Adipose Stem Cell Therapy for Chronic Pancreatitis

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Chronic pancreatitis (CP) is a persistent inflammation of the pancreas that disrupts normal structure and functions. The absence of well-defined criteria for early diagnosis of CP and the multi-factorial features of the disease render it difficult to develop an effective treatment. Stem cell therapy has emerged as a promising therapy for autoimmune diseases and may represent a therapeutic option for CP treatment. In this issue of *Molecular Therapy*, Sun et al.[1] report that the infusion of adipose-derived mesenchymal stem cells (ASCs) into an experimental murine model of CP inhibited the progression of CP, greatly attenuated pancreatic damage, and reduced fibrosis and cell death. The authors argue that the infused ASCs likely differentiated into acinar-like cells that suppressed inflammation and fibrosis, thus limiting pancreatic damage. The results of the study could have an important impact upon individuals with CP who currently lack effective therapeutic options.

CP is characterized by "a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress".[2] CP is mainly characterized by persistent and irreversible inflammation of the pancreas, leading to a progressive loss of exocrine and endocrine function due to recurrent episodes of acute pancreatitis and chronic inflammation. The mechanism involved in the pathophysiology of CP consists of a necrosis-fibrosis loop, owing to severe acute pancreatitis, followed by activation and recruitment of inflammatory cells and the activation of pancreatic stellate cells (PSCs), myofibroblast-like cells residing in the exocrine areas of the pancreas. Following activation, PSCs migrate to sites of injury and participate in the regenerative process. During this process, the induction of oxidative stress leads to acinar cell necrosis, inflammation, and fibrosis. Finally, ductal dysfunction leads to the formation of protein plugs and upstream ductal obstruction. So far, the main treatment options for CP have focused on alleviating the resulting symptoms and pain management, owing to its multimodal aspects.[3]

In the new study, Sun et al.[1] report that a single low-dose ASC infusion into a murine model of CP alleviates disease progression and confers protection to the injured pancreas. Systemic injection of ASCs suppressed pancreatic fibrosis, as revealed by the attenuation of collagen deposition and α-SMA (smooth muscle actin) expression, which are key contributors to the process of fibrosis. Further data showed attenuated inflammation, as revealed by reduced infiltration by inflammatory macrophages, and sustained protection against pancreatic cell death when compared to untreated mice. In a series of tracking studies, the authors clearly demonstrated that the infused ASCs selectively and specifically migrated to the injured pancreas, while there was no evidence of their presence in other tissues. Once localized to the pancreas, the ASCs differentiated into acinar-like cells, as revealed by co-staining of ASC-GFP$^+$ cells with amylase. The pancreatic acinar cell synthesizes, stores, and secretes digestive enzymes. This finding provides a key insight into the main mechanism underlying the functional and regenerative events where cell-to-cell contact and the release of trophic factors by the microenvironment seem to be driving ASC differentiation. This was confirmed in a co-culture assay of ASCs with acinar cells in an acinar cell-polarized medium, confirming the tendency of ASCs to differentiate into acinar-like cells, based on analysis of their gene expression profile and loss of stem cell attributes. Other investigators have already described similar effects; ASCs have been reported to differentiate into acinar-like cells when co-cultured with existing acinar cells. Similar results have been reported using rat bone marrow mesenchymal stem cells (MSCs), human ASCs, and human amniotic epithelial cells.[4] Interestingly, this tissue repair phenomenon likely arises owing to an intrinsic paracrine effect exerted by ASCs,[5–7] allowing their differentiation into acinar-like cells.

The novel and relevant aspects of this paper can be summarized as follows: (1) the use of a low single dose of ASCs (4×10^5 cells) administered to mice; (2) treatment at a later stage of disease (e.g., 3 weeks after establishment of the disease); (3) the persistence of the systemically infused ASCs within the injured pancreas (e.g., 14 days post-treatment); and (5) the differentiation of ASCs into acinar cells.

Whereas Sun et al.[1] clearly demonstrated that the injected ASCs migrated to the damaged pancreas with high efficiency, other investigators have reported less extensive migration of MSCs for the treatment of autoimmune diseases, such as type 1 diabetes (T1D).[8] Others have reported that locally, but not systemically, administered MSCs delayed islet allograft rejection when co-transplanted with allogenic islets, and generated a local immunoprivileged environment, thereby exerting alloimmune immunomodulatory properties.[9] Taken together, these data emphasize the immunoregulatory effects exerted by the injected stem cells, which has been shown to derive from the expression by MSCs of the immunoregulatory molecule PD-L1.[10–12]

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Further studies focusing on the fate of the injected stem cells and their prospective impact on the pancreatic microenvironment should enrich our understanding of the tissue repair mechanisms. Notably, it remains unclear whether there were any effects upon endogenous cells populations or whether the infused ASCs might have differentiated into endocrine-like cells.

MSCs have emerged as an attractive cell source for the treatment of chronic invalidating diseases (e.g., diabetes, liver diseases, and pancreatic and kidneys disorders) owing to their anti-inflammatory properties. Due to their easy collection and availability, ASCs have become a promising emerging therapy platform for CP. In particular, their specific homing to the sites of injury and their local differentiation into acinar-like cells renders them an attractive therapeutic tool, but the new study does not study whether the ASCs exert direct regenerative activity. In addition, the possibility of detrimental events raises a potential safety concern. As with MSCs, ASCs could constitute a potential tumorogenicity risk, mainly due to the extended in vitro expansion, leading to the risk of chromosomal instability and malignant transformation.[11] Moreover, their possible transformation into other mesenchymal lineages or unwanted tissues could limit their potential translation into the clinic. Future studies will certainly focus on investigating possible detrimental side effects caused by ASC therapy as well as pain management, because little is known if it was aggravated or improved by the therapy. Nevertheless, the present findings represent an important addition to the field of regenerative medicine by documenting an extremely beneficial effect afforded by a single low-dose infusion of ASCs, which successfully halted progressive CP-associated necro-inflammatory processes.[13]

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