1016/S0020-1383(16)30012-2

Abstract

Large bone defects caused by fracture, non-union and bone tumor excision has been a major clinical problem. Autogenous bone grafting and Ilizarov method are commonly performed to treat them. However, bone grafting has limitation in volume of available bone, and Ilizarov method requires long periods of time to treat. Accordingly, there is need for stem cell therapy for bone repair and/or regeneration. Mesenchymal stem cells (MSCs) hold the ability to differentiate into osteoblasts and are available from a wide variety of sources. The route of "intramembranous ossification (direct bone formation)" by transplantation of undifferentiated MSCs has been tested but it did not demonstrate the success initially envisaged. Recently another approach has been examined being the transplantation of "MSCs pre-differentiated in vitro into cartilage-forming chondrocytes" into bone defect, in brief, representing the route of "endochondral ossification (indirect bone formation)". It's a paradigm shift of Stem Cell Therapy for bone regeneration. We have already reported on the healing of large femur defects in rats by transplantation of "MSCs pre-differentiated in vitro into cartilage-forming chondrocytes". We named the cells as Mesenchymal Stem Cell-Derived Chondrocytes (MSC-DCs). The success of reconstruction of a massive 15-mm femur defect (approximately 50% of the rat femur shaft length) provides a sound foundation for potential clinical application of this technique. We believe our results may offer a new avenue of reconstruction of large bone defect, especially in view of the their high reproducibility and the excellent biomechanical strength of repaired femora.

Keywords

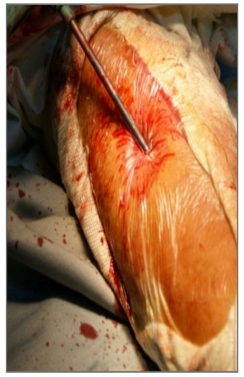
bone defects • fracture healing • progenitor cells • mesenchymal stem cells

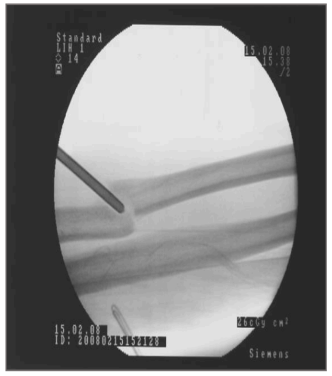
RegenKit EXTRACELL BMC : Bone marrow processing

regenlab

APPLICATIONS

- Non-Union (pseudarthrosis)[2-3]
- Delayed union
- Prosthetic revisions (Hip/Knee)
- Osteonecrosis (avascular necrosis (AVN))[4-5]
- Bone cysts and bone loss (e.g., after bone tumor removal)[6-8]
- Osteotomy (bone lengthening)
- Cartilage surgery





2. Scaglione, M., et al., Long bone nonunions treated with autologous concentrated bone marrow-derived cells combined with dried bone allograft. Musculoskelet Surg, 2014. **98**(2): p. 101-6.
3. Toro, G., et al., Surgical treatment of neglected hip fracture in children with cerebral palsy: case report and review of the literature. Clin Cases Miner Bone Metab, 2017. **14**(3): p. 317-323.
4. Civinini, R., et al., The use of an injectable calcium sulphate/calcium phosphate bioceramic in the treatment of osteonecrosis of the femoral head. Int Orthop, 2012. 36(8): p. 1583-8.
5. De Biase, P., et al., Regenerative Medicine In The Treatment Of Osteonecrosis Of The Hip: A Comparative Clinical Study On The Use Of Autologous Cell Concentrates In The Presence Or Absence Of BMP, in EFORT congress. 2016: Geneva. p. #1343 - Free Papers.
6. De Biase, P., et al., Scaffolds combined with stem cells and growth factors in healing of pseudotumoral lesions of bone. Int J Immunopathol Pharmacol, 2011. 24(1 Suppl 2): p. 11-5.
7.De Biase, P., et al., The "in-Vivo Cell Factory" Concept As An Alternative To Traditional Tissue Engineering In The Repair Of Large Cavitary Bone Defects., in EFORT congress. 2016: Geneva. p. #1344 - Free Papers.
8. Andreani, L., et al., Bone Marrow Concentrate in the Treatment of Aneurysmal Bone Cysts: A Case Series Study. Stem Cells Int, 2020. 2020: p. 8898145..

RegenKit EXTRACELL BMC : Bone marrow processing

regenlab

APPLICATIONS

Complete healing was obtained for around 80% of the lesions[2-7]

BMC are used alone[3, 8], or in combination with bone grafts or synthetic osteoconductive scaffolds[4-8].

