Q3 1025 Suppression of basal and multi-walled carbon nanotube-induced lung inflammation and fibrosis by Nrf2

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Exposure to multi-walled carbon nanotubes (MWCNT) has raised a concern regarding its potential health impact on humans, as certain forms of MWCNT induce prominent and rapid-onset lung inflammation and fibrosis in experimental animals. However, the molecular mechanisms by which MWCNT induce lung pathology remain largely unclear. Oxidative stress has been suggested as one of the major mechanisms of MWCNT toxicity, and the transcription factor Nrf2 serves as a critical regulator of the body's defense against oxidative stress. Therefore, in this study we determined whether Nrf2 functions in the occurrence and progression of inflammation and fibrosis in mouse lungs under basal and MWCNT-challenged conditions. In wild-type lungs, MWCNT exposure resulted in oxidative stress indicated by elevated levels of reactive oxygen species (ROS) production and oxidative stress indicators 8-OHdG, γH2AX and 4-HNE, activation of Nrf2 signaling, and up-regulation of Nrf2 target genes, such as the cytoprotective genes HO-1 and NQO1. In Nrf2 deficient lungs, remarkably higher levels of inflammation and fibrosis, as well as oxidative stress, were detected under both basal and MWCNT-exposed conditions, than in wild-type lungs. These data reveal that oxidative stress promotes MWCNT-induced lung inflammation and fibrosis, and Nrf2 plays a protective function in this process. Meanwhile, Nrf2 has a basal activity and functions in maintaining lung homeostasis under physiological conditions. Our study provides a new mechanism for MWCNT-induced pathologic effects through reactive oxidants in the lungs, and offers direct evidence supporting the defense against oxidative stress, inflammation, and fibrosis in mouse lungs by Nrf2.

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Q3 1026 The Kielin/Chordin-like Protein KCP Attenuates Nonalcoholic Fatty Liver Disease in Mice

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Non-Alcoholic Fatty Liver Disease (NAFLD) is among the most common causes of chronic liver disease and is increasing at an alarming rate with the rising rate of obesity and metabolic disease in the developed world. A variety of signaling pathway are known to influence the rate of lipid deposition in liver, a process known as hepatic steatosis. Among these is the Transforming Growth Factor (TGF) superfamily of ligands, which function through the SMAD family of second messengers. The Kielin/Chordin-like Protein (KCP) is a large secreted protein that can enhance Bone Morphogenetic Protein (BMP) signaling while suppressing TGF-beta mediated signaling in cell culture and in genetically modified mice. In this report, we show that aging KCP mutant mice are increasingly susceptible to developing hepatic steatosis and liver fibrosis. When young mice are put on a high fat diet, KCP mutant mice are also more susceptible to developing liver pathology, compared to their wild-type littermates. Furthermore, mice that express a Pepck-KCP transgene in the liver are resistant to developing liver pathology even when fed a high fat diet. Analyses of liver tissues reveal a significant reduction of P-Smad3, consistent with a role for KCP in suppressing TGF-beta signaling. Whole transcriptome analyses shows that livers from KCP mutants fed a normal diet are more like wild-type livers from mice fed a high fat diet. However, the KCP transgene can suppress many of the changes in liver gene expression that are due to a high fat diet. These data demonstrate that shifting the TGF-beta signaling paradigm with the secreted regulatory protein KCP in liver tissue can significantly alter the liver pathology in aging mice and in diet induced NAFLD.

