Annals of Stem Cells and Regenerative Medicine

Mini Review
Published: 19 Jan, 2018

The Effect of Platelet-Rich Plasma on the Chondrogenic and Osteogenic Differentiation of Stem Cells

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Abstract

Tissue engineering is intended to regenerate the damaged organs or to promote their healing. The techniques used by this branch of regenerative medicine consist in biological active molecules, stem cells and scaffolds. Platelet-Rich Plasma (PRP) is a plasma fraction containing an amount of platelets several times above the baseline. In the last decades the use of PRP has gained popularity in the field of the tissue engineering. Its properties are anti-inflammatory, analgesic and neo-angiogenetic; for this reason it is able to promote tissue formation and remodeling by influencing stem cells migration, proliferation and differentiation. Stem cells used in tissue engineering are harvested from different sources. In orthobiologics, the application of the regenerative medicine in the orthopedic field, Mesenchymal Stem Cells (MSCs) from bone marrow are the most used. Nevertheless there are other alternative sources of MSCs that can be chosen such as adipose tissue, synovial fluid, muscle tissue, umbilical cord and amniotic fluid. The aim of this mini-review is to collect the works present in literature where PRP has been used in combination with stem cells from different origins: this association has shown promising results both *in vitro*, in chondrogenic and osteogenic differentiation and *in vivo*, in osteochondral defects healing.

Keywords: Platelet rich plasma; Orthobiologics; Stem cells; Mesenchymal stem cells

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Received Date: *20 Nov 2017*
Accepted Date: *12 Jan 2018*
Published Date: *19 Jan 2018*

Citation:
Pantalone A, Giannetti A, Vanni D, Verna S, Di Gregorio P, Salini V. The Effect of Platelet-Rich Plasma on the Chondrogenic and Osteogenic Differentiation of Stem Cells. Annals Stem Cell Regenerat Med. 2018; 1(1): 1003.

Introduction

Platelet-Rich Plasma (PRP)

Platelet-Rich Plasma (PRP) consists in a plasma fraction containing an amount of platelets several times more than the normal platelet count (150 000-350 000/µl) [1-4]. Platelets or thrombocytes are biconvex discoid elements of the blood (2-3µm diameter), represented by fragments of cytoplasm originating from megakaryocytes in the bone marrow [1,2,5]. About 40 years ago, platelets were only known as hemostatic cells until, in 1974, Ross et al. [6] noticed that the addition of activated platelets into a smooth muscle cell culture increased the mitogenic activity of the cells. Thrombocytes lack the nuclei and some organelles such as the Golgi apparatus and the endoplasmic reticulum, but they have structures like α, δ, λ granules [7]. Granules α contain more than 30 bioactive proteins such as PDGF, TGF-β, PF-4, IL-1, PDAF, VEGF, EGF, PDEGF, ECGF, IGF, osteocalcin, osteonectin, fibrinogen, vitronectin, fibronectin, and thrombospondin [1,2,4,8-18]. These factors are released after platelet activation, 70% of them within 10 minutes and after 1 hour the 95% of the proteins are released [2,5,18-20].

The interest in the use of PRP depends on the presence of these cytokines, chemokines and growth factors. The PRP activation is usually obtained by adding calcium chloride, autologous or bovine thrombine, batroxobin and collagen type I [1,2,9,18,21-23]. For the *in vitro* use, the activation of PRP is imperative, on the other hand for the *in vivo* use, the activation is obtained in situ by the effect of the endogenous collagen and thromboplastin of the connective tissue [2,3,8,18, 20, 21,24-27]. PRP is produced by centrifugating the whole blood in order to separate the various components according to their own density. There are different techniques to prepare the PRP [8,28] and there are different kinds of PRP as well, such as Pure PRP or leukocytes-poor platelet-rich plasma, and leukocytes-rich platelet-rich plasma [29-31]. This latter seems to have some antibacterial properties but, at same time, the leukocytes in PRP releases pro-inflammatory cytokines like IL-1β and TNF-α that, activating the NF-kB pathway, inhibit tissue healing [8,20,32-38]. In the last decades the use of PRP has gained popularity in the field of the tissue engineering because of its anti-inflammatory and analgesic properties, its capacity to induce neo-angiogenesis, tissue formation and remodeling

by influencing stem cells migration, proliferation and differentiation [2,8,9,21,28,32,39-48].

