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Evidence supporting the preventive effect of Platelet-rich plasma (PRP) on TGFβ1-induced fibroblast/myofibroblast transition via the involvement of VEGF receptor-1 (FLT-1) signaling

Chiara Sassoli[1], Flaminia Chellini[1], Alessia Tani[1], Larissa Vallone[1], Paola Pavan[2], Franco Bambi[2], Sandra Zecchi-Orlandini[1]

[1] Università di Firenze, Dipartimento di Medicina Sperimentale e Clinica, Firenze, Italia
[2] Ospedale Meyer, Medicina Trasfusionale, Firenze, Italia

Platelet-rich plasma (PRP), defined as a plasma fraction with platelet concentration higher than the baseline concentration in whole blood, represents a cost-effective reservoir of numerous platelet-derived biologically active molecules including growth factors and cytokines, holding a strong potential for improving tissue healing and regeneration. Many studies have demonstrated that the contribution of PRP to the morpho-functional recovery of different damaged tissues/organs depend on its ability to modulate inflammatory responses, promote re-vascularization and stimulate the endogenous mechanisms of tissue repair/regeneration by influencing the cell fate of local stem cells progenitors [1-4]. The positive role of PRP in reducing fibrosis in different damaged and/or diseased organs has also been observed. However, the antifibrotic potential of PRP is still controversial [5,6]. Moreover the bioactive factors contained in PRP, as well as their cellular targets and molecular mechanisms of action need to be clearly identified. On the basis of these considerations, the aim of the present study was to examine the effect of PRP on the in vitro transition of fibroblastic NIH/3T3 cells into myofibroblasts, considered as the key cell effectors of tissue scarring and to investigate the underlying molecular mechanisms. Our results showed that PRP inhibits fibroblast/myo-fibroblast transition promoted by the pro-fibrotic agent TGF–β1, as judged by reduction of stress fibres formation, vinculin rich focal adhesion clustering, α-smooth muscle actin (sma) and type-1 collagen expression. Interestingly we found that VEGF receptor-1 (VEGFR-1/Flt-1) pathway was implicated in PRP-mediated inhibition of fibroblast/myofibroblast transition based on: i) VEGFR-1 expression was reduced by the administration of TGF-β1 as compared with the control cells and PRP was able to prevent this TGF-β1 induced reduction; ii) the selective pharmacological VEGFR-1 inhibitor, KRN633 prevented the effect of down regulation of α-sma expression promoted by PRP, iii) the addition to the differentiation medium of soluble VEGF caused a marked decrease of α-sma expression in TGF-β1-treated fibroblasts , iv) the expression of Smad3, the TGF-β1 downstream signaling molecule, appeared downregulated in fibroblasts cultured in the presence of TGF-β1 +PRP or TGF-β1+ soluble VEGF. Conversely, the addition of KRN633 to TGF-β1-stimulated cells in the presence of PRP determined an increase of Smad3 expression levels. Altogether these findings demonstrated that PRP counteracted the fibroblast/myofibroblast transition by interfering with the TGF-β1-mediated intracellular signaling possibly via VEGFR-1 mediated activation.

References

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Key words

Fibroblasts, myofibroblasts, fibrosis, regenerative medicine, TGF-β1/smad3 signaling, Platelet-Rich Plasma, VEGF receptor-1.