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The ears have it: restitution of auricular cartilage

Although much attention is given to utilizing stem cells of mesodermal origin to generate endodermal or ectodermal tissue, a particularly strong body of research pertains to using mesodermal stem cells for generation of mesodermal tissue. Bone, cartilage, and muscle are of specific interest (generation of adipose tissue is not a major goal), and restitution of functional tissue mass may have profound therapeutic benefit. Reconstruction of cartilage is a very attractive goal, but other methods of so doing, primarily surgical transplantation, are constrained by the limited availability of autologous donor sites by the regeneration availability of autologous donor sites. Hence, there is strong motivation for establishing self-generating systems for cartilage regeneration. Mesenchymal stem cells, as obtained from the bone marrow cavity, are proposed as a possible source for cartilage regeneration, but the yield of chondrocytes and ensuing extracellular matrix may be quite limited. In this issue, **Togo et al**¹ (p. 445) examined a primary cartilaginous site, auricular cartilage, as a potential source of stem cells, specifically progenitor cells for cartilage. Chondrocytes were isolated from rabbit auricular cartilage, as was a population of self-renewing progenitor cells from the perichondrial inner ‘cambium’ layer (as distinguished from the outer fibrous layer of the perichondrial sheath). The perichondrial progenitor cells were capable of robust chondrocyte differentiation and proliferation; they were capable of differentiating into adipocytes and osteocytes as well, under appropriate *in vitro* conditions. Using subcutaneous implantation into nude mice, the perichondrial progenitor cells generated an order of magnitude more cartilaginous tissue mass than could mesenchymal stem cells isolated from rabbit bone marrow. In these *in vivo* implantation experiments, a collagen scaffolding ‘sponge’ was used as a reconstitution matrix. Salient features of this study are the first time demonstration of cartilage progenitor cells in auricular perichondrial tissue, and that these perichondrial progenitor cells are more capable of sustained cartilage restitution than are chondrocytes themselves or mesenchymal stem cells. Key questions that now arise are the very long-term stability of cartilage generated from perichondrial progenitor cells (measured in years), and whether such tissue has potential use in restitution of mechanically stressed cartilage, over and above the obvious implications for cosmetic restitution.

Reference

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Macrophage indigestion: impaired phagocytosis of lung surfactant

Lung surfactant is a mixture of phospholipids, proteins, and neutral lipids that is synthesized by alveolar epithelial type II cells. Increased production of lung surfactant has been reported in a number of inflammatory and fibrogenic conditions. Apoptosis of alveolar lining cells is also a normal physiological process for lung tissue homeostasis; impaired regulation of apoptosis has been associated with several pulmonary diseases. Despite growing evidence for a role of increased lung surfactant and apoptosis in pulmonary diseases, the relationship between these two processes is not clear. Lung surfactant could either induce apoptosis or promote the accumulation of apoptotic cells. On the other hand, certain components of lung surfactant, such as SP-A and SP-D, have been reported to increase clearance of apoptotic debris by macrophages. In a study presented in this issue, **Wang et al**¹ (p. 458) directly tested the relationship between increased lung surfactant generation and apoptosis in a rat model. They used exogenous Survanta, which contains natural phospholipids and SP-B and SP-C, but not SP-A and SP-D, at a dose similar to what has been described for silica exposure in rats. The authors showed that pulmonary administration of high doses of Survanta is associated with an increased number of apoptotic lung cells, increased pulmonary macrophage infiltrates, and impaired phagocytic clearance of apoptotic cells. The authors provided three pieces of evidence supporting an impaired clearance of apoptotic cells rather than increased apoptosis as the mechanism accounting for the increased number of apoptotic cells found in the lungs of rats instilled with Survanta: (1) the dose-dependent decrease in apoptotic cell clearance, (2) the reduced clearance of instilled *Listeria*, and (3) the large and foamy appearance of macrophages, suggesting that their impaired function is the result of their active phagocytosis of Survanta. These new results demonstrate an indirect role of lung surfactant on macrophage phagocytosis, which should prompt new studies to determine if it is restricted to specific components and specific doses of the Survanta formulation. It will also be of interest to further

characterize how lung macrophages become incapacitated by an overdose of surfactant.

