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Recipes for Researchers

Roles for mesenchymal stem cells as medicinal signaling cells

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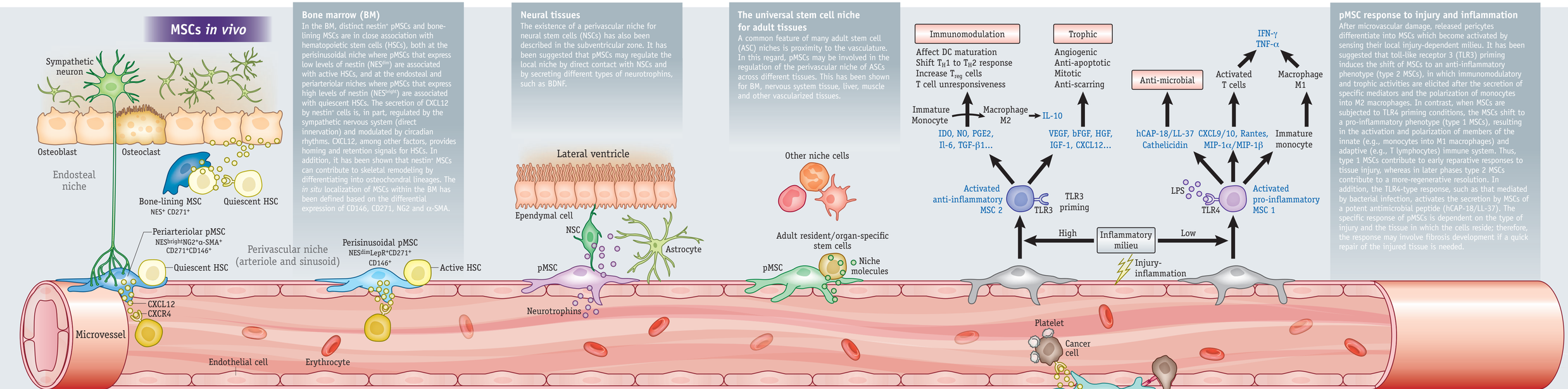
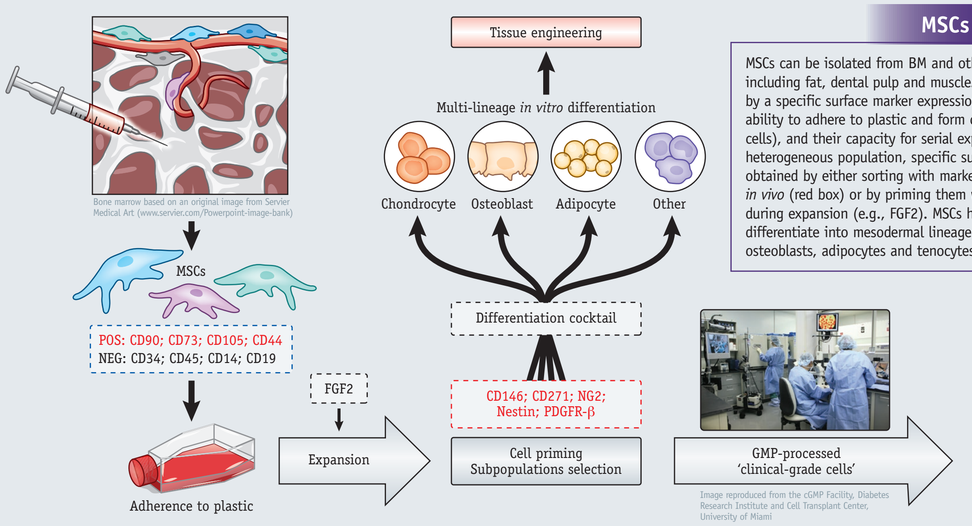
Understanding the *in vivo* identity and function of mesenchymal stem cells (MSCs) is vital to fully exploiting their therapeutic potential. New data are emerging that demonstrate previously undescribed roles of MSCs *in vivo*. Understanding the behavior of MSCs *in vivo* is crucial as recent results suggest these additional roles enable MSCs to function as medicinal signaling cells. This medicinal signaling activity is in addition to the contribution of MSCs to the maintenance of the stem cell niche and homeostasis. There is increasing evidence that not all cells described as MSCs share the same properties. Most MSCs reside in a perivascular location and have some functionalities in common with those of the pericytes and adventitial cells located around the microvasculature and larger vessels, respectively. Here we focus on the characteristics of MSCs that have been demonstrated to be similar to those of pericytes located around the microvasculature, defined as perivascular MSCs (pMSCs). Although we focus here on pMSCs, it is important to bear in mind that pericytes are found in many types of blood vessels, and that not all pericytes are thought to be MSCs.