BMC can also be combined with platelet-rich plasma and autologous thrombin serum prepared with RegenKit® Surgery to obtain a gel.

Bone substitute or morselized allograft can also be added to this combination to make a bone putty[9].

2. Scaglione, M., et al., Long bone nonunions treated with autologous concentrated bone marrow-derived cells combined with dried bone allograft. Musculoskelet Surg, 2014. **98**(2): p. 101-6.
3. Toro, G., et al., Surgical treatment of neglected hip fracture in children with cerebral palsy: case report and review of the literature. Clin Cases Miner Bone Metab, 2017. **14**(3): p. 317-323.
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6. De Biase, P., et al., Scaffolds combined with stem cells and growth factors in healing of pseudotumoral lesions of bone. Int J Immunopathol Pharmacol, 2011. 24(1 Suppl 2): p. 11-5.
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9. Bertolai, R., et al., Bone graft and mesenchimal stem cells: clinical observations and histological analysis. Clin Cases Miner Bone Metab, 2015. 12(2): p. 183-7.

4/NECROSE DE HANCHE

Pr. Philippe HERNIGOU

Professeur émérite
Consultant - ancien chef de service
Chirurgie de la hanche et du genou
Thérapie cellulaire

Lauréat de la Faculté
Ancien Interne et ancien Assistant des Hôpitaux de Paris
Ancien Chef de Clinique à la Faculté de Médecine

Parcours professionnel

Professeur émérite : Hôpital Henri Mondor (AP-HP) & Faculté de Médecine (UPEC), Créteil
Praticien Hospitalier - Professeur des Universités : Hôpital Henri Mondor (AP-HP) & Faculté de Médecine (UPEC), Créteil
Chef de Clinique-Assistant : Hôpital Henri Mondor (AP-HP) & Faculté de Médecine (UPEC), Créteil
Interne : Assistance Publique - Hôpitaux de Paris

Principaux diplômes

Concours de recrutement de Professeurs des Universités de type 1 en Chirurgie Orthopédique et Traumatologique
Habilitation à Diriger des Recherches
Spécialiste en Chirurgie Orthopédique et Traumatologique
Diplôme de Chirurgie générale
Doctorat en médecine

Appartenance à des Sociétés Scientifiques

Président de la Société Française de Chirurgie Orthopédique et Traumatologique (SOFCOT) (2015-2016)
Membre de la Société Française de Chirurgie Orthopédique et Traumatologique (SOFCOT)
Membre de la Société Française de Chirurgie Hanche et Genou (SFHG)
Membre du Collège des Chirurgiens Orthopédistes et Traumatologues (CFCOT)

Activités de recherche

Membre de l'équipe Inserm n°10 de l'Institut Mondor de Recherche Biomédicale (IMRB) – UMR955 (F. RELAIX)
Recherche fondamentale :
- Utilisation des biothérapies dans le traitement des pseudarthroses des os longs et des ostéonécroses aseptiques des têtes fémorales
Recherche clinique :
- Evaluation de l'utilisation des cellules souches dans le traitement des pseudarthroses des os longs et des ostéonécroses aseptiques des têtes fémorales (Projet Européen REBORNE)