PRP is being used in different applications in medicine such as in the area of aesthetic medicine, maxillofacial surgery and orthopedics [8,49-52]. Nevertheless, the evidences in the literature of the use of PRP are conflicting, in fact in some studies the use of PRP leads to benefits while in others the effect of PRP is not relevant [8]. On the other hand the combination of PRP and stem cells, harvested from different sources, represents a new promising branch of the orthobiology giving encouraging results both *in vitro* and *in vivo*.

Stem cells

Adult stem cells have a central role in regenerative medicine, they in fact dominate the market compared to the embryonic stem cells because of their ease of isolation, that does not give rise to ethical controversies, because of their multipotentiality and their capacity of self-renewal, lower maintenance cost, lower risk of induction of teratomas after *in vivo* transplantation and better immunocompatibility [53-62].

Mesenchymal Stem Cells (MSC) could be harvested from different sources such as bone marrow, adipose tissue, peripheral blood, lungs, synovial membrane, dental pulp, satellite muscle cells, placenta, umbilical cord and cord blood [53,63-77].Furthermore it has to be said that the properties, markers expression, differentiation capacities, efficiency and paracrine functions change according to the source of stem cells chosen. Therefore the choice of the type of stem cells could depend on the clinical application [53,78-86].

PRP and Bone Marrow Stem Cells (BMSCs)

BMSCs are the most studied and used cells in regenerative medicine [53]. These cells are isolated from the heterogeneous cell population present in the bone marrow aspiration. The isolation of the stem cells is obtained using a culture protocol in which the non-adherent cells are eliminated with the medium changes and after 9-10 days most of the cells remained are mesenchymal stem cells [87]. There are different methods of isolation with different degrees of sophistication [87-91].

In the definition of MSC there is the capacity to differentiate into mesodermal lineages like fat, bone and cartilage. However when MSCs are co-cultured with specific inducing factors, they demonstrated to have endodermic and neuro-ectodermic differentiation potential as well [87,92-96].

The combination of PRP and BMSCs could be an alternative to the autologous or allogenic graft for osteochondral lesions [97,98]. This association has often been used in orthobiologics to face the most common diseases in orthopedics such as cartilage and bone defects [99-102].

A recent study from Wei et al. [103] has demonstrated that using PRP and BMSCs for the treatment of osteoporosis in ovariectomized rats has led to better results than using PRP or BMSCs alone. Therefore this study suggests an alternative strategy to treat osteoporotic bone loss and heal bone defects in general.

PRP and BMSCs have been used together also with a combination of scaffolds, as well as done by Li et al. [104], that successfully managed osteochondral defects in beagles.

PRP and Adipose-derived Stem Cells (ADSCs)

ADSCs could represent a good alternative to the BMSCs for their ease of isolation, abundance, proliferation and differentiation properties into different cell lineages (adipogenic, chondrogenic, osteogenic, myogenic, neurogenic lineage) [105,106-110]. ADSCs can be obtained by lipoaspirates from patients inguinal fat pads. Stem cells from adipose tissue are more numerous than those from other stem cells sources (10^7 ADSCs from 300 ml of lipoaspirate) [105,111,112].

The growth factors founded in the PRP can influence the migration, proliferation and differentiation of ADSCs. In addiction the fibrin network in the PRP works as a scaffold. Thereby this cooperation can certainly be used in the regenerative medicine [105,113-119].

