ISSN: 2573-9565

Review Article

Journal of Clinical Review & Case Reports

History and Physiology of Plasmatic Growth Factors in Regenerative Medicine

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Submitted: 22 Nov 2017; **Accepted**: 27 Nov 2017; **Published**: 31 Jan 2018

Abstract

There is no doubt that the use of plasma growth factors, within what is known as regenerative medicine, is emerging as a new medical discipline with a lot of clinical applications. Since its inception in use in sports medicine and dental implants in the mid-80s, gradually it has expanded its field of use in clinical specialties. More and more data on the physiology of angiotrope, immunomodulatory and cellular trophic power are known every day. Both the growth factors present in platelets and leukocytes produce on the cellular biological cycle, intervening in the processes of duplication, differentiation and apoptosis such as biochemical signals in the form of cytokine or chemokine cascades that intervene in the activation of these phenomena, through inflammation or ischemia, as well as the interrelationship between themNotwithstanding the great offer of existing indications and duplication of procedures for obtaining, which surpasses the scientific production capacity on this subject, that is questioning a biotechnology that well used in the near future will help improve the quality of life of the patients , optimizing those medical indications where it really is useful.

Keywords: Plasma growth factors (PGF), Platelet rich plasma (PRP), Centrifugation, Leucocyte growth factors (LGF).

Brief Historical Review about Use of Plasmatic Growth Factors

Previously it was believed that platelets had only hemostatic activity. Today we know that platelet functions go far beyond hemostasis. About 1970 researchers studied the proliferation of smooth muscle cells in the vascular endothelial lining and it was known that 10% of plasma was crucial for cell growth, but it was not known what the plasma component was for that observed anabolic effect. These investigators also knew that the addition of calcium to the platelet-poor plasma produced a stimulation of these.

In 1974 Ross et al. (1978) determined that intact platelets together with calcium significantly increased mitogenic activity of blood plasma. Concluding, therefore, platelets must be the major cause of the proliferative effect on blood plasma.

The first growth factor discovered was by neurophysiologist Rita Levi in 1948 who was awarded the Nobel Prize in Medicine in 1986 with Stanley Cohen for discovering the Nerve growth factor (NGF). In 1978 Witte et al. They described the term "platelet-derived growth factor" (PDGF) and in the following years Kaplan et al. (1979), used subcellular fractionation to determine that PDGF resides in α-platelet granules that are dense. IGF-1 (Karey and Sirbasku 1989), TGF-β (Assoian et al., 1983), FGF-β (Brunner et al., 1993) and VEGF (Banks et al., 1998) were also identified over 20 years later [1-5].

Since 1990, platelet suspensions in plasma (platelet concentrates) have been used for the treatment of thrombopenia of central origin. (Diamond 1914). Its use in non-hemostatic therapy did not reach the mid-1990s, after the discovery of growth factors. Also in 1900 the term "regenerative medicine" was created and a new field was born with platelet-rich plasma. (Torricelli et al., 2011). The main advantages of this treatment include high availability, minimal invasion and affordability of the process. In addition the preparation is fast and requires a minimum specialized equipment [6,7].

The first clinical case of PRP used for tissue repair was published in 1998 in a man who had a bone graft due to a defect in the mandible (Marx et al 1998). PRP is now a very common method used in all types of interventions and injuries, such as in maxillofacial surgery and implantology to accelerate the repair process of damaged tissue (Del Fabbro et al., 2011). In addition, PRP has recently been used for the treatment of musculoskeletal and traumatological damage (Torricelli et al., 2011; Taylor et al., 2011; Waselau et al., 2008) [6-8].

Physiology of Platelets and Growth Factors

Platelets are enucleated cell fragments derived from the cytoplasm of megakaryocytes from the bone marrow. Best known function is in the process of primary hemostasis, as they are essential for clot formation, but also play an important role in inflammation, immunomodulation, cell progression, differentiation and course thrombosis. Platelets express and release a series of inflammatory chemokines and cytokines, including CD40L, platelet factor 4 (PF-4),

RANTES, and IL1-β (Nurden 2011; Semple et al 2011). They attract, bind and activate the leukocytes through binding between platelet P-selectin and leukocyte PSGL-1, (Weyrich et al., 2003). Once bound, platelet ligands (such as CD40L and CD154) induce direct effects on leukocyte receptors, and as a result activation, migration, and generation of proinflammatory cytokines occur (Semple et al., 2011). Platelets, being primary immune cells, contain microbicidal proteins that can kill bacteria and also have well-known antifungal activities (Krijgsveld et al., 2000). Despite this, the antibacterial effects induced by platelet activation play a significant deleterious role in septic processes, (Cox et al., 2011; Leslie 2010, Semple et al. platelets are directly related to proinflammatory diseases. Electron microscopy, shows that platelets contain various organelles: mitochondria, peroxisomes, ribosomes and glycogen granules, the latter are divided into three types: 1) Alpha: containing fibrinogen, Von-Willebrand factor, platelet derived growth factor, ectodermal growth factor, vasculo-endothelial growth factor, insulin-like growth factor 1 and other growth factors, 2) dense delta: that containing ADP, ATP, serotonin, epinephrine, norepinephrine and dopamine and 3) lambda: they are lysosomes, which help dissolve the clot once it has fulfilled its function [3,4,9]. Figure 1 y 2.

