

**Human gingival mesenchymal stem cell trophism is modulated by inflammatory microenvironment: effects of Ribes nigrum bud extract.**

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Adult mesenchymal stem cells (MSCs) play a crucial role in the maintenance of tissue homeostasis and in promoting regenerative processes. Among the different MSC types, the gingival mesenchymal stem cells (GMSCs) have arisen as a promising tool to promote the repair of damaged tissues secreting trophic, regeneration-promoting mediators. TNF- $\alpha$  is one of the key mediators of inflammation that could affect tissue regenerative processes and modify the MSC properties in in vitro application. Herein, we investigated 1) the effects of TNF-alpha on GMSC trophism and 2) the ability of Ribes Nigrum bud extract (RBE) to modulate the effect of this cytokine on GMSC properties. GMSC were isolated and characterized from health subjects. TNF- $\alpha$  affected GMSC proliferation and the expression of inflammatory-related protein (IL-6, IL-10, TGF- $\beta$ , and COX-2) in dependence on its concentration. A high TNF- $\alpha$  concentration decreased the GMSC viability and impaired the trophic effect of GMSCs on endothelial cells, likely by enhancing the amount of pro-inflammatory mediators in GMSC secretome. GMSC incubation with RBE changed secretoma cell composition so restoring the GMSC beneficial effects on endothelial viability and motility. These results demonstrated that a high TNF- $\alpha$  concentration, as occurred under chronic inflammatory conditions, decreased the GMSC well-being and alter their trophic activity impairing GMSC-endothelial cell communication. These data highlight that the control of inflammatory microenvironment is crucial to guarantee MSC-driven reparative processes. Furthermore, the use of natural anti-inflammatory agents restored the GMSC regenerative properties on endothelial cells opening the way to the use and the development of natural extracts in wound healing, periodontal regeneration and tissue engineering application that use MSCs.

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