In orthopedics PRP and ADSCs have been largely investigated both for bone defects and cartilage lesions [120-123]. Tajima et al. [124] demonstrated that bone healing in rats was significantly greater when PRP and ADSCs were used together instead of alone. In a similar way Van Pham et al. [125] showed with their work the capacity of ADSCs and PRP of promoting injured particular cartilage healing that was more efficient than the one with untreated ADSCs.

PRP and Synovial Fluid Mesenchymal Stem Cells (SF-MSCs)

Stem cells from human synovial membrane were isolated for the first time in 2001 by De Bari et al. [126]. Likely all the MSCs SF-MSCs have high proliferation capacities and they are able to differentiate into adipogenic, chondrogenic and osteogenic lineages [127,128] however SF-MSCs show greater chondrogenesis compared to the stem cells from other tissues [127,129]. Furthermore SF-MSCs isolation is easier and less invasive than other MSCs; in fact it is obtained by a simple Arthrocentesis. The number of stem cells that can be found in the synovial fluid is greater if the patient is affected by osteoarthritis, anterior cruciate ligament injuries or meniscus lesions [127,130-133].

The effectiveness of the combination of PRP and SF-MSCs has been proved both *in vitro* and *in vivo*. *In vitro* the chondrogenic and osteogenic differentiation was obtained [127], while the *in vivo* study performed in an animal model, has shown good results on the treatment of damaged articular cartilage in rabbits [133].

PRP and Muscle-Derived Stem Cells (MDSCs)

MDSCs or Muscle Satellite Cells were described for the first time by Mauro [134,135]. Their capacity of self-renewal, long-term proliferation, and multi-lineage differentiation potential both *in vitro* and *in vivo* has been demonstrated [135,136-138].

Although the literature is poor of studies concerning the combination of PRP and MDSCs, some authors like [139] and Huang et al. [135] have investigated this association and they affirm the both *in vitro* and *in vivo* efficacy of PRP in promoting proliferation, osteogenic and chondrogenic differentiation in Muscle Satellite Cells.

PRP and Umbilical Cord Stem Cells (UCSCs)

Mesenchymal Stem Cells obtained from the umbilical cord blood are already known for their self-renewal capacity and their ability to differentiate into adipose, muscle, bone and cartilage tissue [140-145].

Theoretically because of their immunologic immaturity, UCSCs can offer some advantages compared with the stem cells from bone marrow aspirates, but on the other hand, the low quantity of stem cells present in a single sample from the umbilical cord blood could represent a limitation for their clinical application in an adult population with high body weight [146]. Despite this observation [140] and [147] have believed in the potential of the use of UCSCs in the regenerative medicine and demonstrated their ability to differentiate into bone lineage *in vitro* and to accelerate bone regeneration *in vivo* when combined with PRP.

PRP and Amniotic Fluid Stem Cells (AFSCs)

Amniotic fluid could represent a new source from where harvest stems cells. AFSCs are collected through amniocentesis in women undergoing prenatal diagnosis (16^{th}-18^{th} week of pregnancy) [98,148-155]. These cells possess interesting characteristics; in fact AFSCs have intermediate properties between embryonic stem cells and adult stem cells. Indeed AFSCs present a greater potency than adult stem cells while, comparing embryonic fluid stem cells with AFSCs, these latter are easier to collect and more ethically accept because no embryo needs to be suppressed. In addiction they are more genetically stable and therefore they do not induce teratomas after *in vivo* transplantation [98,156-159].

For the use in orthobiologics AFSCs may represent a new alternative, considering their ability to differentiate *in vitro* into osteogenic precursors, in fact it was demonstrated that 85% of AFSCs versus 50% of MSCs lead to the formation of osteogenic colonies [98,159-167]. Wang et al. [168] have investigated the AFSCs *in vivo* potential as well; in fact in their work they obtained a promotion of maxillary alveolar bone defect in rats combining AFSCs and PRP.

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