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Hypoxia in stem cell niche: How stromal cells answer on low oxygen demand?

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Multipotent mesenchymal stem cells (MSCs) play an important role in the regulation of stem cell niche, where low oxygen tension seems to be a common *in vivo* feature. Recently we have demonstrated that MSCs permanently expanded at low; the niche comparable (1-5%) O_2 displayed an increased proliferation, attenuation of osteo and adipo differentiation, delay of replicative senescence, which is based on changes in energetic metabolism. The data of the global gene expression array demonstrated the up-regulation of genes responsible for cell signaling, proliferation, motility/migration and cellular metabolism and down-regulation of cytoskeleton, electron transfer and extracellular matrix proteins' genes. It is generally considered that the most of the hypoxic effects are regulated HIFs proteins, primarily by HIF-1a. By RT-PCR analysis we detected the different dynamics in expression of HIF family proteins. After permanent expansion at 5% O2 the HIF-1a and HIF-3α expression was the same as at 20% O_2, while at 1% O_2 HIF-1a was down-regulated and on the contrary, HIF-3α was up-regulated. Under hypoxia the expression of apoptosis-associated genes (BAX, *DAPK3 & CASP1*) was reduced, proliferation-associated genes were up-regulated (IGF2, IL1A, MT3, VEGFa & GPI). After MSC/HSPCs (hematopoietic stem and progenitor cells) interaction, the up-regulation of cell adhesion molecule genes (*ICAM-1, VCAM-1, CDH1*), and down-regulation of genes involved in matrix remodeling (*COLs, MMPs, TIMPs, ADAMs, HAS1*) and cell-matrix contacts (*ITGs*) was demonstrated with RT- PCR. These data indicate on activation of MSCs, which most effectively increased at 5% O2. Indeed, the number of CFCs at 5 % O2 was 1.6 times higher than at 20% O_2 due to increase in number of multipotent precursors BFU-E, CFU-GEMM and CFU-GM. These changes were at least partly ensured by increased concentration of MCP-1 and IL-8at 5% O_2.Our data demonstrate that MSCs in hypoxic micro-environment significantly modulate their physiology and ensure a better maintenance/expansion of HSPCs, pointing to the hypoxia as a physiological regulatory factor as well as a cell engineering tool.

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Platelet-rich concentrates differentially release growth factors for bone regeneration

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In recent years, one of the hot topics in tissue engineering and regenerative medicine is the development of controlled release systems for bone regeneration. This study aimed for a biomimetic strategy that designed scaffolds resultant from the mixing of Platelet-rich fibrin (PRF) , a growth factor-enriched endogenous scaffold, and lyophilized Platelet-rich fibrin(L-PRF) with different ratio, tailored for different delivery rates of growth fators, seeking delivery systems of bioactive factors for tissue healing. To test this concept *in vitro*, the biological effects of autologous PRF on rabbit BMSCs was investigated, including cell proliferation, osteogenic differentiation potential, alkaline phosphatase (ALP) activity, and mineralization nodes. Compared with PRF and L-PRF, mixed PRF (PRF and L-PRF at weight ratios of 1:1, 1:3, 1:5) induced a significant and continuous stimulation of proliferation on rabbit BMSCs throughout the 7-day incubation period. Furthermore, the mixed PRF promoted the osteoblastic differentiation of BMSCs by increasing ALP activity and mineralization nodes formation during the testing period. To investigate the effects of PRF on bone regeneration, critical size cranial bone defects were created and covered with PRF, L-PRF and mixed PRF (at weight ratio of 1:1). The results were analyzed by micro-CT and histology. Six and twelve weeks after surgery, mixed PRF group achieved a more effective way to do bone reconstruction. With the confirmation from the micro-CT results, which showed bone-like density at the margins of the defects and a homogeneous radiolucent area in the central part of the defect. A far better result compared with the others tested within the groups.These findings indicated that mixed PRF allowed for sustained-release growth factors, which was an effective strategy to overcome the challenge and to enhance the function of biomimetic constructs for bone regeneration.

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