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LETTER TO THE EDITOR

The P makes the difference in plasma rich in growth factors (PRGF) technology

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To the editor

In their interesting research article [1], Lippross et al. describe a method to step forward in the design of alternative autologous culture conditions for human stem cells, which reduce the use of products from animal origin, thus reducing the risks of contamination. To address this objective, endothelial progenitor cells were cultured with a classical media supplement enriched in different growth factor containing media such as 10% fetal calf serum (FCS), 5% FCS + 5% platelet-released growth factors (PRGFs) or 10% PRGF. Results show that the hybrid medium containing 5% FCS + 5% PRGF was superior to the others with regard to its performance on cell growth.

There are some important considerations that should be clarified when reading and interpreting the results from this manuscript. First, the concept of PRGF needs to be correctly defined in order to avoid misunderstanding and possible confusion with the terminology in this scientific field. In fact, PRGF was defined in 1999 as plasma rich in growth factors [2] (currently PRGF-Endoret) and not *platelet released growth factors*. At that time, it was the pioneering autologous platelet-rich plasma technology for accelerating wound healing and tissue regeneration as it was based on a 100% autologous protocol, presented a moderate platelet concentration, did not contain leukocytes and provided almost four different therapeutic plasma-based formulations from small blood volumes [3–5]. Assuming the variety of terms currently available for defining platelet-rich plasma products, we understand that it is necessary to identify each term with each technology, as their composition in terms of platelets, platelet-derived growth factors, plasma-derived growth factors, activation protocols, and presence or absence of leukocytes among others differ clearly and so also do their potential therapeutic effects [6].

Lippross et al. describe a platelet-rich plasma that increases platelet density 10 times and does not contain plasma-derived proteins and growth factors. On the contrary, PRGF-Endoret combines the proteins and cytokines from plasma and platelets being the platelet concentration 3 times higher than in peripheral blood. In our opinion, this may be critical for the final cocktail of proteins present in the biological product. In fact, some of the most important biologically active mediators from PRGF-Endoret are mainly present in plasma and not in platelets. For example, insulin-like growth factor (IGF-I) circulates in plasma as a complex with binding proteins (IGFBP) [7]. It stimulates the formation of bone matrix by promoting proliferation of pre-osteoblasts [8, 9] and stimulates the synthesis of osteocalcin, alkaline phosphatase, and collagen type I by osteoblasts [10]. It also stimulates the proliferation and chondrogenic [11], adipogenic and myogenic differentiation of mesenchymal stem cells, also promotes neuronal differentiation [12] and induces a chemotactic effect on vascular endothelial cells. In addition, it has also been demonstrated that hepatocyte growth factor (HGF), mainly present in the plasma, stimulates cell proliferation [13] and migration while inhibits NF-κB, a key nuclear factor implicated in inflammatory responses [14]. It is also remarkable the influence of HGF as an antifibrotic mediator [15, 16].

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We hypothesize that eliminating the pool of mediators present in plasma may reduce the ''biological potential and value'' of the pool of autologous proteins for cell culture. The latter could explain why an additional supplement with FCS is needed. In our hands, the combination of plasma and platelet proteins represents an excellent culture media for a wide range of cells including tenocytes [17], keratocytes and conjunctival fibroblasts [18], osteoblasts, and even stem cells. Such an approach will definitely avoid the use of products from animal origin and possible immunological concerns.

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