International Orthopaedics (SICOT) (2012) 36:1583–1588

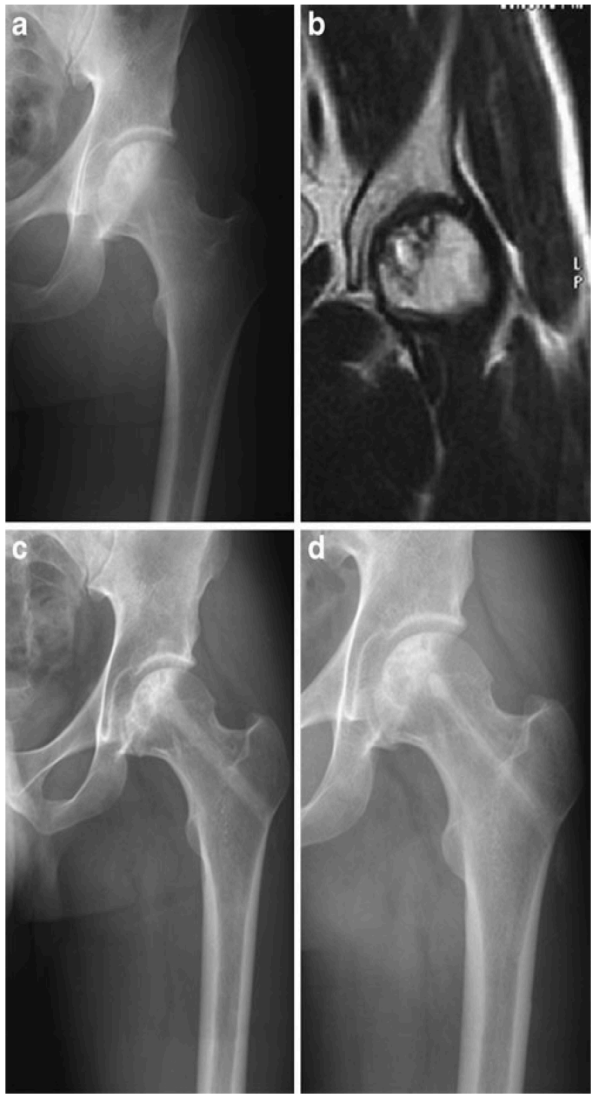

Fig. 2 **a** Preoperative anteroposterior (AP) radiograph of the left hip in a symptomatic 42-year-old man with osteonecrosis of the femoral head (ONFH). **b** Preoperative MRI of the femoral heads confirms the presence of a Steinberg 2c osteonecrotic lesion. **c** Six months follow-up AP radiograph of the same hip after core decompression, injection of autologous bone marrow concentration and backfilling of core tract with PRO-DENSE. **d** An AP radiograph taken 30 months after the index procedure shows no collapse of the femoral head and degradation of the ceramic with

ELSEVIER

Revue du Rhumatisme Monographies
Volume 86, Issue 4, September 2019, Pages 301-305

La médecine régénérative au service de l'ostéonécrose

Cell therapy in osteonecrosis

Philippe Hernigou [a] [b] ✉, Skender Ukaj [c], Jacques Pariat [a, b], Charles-Henri Flouzat-Lachaniette [a, b]

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https://doi.org/10.1016/j.monrhu.2019.05.003

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Résumé

Les cellules-souches mésenchymateuses (CSM) comprennent un mélange de différentes cellules-souches dans un tissu myéloïde ayant une capacité de différenciation multipotente. Elles peuvent se différencier en cellules osseuses dans des conditions spécifiques et peuvent être utilisées pour traiter l'ostéonécrose de la tête fémorale par transplantation de cellules. Cette revue résume les recherches menées au cours des 30 dernières années sur les CSM dans le traitement de l'ostéonécrose de hanche, révèle les progrès réalisés, et analyse certains des défis posés par l'utilisation des CSM dans des applications cliniques.

Abstract

Mesenchymal stem cells (MSCs) comprise a mixture of various stem cells in myeloid tissue with multipotential differentiation capacity. They can differentiate into bone cells under specific conditions and can be used to treat osteonecrosis of the femoral head (ONFH) through cell transplantation. This review summarizes research on MSCs in the field of ONFH performed during the last 30 years, reveals the progress realized, describes their potential to treat osteonecrosis disease, and analyzes some existing challenges of using MSCs in clinical applications.

5/LES TENDINOPATHIES

1/Injections de MSCs seules ou associées au PRP

2/Injections intra-tendineuses externes écho-guidées ou injection pendant la Chirurgie

(« PRP augmentation » lors d'une arthroscopie)

Hindawi
Stem Cells International
Volume 2021, Article ID 5558040, 12 pages
https://doi.org/10.1155/2021/5558040

Review Article

Cell-Based Therapies for the Treatment of Shoulder and Elbow Tendinopathies: A Scoping Review

Berardo Di Matteo,[1,2] **Riccardo Ranieri**,[1,3] **Angelo Manca**,[1,3] **Simone Cappato**,[4] **Maurilio Marcacci**,[1,3] **Elizaveta Kon**,[1,2,3] **and Alessandro Castagna**[1,3]

[1]*Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy*
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Academic Editor: Christian Morsczeck