Reference

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Oval cell migration: irresistible attraction

Oval cells represent a population of multipotent liver progenitor cells that participate in liver regeneration in certain forms of hepatic injury involving concurrent stimulation of liver growth and inhibition of normal mechanisms for liver tissue restoration (ie blockade of the proliferation of hepatocytes). Typically, the experimental stimulus for liver growth is satisfied by partial hepatectomy (PH); inhibition of hepatocyte proliferation is achieved through the use of chemicals that impede or prevent mitotic division of mature hepatocytes (such as 2-acetylaminofluorene, 2-AAF). The 2AAF/PH model¹ of oval cell-mediated liver regeneration is characterized by (i) proliferation of oval cells in or around the portal spaces, (ii) invasion of the lobular parenchyma by the proliferating oval cells, (iii) appearance of transitional cell types and immature hepatocytes, and (iv) maturation of hepatocytes and restoration of normal liver structure. As they proliferate, oval cells migrate from periportal regions into the lobular parenchyma, where they engraft into the hepatic plates and differentiate into hepatocytes. While the activation, proliferation, and hepatocytic differentiation of oval cells has been well documented in experimental models of liver injury and regeneration,² much less is known about the mechanisms that govern oval cell migration into the hepatic parenchyma, homing of these cells to specific zones of the liver, and their engraftment into the hepatic plates. Numerous cellular and tissue features are likely to contribute to these processes, including extracellular matrix proteins, cell adhesion molecules, and chemotactic factors. However, to date no specific signaling molecules have been implicated in the migration and homing of oval cells during liver regeneration.

In the current issue, Jung *et al*³ (p. 477) investigated the potential role of somatostatin (SST) and one of its receptors (SSTR4) in the migration of oval cells using the 2AAF/PH model of liver injury and regeneration.³ SST is a regulatory hormone that exerts its biological activity through a family of receptors (SSTR), and has been implicated in the proliferation, migration, and differentiation of various cell types, including hematopoietic progenitor cells. Based upon these observations, Jung and co-workers hypothesized that SST/SSTR may function in the regulation of oval cell migration and homing.

To address this possibility, these investigators examined SST/SSTR expression and function in the 2AAF/PH model *in vivo* and using isolated/cultured oval cells *in vitro*. The results show that SST expression increased *in vivo* after 2AAF/PH, during the period of oval cell proliferation. In cell culture assays using isolated oval cells, SST did not induce cell proliferation, but did promote migration of oval cells in a transwell assay system in a dose-dependent manner. Although oval cells were found to express several SSTR family members, only SSTR4 was uniquely expressed by this population of cells, suggesting a possible role for SSTR4 in SST-mediated oval cell migration. Confirmation of the importance of SSTR4 was obtained in cell migration studies that employed an inhibitory anti-SSTR4 antibody. When SSTR4 activity was inhibited, SST-mediated migration of oval cells was severely impeded.

With the advent of regenerative medicine and its potential in the treatment of numerous human diseases,⁴ there is a newfound interest in the exploration of mechanisms that control the activation, proliferation, migration, homing, and differentiation of stem-like progenitor cell populations. Liver progenitor cells have been studied for several decades, and their participation in liver regeneration has been well documented. Thus, liver represents an excellent model for investigation of the mechanisms that regulate these cellular processes during progenitor cell-mediated tissue repair/regeneration. Jung *et al*³ provide the first evidence for the involvement of specific regulatory molecules (SST/SSTR4) in oval cell migration and homing in the liver. This study forms the basis for additional investigations of other signaling molecules in the movement of oval cells during liver repair/regeneration, as well as studies to directly address the role of SST/SSTR4 in oval cell migration and homing *in vivo*.

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References

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- 3 Jung Y, Oh S, Zheng D, *et al.* A potential role of Somatostatin and its receptor SSTR4 in the migration of hepatic oval cells. *Lab Invest* 2006; 86:477–489.
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