

The Fibrocyte's Role in NSF

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In both healing wounds and in the fibrotic lesions in fibrosing diseases such as congestive heart failure and pulmonary fibrosis, a subset of circulating monocytes leaves the blood, enters the tissue, and differentiates into fibroblast-like cells called fibrocytes. Fibrocytes can promote angiogenesis, secrete factors such as TGF-beta that activate resident fibroblasts, and differentiate into contractile cells called myofibroblasts. Fibrocytes express markers such as CD34 that are characteristic of hematopoietic cells, as well as markers such as collagen I that are characteristic of stromal cells. This dual positive phenotype can allow one to identify fibrocytes in a histology section. A variety of factors can promote or inhibit fibrocyte differentiation. For instance, fibrocyte differentiation is inhibited by serum amyloid P (SAP), a pentameric protein that is similar to carbohydrate-reactive protein (CRP) and which is made by the liver and secreted into the blood. In animal models, SAP injections can inhibit the development of fibrosis, suggesting that fibrocytes play an important role in fibrosis.

Fibrocytes have been found in the fibrotic lesions associated with Nephrogenic Systemic Fibrosis (NSF). The exposure of some renally-insufficient patients to gadolinium-containing magnetic resonance imaging contrast agents such as Omniscan has been associated with these patients developing NSF. To determine if Omniscan can affect the differentiation of monocytes into fibrocytes, peripheral blood mononuclear cells (PBMCs) from NSF patients, hemodialysis patients without NSF, and healthy, renally sufficient controls were exposed to Omniscan in a standardized *in vitro* fibrocyte differentiation protocol. When added to PBMCs, Omniscan generally had little effect on fibrocyte differentiation. However, 10^{-8} - 10^{-3} mg/ml Omniscan reduced the ability of SAP to decrease fibrocyte differentiation in PBMCs from 15 of 17 healthy controls and one of three NSF patients. Omniscan reduced the ability of SAP to decrease fibrocyte differentiation from purified monocytes, indicating that the Omniscan effect does not require the presence of other cells (such as T cells) in the PBMC. Omniscan also reduced the ability of a different fibrocyte differentiation inhibitor, interleukin-12, to decrease fibrocyte differentiation. These data suggest that Omniscan can interfere with the regulatory action of signals that inhibit the differentiation of monocytes to fibrocytes.

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