Introduction. Tendinopathies are a common cause of disability among the general population, and their management is challenging due to the degenerative nature of these disorders. The aim of this paper is to perform a scoping review of the available clinical evidence on the application of cell-based therapies for the management of elbow and rotator cuff tendinopathies, in order to summarize the current application methods and to shed light on the therapeutic potential and current limitations of these biologic approaches. *Materials and Methods.* A scoping review of the literature was performed on the PubMed and Scopus databases using the following inclusion criteria: clinical reports of any level of evidence, written in English, with no time limitation, on the use of cell-based approaches to treat rotator cuff or elbow tendinopathies, including studies on biological augmentation during the surgical procedure. Exclusion criteria were as follows: case reports or mini case series (<5 patients), articles not written in English, and reviews. Relevant data were then extracted and collected in a single database with the consensus of the two observers to be analyzed for the purposes of the present manuscript. *Results.* Seven papers dealing with rotator cuff tears were included. Four of them investigated the effect of injections, either MSCs alone or in combination with PRP, whereas three studies investigated the use of MSCs in combination with surgery. In all cases, an improvement was found in terms of clinical scores, with even evidence of tendon healing documented at second-look arthroscopy. Six papers dealt with elbow tendinopathies: three studies described the use of MSCs either with or without surgery, reporting significant clinical improvement and three studies analyzed the use of different types of cells (collagen-producing cells and autologous tenocytes) and, even in this case, clinical improvement was reported. *Conclusion.* All the papers included suggested a beneficial role of cell-based approaches to treat common upper limb tendinopathies, with an overall satisfactory safety profile. However, the lack of high-level evidence and the presence of controversial issues, such as interproduct variability, harvest source, and application strategies, do not allow standardization of these novel biologic approaches, whose efficacy needs to be confirmed with properly designed randomized trials.

› Stem Cells. 2018 Sep;36(9):1441-1450. doi: 10.1002/stem.2855. Epub 2018 Jul 16.

Intratendinous Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Rotator Cuff Disease: A First-In-Human Trial

Chris H Jo [1 2], Jee Won Chai [3], Eui Cheol Jeong [4], Sohee Oh [5], Paul S Kim [1], Jeong Yong Yoon [1], Kang Sup Yoon [1]

Affiliations + expand

PMID: 29790618 DOI: 10.1002/stem.2855

Free article

Abstract

Despite relatively good results of current symptomatic treatments for rotator cuff disease, there has been an unmet need for fundamental treatments to halt or reverse the progress of disease. The purpose of this study was to assess the safety and efficacy of intratendinous injection of autologous adipose tissue-derived mesenchymal stem cells (AD MSCs) in patients with rotator cuff disease. The first part of the study consists of three dose-escalation cohorts; the low- (1.0×10^7 cells), mid- (5.0×10^7), and high-dose (1.0×10^8) groups with three patients each for the evaluation of the safety and tolerability. The second part included nine patients receiving the high-dose for the evaluation of the exploratory efficacy. The primary outcomes were the safety and the shoulder pain and disability index (SPADI). Secondary outcomes included clinical, radiological, and arthroscopic evaluations. Twenty patients were enrolled in the study, and two patients were excluded. Intratendinous injection of AD MSCs was not associated with adverse events. It significantly decreased the SPADI scores by 80% and 77% in the mid- and high-dose groups, respectively. Shoulder pain was significantly alleviated by 71% in the high-dose group. Magnetic resonance imaging examination showed that volume of the bursal-side defect significantly decreased by 90% in the high-dose group. Arthroscopic examination demonstrated that volume of the articular- and bursal-side defects decreased by 83% and 90% in the mid- and high-dose groups, respectively. Intratendinous injection of autologous AD MSCs in patient with a partial-thickness rotator cuff tear did not cause adverse events, but improved shoulder function, and relieved pain through regeneration of rotator cuff tendon. Stem Cells 2018;36:1441-1450.

Keywords: Clinical trial; Intratendinous injection; Mesenchymal stem cells; Rotator cuff disease; Rotator cuff tear.

Conclusions Cartilage : *L'Avenir ? Expérimentation et Nouvelles Voies*
Exosomes, micro-ARN impliqué dans l'arthrose, implants
3D Bioprinting du Cartilage