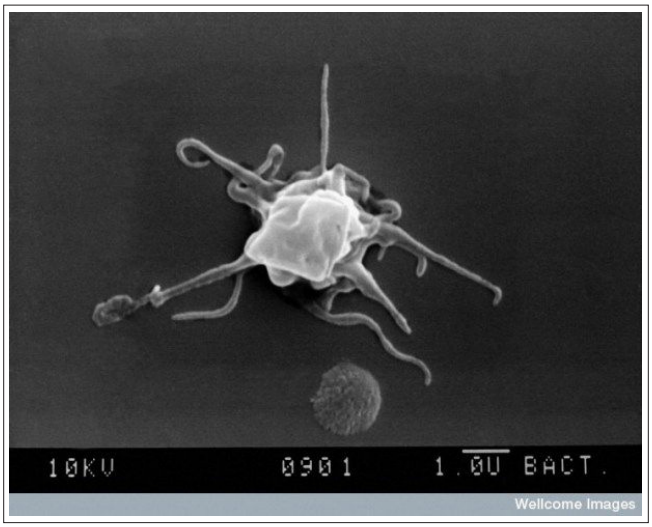

Figure 1: Platelet by electron microscopy

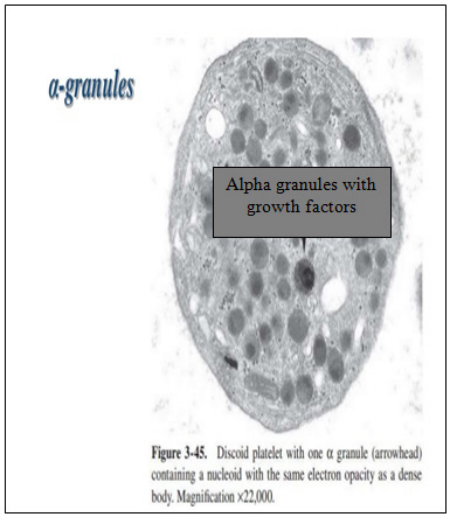

Figure 2: Platelet growth factors in alpha Granules by transmission Electronic microscopy

Recent discoveries have shown their ability to protein synthesis, mRNA containing copies of almost 1/3 of known proteins in the human genome, despite the lack of core, has totally changed the perception they had of them, recognizing their ability to synthesize proteins to changes in their environment. Platelets have been shown to play a crucial role in the formation of new tissue from ovulation (Furukawa et al., 2007) for embryogenesis (Finney et al., 2012) and also at maturity (Olorundare et al. 2001), both in health and disease (Luttenberger et al 2000, Dees et al 2011). On the other hand, the creation and remodeling of the extracellular matrix are induced by the combined effects of platelet-derived growth factors (Montesano and Orci 1988), serotonin (Dees et al., 2011), matrix metalloproteinases TIMPs (Nurden 2011). In wound healing, fibroblasts are organized into the fibrin clot by the chemotactic gradient provided by PDGF and TGFb that synthesize platelets. Fibroblasts begin to synthesize more fibronectin and collagen under the influence of platelet-derived serotonin (Dees et al., 2011). In addition, platelets are inducers of cell proliferation and differentiation (Luttenberger et al 2000; Kakudo et al 2008; Mishra et al 2009; Wang et al. (1998), Kajikawa et al., 2008, Loppnow et al., 1998, Ogino et al., 2006, Slater et al 1995, Zhang and Wang 2010, Mishra et al 2009, Stellos and Gawaz 2007).

Platelets have a crucial role in angiogenesis since they directly stimulate the formation of new blood vessels (Kurita et al 2011, Bosch et al 2011a) and help repair them by recruiting and anchoring the cells endothelial progenitors (Stellos and Gawaz 2007). In the field of wound healing, platelet fibrin clot has been referred to as a "provisional matrix" (Greiling and Clark 1997), as it provides the basic anchor for the formation of new tissue.

These functions are precisely those that have led to propose the use of autologous platelet-rich plasma for the repair and regeneration of various tissues [1-10].