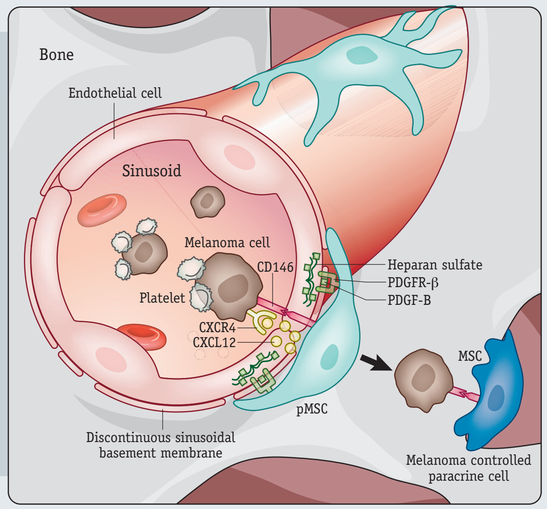


MSCs *in vitro* and therapeutic applications

MSCs can be isolated from BM and other vascularized tissues including fat, dental pulp and muscle. They are defined *in vitro* by a specific surface marker expression profile (blue box), their ability to adhere to plastic and form colonies (i.e., CFU-F cells), and their capacity for serial expansion. From an initial heterogeneous population, specific subpopulations can be obtained by either sorting with markers related to their roles *in vivo* (red box) or by priming them with stimulating solutions during expansion (e.g., FGF2). MSCs have the *in vitro* ability to differentiate into mesodermal lineages such as chondrocytes, osteoblasts, adipocytes and tenocytes, and this differentiation is achieved by supplementing cultures with lineage-specific soluble factors and specific microenvironmental cues. GMP-processed human MSCs (i.e., cells of clinical grade) are used in clinical trials for cell therapy, as the basis for novel therapeutic approaches for regenerative medicine. The availability and versatility of these cells make them an excellent option for a wide variety of clinical conditions associated with inflammation, ischemia, autoimmunity and trauma. When supplied exogenously, MSCs home to sites of injury, readopting their perivascular localization. At these sites, MSCs exert their local immunomodulatory and trophic activities.

MSCs in cancer metastasis

PDGFR-β–expressing MSCs are attracted to an abluminal location by gradients of endothelial cell-secreted, heparan sulfate–bound PDGF-β. Once in their perivascular niche, they have a pivotal role in controlling the extravasation of circulating cancer cells (e.g., in melanoma and breast cancer) into bone and liver parenchyma. The molecular mechanisms underlying this regulatory process involve the action of (i) secreted chemokines (e.g., CXCL12) by pMSCs recruiting CXCR4-expressing cancer cells close to the endothelium; and (ii) intercellular adhesion molecules (such as CD146) expressed by both cells, generating a migratory cellular complex. These mechanisms may serve as a platform for the development of novel therapies aimed at controlling the establishment and progression of skeletal and liver metastasis by targeting pMSCs. Moreover, based on the known pericytic mimicry capability of angiotropic tumor cells, targeting of perivascular cells may aid in the control of metastatic dissemination of cancer cells that use this alternative mechanism of tumor spread.



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Abbreviations

α-SMA: Alpha smooth muscle actin; ASC: Adult stem cell; BDNF: Brain-derived neurotrophic factor; CCL5: C-C motif chemokine 5 (Rantes); CXCR4: Chemokine (C-X-C motif) receptor 4; CXCL9: Chemokine (C-X-C motif) ligand 9; CXCL10: Chemokine (C-X-C motif) ligand 10; CXCL12: Chemokine (C-X-C motif) ligand 12; DC: Dendritic cell; FGF2: Fibroblast growth factor 2; GMP: Good manufacturing practice; hCAP-18/LL-37: Human cationic antimicrobial protein; HGF: Hepatocyte growth factor; HSC: Hematopoietic stem cell; IDO: Indoleamine 2,3-dioxygenase; LPS: Lipopolysaccharide; IGF-1: Insulin-like growth factor-1; IL-6: Interleukin-6; IL-10: Interleukin-10; IFN-γ: Interferon gamma; LepR: Leptin receptor; MIP: Macrophage inflammatory protein; NES: Nestin; NG2: Neural/glial antigen 2; NO: Nitric oxide; NSC: Neural stem cell; PDGFR-β: Platelet-derived growth factor receptor beta; PGE2: Prostaglandin E2; pMSC: Perivascular mesenchymal stem cell; TH: T helper; TLR3: Toll-like receptor-3; TLR4: Toll-like receptor-4; TNF-α: Tumor necrosis factor alpha; VEGF: Vascular endothelial growth factor

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