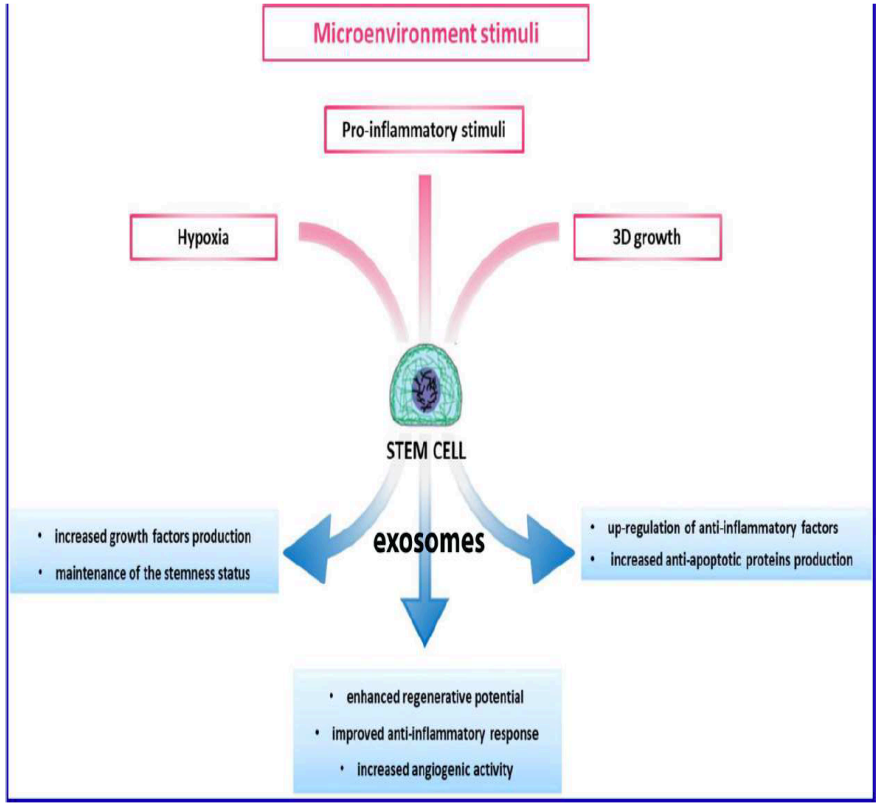

Figure 5. Different modes of action of exosomes.

Un nouvel implant devrait permettre de reconstituer intégralement une articulation abimée. Composé de différentes couches, il inclut des facteurs de croissance de l'os ainsi que des cellules souches. Un essai clinique pourrait démarrer en 2016 pour tester cette innovation chez des patients présentant des lésions au niveau du genou.

Un implant vivant et en 3D recouvrira peut-être bientôt votre articulation si elle est abimée.

Réparer le cartilage d'une articulation en cas de lésion ou de dégénérescence n'est pas une mince affaire ! Face à cette difficulté, une équipe de chercheurs spécialisés en **nanomédecine régénérative**, travaillant au sein de l'Université de Strasbourg et des hôpitaux universitaires de Strasbourg sous la direction de Nadia Benkirane-Jessel*, a imaginé une nouvelle approche d'**implant ostéo-articulaire**.

Réparer toute l'articulation

Actuellement, la stratégie de reconstruction du cartilage (en dehors de la pose d'une prothèse) consiste à injecter dans l'articulation du patient un échantillon de ses propres cellules de cartilage (chondrocytes). Mais le résultat est souvent décevant car la régénération a alors lieu sur un os lésé. « *En cas de dégénérescence du cartilage, il est très rare de développer des symptômes au stade de l'érosion : la douleur apparaît quand le cartilage a totalement disparu et que l'os sous-chondral, situé juste en dessous, commence à s'abimer. Il faut donc* ***s'attaquer en parallèle à la réparation des deux couches : l'os et le cartilage*** », clarifie Nadia Jessel-Benkirane, coauteur des travaux avec Laetitia Keller.

Deux compartiments superposés

Pour cela, les chercheurs ont créé un implant composé de deux compartiments :

- Le premier est **une membrane nanofibreuse, à base de collagène ou de polymères, dotée de nanoréservoirs de facteurs de croissance osseux**, pour favoriser la **réparation de l'os**.
- Le second est **une couche d'hydrogel (alginate) renfermant de l'acide hyaluronique et des cellules souches dérivées de la moelle osseuse du patient**, favorisant la **régénération du cartilage**.

L'organisation en trois dimensions du dispositif favorise la croissance et la différenciation des cellules souches en cellules du cartilage. « *Imaginez la membrane nanofibreuse comme une feuille de papier déposée par le chirurgien sur l'os abimé. Immédiatement après, il dépose la seconde couche contenant les cellules souches et termine son intervention. Ensuite, le travail se fait seul ! L'objectif est d'obtenir une régénération totale de l'articulation -os sous-chondral et cartilage– dans les mois qui suivent* », explique la chercheuse.

changes [122].A new promising therapeutic approach c is characterized by the bio fabrication of 3D structures mimicking articular cartilage propriety due to 3D bioprinting technique. This brand new technology can be used to reproduce complex scaffold characterized by cells, growth factors, extracellular matrix, to be used to physically substitute injured cartilage [123]. Some authors have biofabricated human cartilage using adipose tissue deriving from infrapatellar fat succeeding in production of hyaline cartilage on a bio scaffold in order to produce a patient tailored cartilage to replace the injured one [124]. To conclude, this technology can be used to develop in vitro model of osteoarthritis that can be used for further scientific research [125–130].