Physiology of Leukocytes and Growth Factors

Leukocyte growth factors are natural molecules which are responsible for the proliferation and differentiation of normal blood stem cells. These proteins are found in the lysozyme of the mononuclear fraction of the leukocyte series, although the possibility of detecting them in other leukocyte cell extracts as well as in the hematopoietic progenitors is not ruled out. Figure 3

It has been objectified at the biochemical level an activation of inflammatory phenomena that would induce cell differentiation and proliferation, closely related to positive signaling from platelet growth factors. Platelets express and release a series of inflammatory chemokines and cytokines, including CD40L, platelet factor 4 (PF-4), RANTES, and IL1-β (Nurden 2011; Semple et al 2011). They attract, bind and activate the leukocytes through binding between platelet P-selectin and leukocyte PSGL-1, (Weyrich et al., 2003). Once bound, platelet ligands (such as CD40L and CD154) induce direct effects on leukocyte receptors, and as a result activation, migration, and generation of proinflammatory cytokines occur (Semple et al., 2011) [6-9]. Figure 4

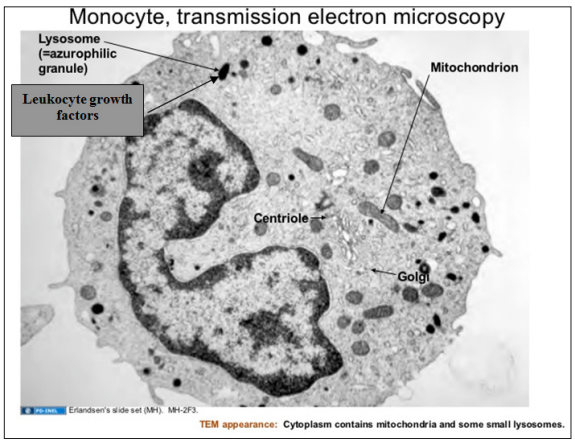

Figure 3: Leukocyte growth factors in lysozymes from Mononuclear cell by electronic microscopy

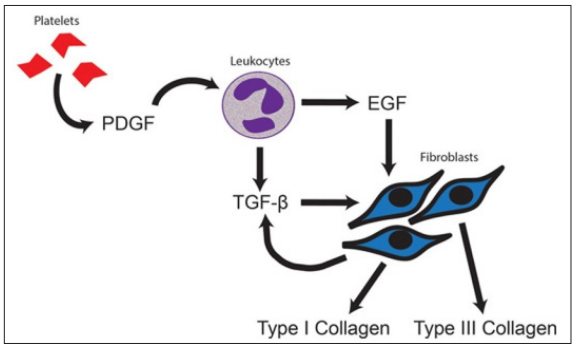

Figure 4: Phenomenon of positive interrelation in the activation of leukocyte growth factors, mediated by platelet growth factors

Definition of Plasma Rich in Growth Factors

Defining PRP: The PRP is an autologous concentration of platelets in a small volume of plasma which represents an increase over normal baseline platelet levels, making it a source of easy access to growth factors contained therein. It has a pH between 6.5 and 6.7. It comes from the patient's own blood, so it is free of communicable disease and can not cause hypersensitivity reactions. The platelet count of PRP is optimal debatable. According to the Competent Authority, it must contain a levels of platelets higher than the basal serum levels considered normal (between 200,000 and 450,000 platelets / mm 3). But increasingly the authors dedicated to this area considered a PRP quality when platelet counts obtained in the final product exceeds 1,000,000 / mm3 [7,8].

Defining LRP (Plasma rich in Leukocyte growth factors): The LRP is an autologous concentration of Human Buffy-coat mononuclear type Leukocyte, in a small volume of plasma, by ficol method, wich represents an increase over normal baseline Leukocyte levels, making it source of easy acces to growth factors contained therein. It has a pH between 6.5 and 6.7. It comes from the patient's own blood, so it is free of communicable disease and could produce Hypersensitivity reactions (about 3% patients) like skin rash or fever easily controlled with antipyretics or antihistamines. Experts considered a PRP quality when Leukocyte counts obtained in the final product exceeds 20,000 / mm3 [7,8].

Conclusion

Surely we are facing a new era of treatment in the new field of what is called regenerative medicine with an extraordinary range of possibilities for clinical applications increased, but that requires a process of scientific and medical systematization which allows channel it safely and effectively in applications where there is scientific evidence really enough weight so apply. To do this it is necessary both consensus of the authors engaged in the production and application of this therapy in order to standardize procedures for obtaining those more effective and allow adequate traceability and monitoring of the end product, depending clinical application given their intended and secondly design of clinical trials which management and establish appropriate guidelines to that effect. As a starting point, it is crucial to know the physiology and functioning of growth factors as well as the definition of the different concentrates that can be obtained to achieve maximum efficiency and optimize their clinical applicability.

Acknowledgements

My wife and my sons, for his patience and dedication, for their encouragement a, without which it would not have been possible to implement this article.

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