FEATURES

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MSC-Derived Factors for Tissue Repair

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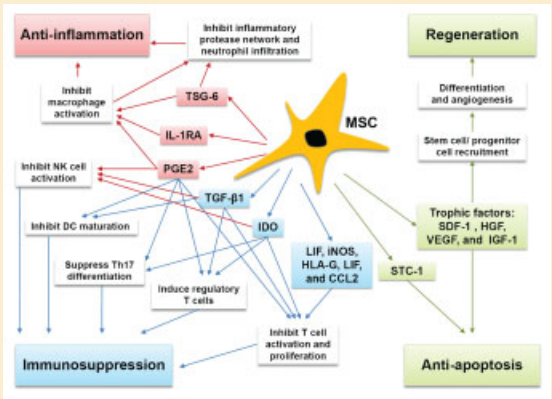
Currently, considerable efforts are being made to develop cell therapies using multipotent mesenchymal stromal cells often referred to as mesenchymal stem cells (MSCs). MSCs are readily isolated from small aspirates of a patient's bone marrow, expand rapidly in culture, and differentiate into several cellular phenotypes. Therefore, they were originally sought to repair injured tissues by engrafting and differentiating. However, in most clinical and experimental situations, systemic administration of MSCs resulted in functional improvements without evidence of long-term engraftment or differentiation. Emerging evidence suggests that most of the beneficial effects of MSCs could be explained by secretion of therapeutic factors that have multiple effects including modulation of inflammatory and immune reactions, protection from cell death, and stimulation of endogenous progenitor cells. In this review, Lee et al focus on the MSC-derived therapeutic factors including TSG-6, IDO, PGE2, NO, STC-1 and many trophic factors that account for the beneficial effects of MSCs in animal models of human diseases. Defining these therapeutic factors secreted by MSCs leads to a better understanding of MSC function and will further help to utilize MSCs for treating human diseases.



SPARC-Like Fragments Associated With Neovasculature

Matt Weaver, Gail Workman, Chad R. Schultz, Nancy Lemke, Sandra A. Rempel, and E. Helene Sage

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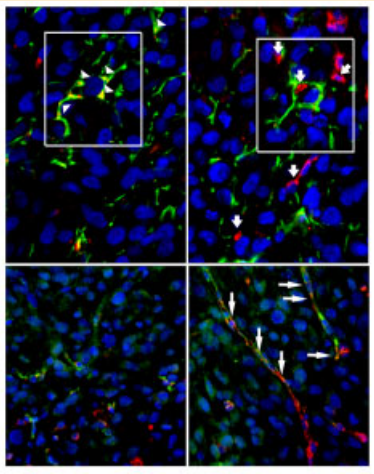
The concept of matricellular proteins as mediators of cell-extracellular matrix interactions and signaling was presented 20 years ago and has been re-defined to include several family members that participate actively in cancer. The prototype of this group, SPARC, was previously shown to modulate cell shape, collagen assembly, and angiogenesis, and its peptides produced via proteolysis displayed functions that in some cases were distinct from those of the uncleaved protein. The SPARC homolog, hevin, is prominent in brain and might compensate for (or antagonize) SPARC, especially in pathologic tissues with high levels of proteolytic activity. Weaver et al. now show that in a murine model of human glioma, a malignant tumor characterized by its high levels of SPARC and proteinases, rapid incursion of neovascular cells, and trapping of adjacent normal brain tissue upon invasion, a SPARC-like fragment (SLF) produced by the cleavage of hevin by matrix metalloproteinase-3 was associated with the tumor angiogenic response. In contrast, uncleaved hevin was found in the astrocytes encompassed by the infiltrating tumor. Weaver et al. have identified the SLF as a unique peptide and new marker of neovessels in glioma, where it is postulated to influence the angiogenic response to this tumor.



Journal of Cellular Biochemistry

Most Cancer/Testis Antigens are Disordered Proteins

Krithika Rajagopalan, Steven M. Mooney, Nehal Parekh, Robert H. Getzenberg, and Prakash Kulkarni

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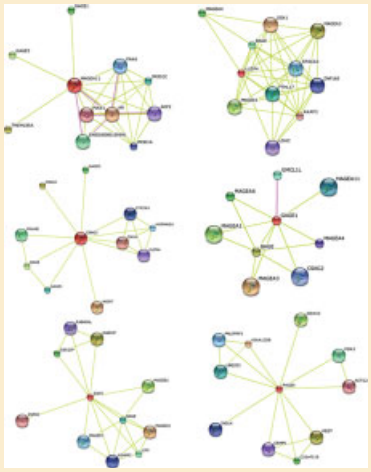

The Cancer/Testis Antigens (CTAs) are a group of tumor-associated proteins that are typically expressed in the testis but aberrantly expressed in several cancers. Because of their unique expression patterns, the CTAs have largely been explored as potential immunotherapeutic and biomarker candidates but the functions of most CTAs, particularly those located on the X chromosome, remain elusive. In this issue of JCB, Rajagopalan et al. demonstrate for the first time that a majority of the CTAs are intrinsically disordered proteins (IDPs), proteins that lack a rigid structure at least *in vitro*, and are frequently over-expressed in several pathological conditions. The inherent ability of IDPs to engage in promiscuous interactions when present in increased concentrations is thought to be the mechanism underlying their toxicity/pathological effects. Furthermore, the authors demonstrate that the disordered CTAs appear to occupy 'hub' positions in protein regulatory networks that typically adopt a 'scale-free' power law distribution. Taken together, this landmark study provides a novel perspective on the CTAs, implicating them in processing and transducing information in altered physiological states in a dosage-sensitive manner. These remarkable findings should allow a better understanding of their functions as well as the development of novel therapeutics to treat cancer.

Hypoxia-Induced Autophagy and Starvation Tolerance as Targets for Hepatocellular Carcinoma

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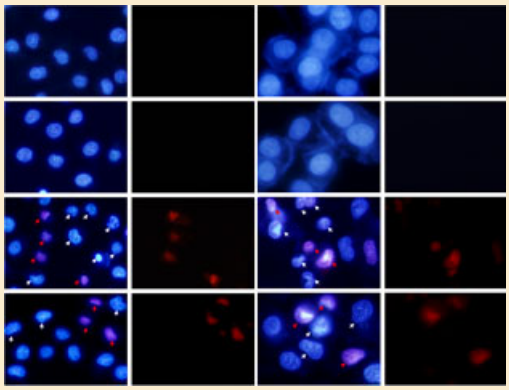

Autophagy has been studied extensively, but the role of autophagy in hypoxia followed by nutrient deprivation has not been understood clearly. Song et al investigated the role of autophagy in oxygen-nutrient-deprived conditions after a period of hypoxic preconditioning which simulated the tumor microenvironment in hepatocellular carcinoma. Cell death induced by starvation in hypoxia was less frequent than that in normoxia. Decreased cell death was primarily attributed to decreased apoptosis. Meanwhile, autophagy was activated significantly during hypoxia preconditioning. However, inhibiting autophagy abrogated apoptosis reduction in hypoxia, which implied the involvement of autophagy in the protection against apoptosis induced by starvation. Beclin 1 proved indispensable in hypoxia-induced autophagy. These results indicate that autophagy activated by hypoxia in tumors could enhance cancer cells' tolerance to Beclin 1 dependent nutrient deprivation. Using hypoxia preconditioning as a hypoxic model, Song et al demonstrate the significance of hypoxia-induced autophagy in starvation tolerance, which suggests a potential new target for treatment for hepatocellular carcinoma.