Ils ont identifié, une molécule : le micro-RNA-181a-5p qui est responsable du déclenchement de l'inflammation, de la destruction du cartilage, du blocage des chondrocytes (synthétisant la matrice extracellulaire du cartilage) et donc de l'épuisement du collagène. Ils se sont alors penchés sur un moyen de bloquer ce fameux déclencheur, dans le but d'arrêter la dégénérescence du cartilage et de le protéger.

C'est avec une mise au point d'un bloqueur spécifique d'ARN messager sous forme d'un antisens, (« une séquence d'acides nucléiques complémentaires de l'ARN »), qu'ils sont parvenus à bloquer le micro-ARN responsable ; pour lequel un arrêt de la destruction du cartilage a été observé.

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LA SUITE DE L'HISTOIRE du NGF : les Stem Cells et la moelle épinière

frontiers in Cellular Neuroscience

REVIEW
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Regeneration of Spinal Cord Connectivity Through Stem Cell Transplantation and Biomaterial Scaffolds

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RESTAURER LA CONNECTIVITE

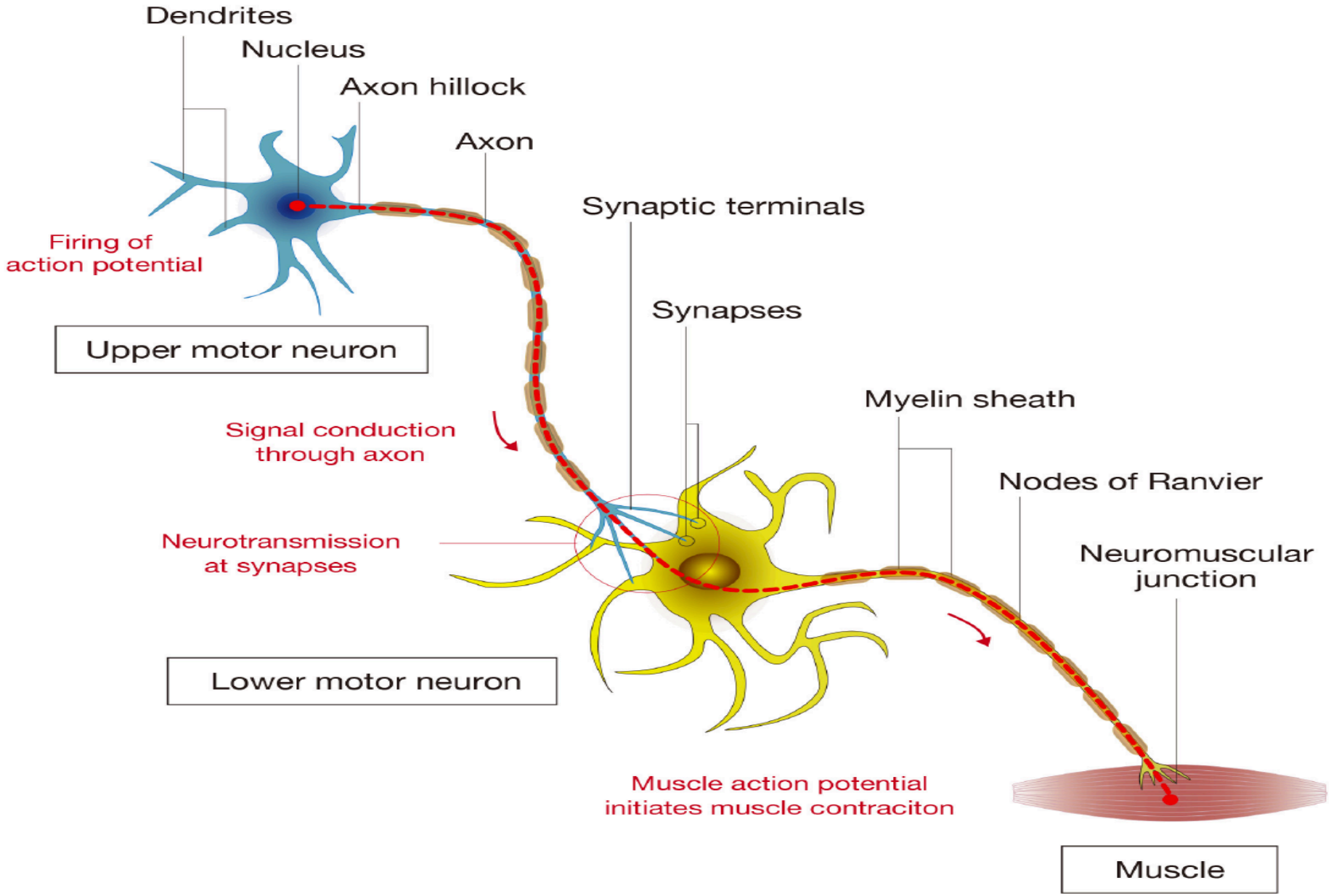
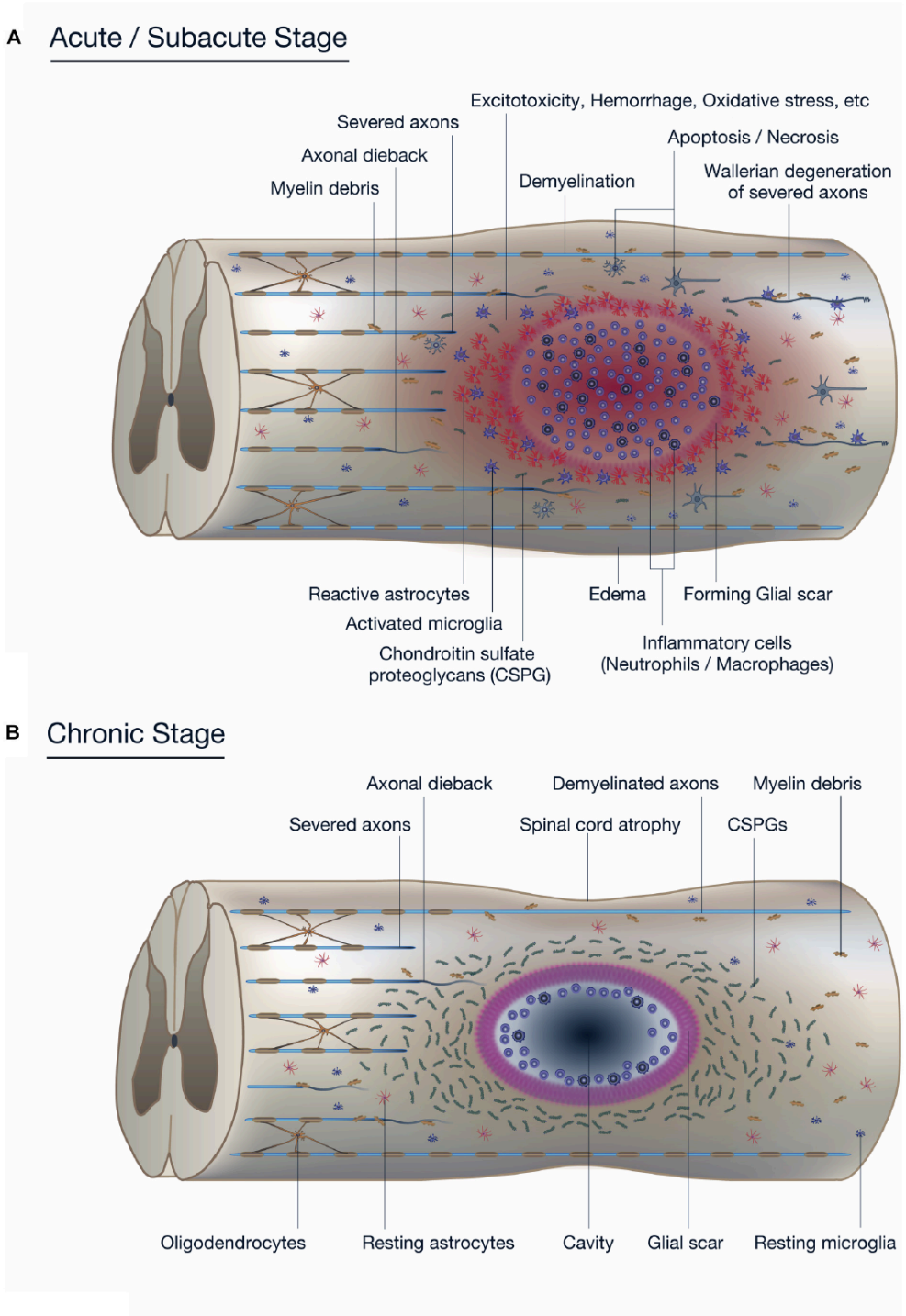


FIGURE 2 | Components of spinal cord connectivity. The diagram shows the simplified components of spinal connectivity composed of an upper motor neuron, a



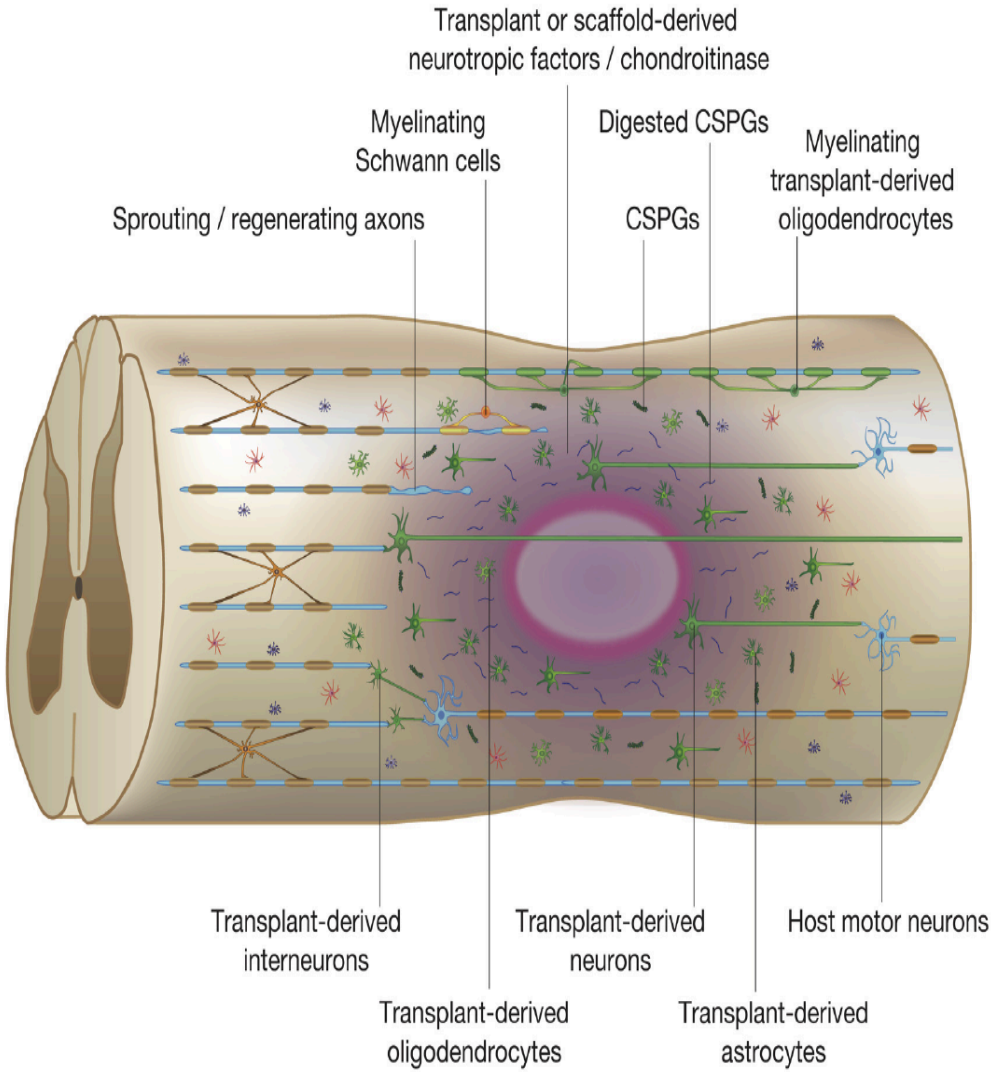


FIGURE 3 | Potential mechanisms of spinal cord repair by stem cell transplantation. The diagram shows potential mechanisms of regeneration brought about by stem cell transplantation. The transplanted stem cells differentiate into neural cells of the three lineages: neurons, astrocytes, and oligodendrocytes (shown in green). The transplanted stem cells and differentiated cells secrete neurotrophic factors that reduce inflammation, degrade CSPGs, and promote endogenous tissue repair. Differentiated oligodendrocytes remyelinate denuded axons. The grafted neurons form synapses with propriospinal neurons and lumbar motor neurons, which reorganize the neuronal circuits by forming *de novo* synaptic connectivity between host and grafted neurons. The regenerated neuronal circuits bridge the lesion by creating a detour route that passes through areas more favorable to regenerating axons. Transplant-derived interneurons indirectly connect the host injured neural tracts through the propriospinal circuits, whereas transplant-derived neurons participate in the regeneration of the injured corticospinal tract (CST) and directly activate muscle contraction.

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