Q3 1027 Pirfenidone reverses murine chronic graft versus host disease

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Skin and internal organ fibrosis is common in chronic graft versus host disease (cGVHD). In particular, bronchiolitis obliterans syndrome (BOS) and scleroderma resulting from fibrotic bronchiolar and cutaneous response, respectively, are two devastating outcomes for cGVHD patients. Because fibrotic manifestations often are considered irreversible and progressive, pulmonary fibrosis may lead to lung transplant; therefore, new therapies are urgently needed. Pirfenidone is a Food and Drug Administration approved anti-fibrosis drug for idiopathic pulmonary fibrosis. Here, we evaluated whether Pirfenidone could reverse established cGVHD in 2 pathophysiologically distinct murine cGVHD models: a multi-organ system model that induces BOS that is etiologically linked to antibody deposition driven by cGVHD-induced germinal center reaction, and a model in which severe scleroderma is the major manifestation. In the BOS model, we found that cGVHD is associated with increased F4/80$^+$ macrophage infiltration and TGF-β production in the collagen deposited area. Pirfenidone restored pulmonary function of cGVHD mice with established fibrosis and reversed pathologic changes in lung. Germinal center reaction, macrophage infiltration and TGF-β production were normalized by Pirfenidone. However, Pirfenidone did not affect sheep red blood cell induced germinal center reaction, suggesting Pirfenidone's effect on germinal center reaction in cGVHD mice is not through direct immune-regulation, but through a cGVHD dependent mechanism. In the sclerodermatous cGVHD model, Pirfenidone decreased the number of IL-17–secreting cells, ameliorated skin sclerosis, alopecia, and cutaneous erosion and improved survival. Taken together, our data suggest that Pirfenidone reverses cGVHD through its anti-fibrosis and immune-regulating functions, and highlights its potential therapeutic utility for cGVHD.

Q3 1028 Mature adipocytes regulate dermal fibrosis

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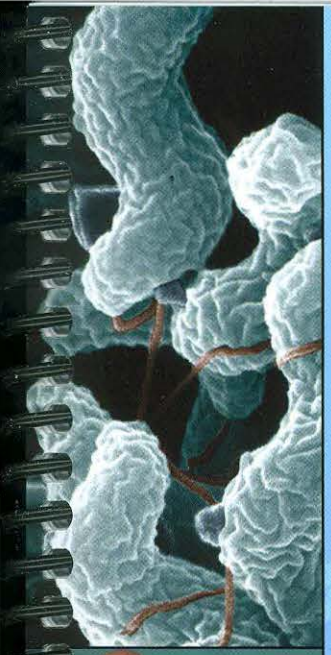
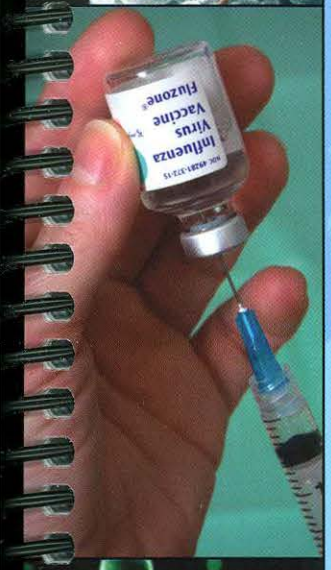
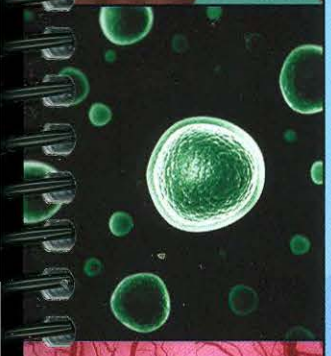
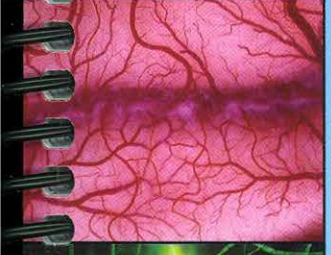
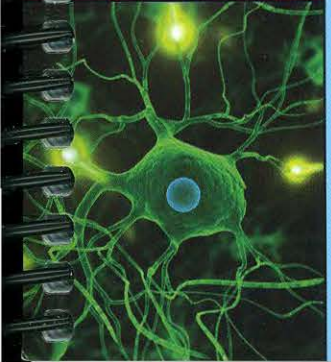
Fibrosis, a chronic pathology of connective tissue, develops from disruptions in stromal cell homeostasis. A notable feature of skin fibrosis associated with scleroderma is expansion of the dermis and increased collagen deposition accompanied by an atrophy of dermal adipose tissue, both in humans and in animal models of fibrosis. Our laboratory has shown that mature adipocytes have profound effects on the function of dermal fibroblasts, as they promote fibroblast migration and dermal regeneration following acute wounding. While others have indicated that adipocytes can generate skin fibroblasts during fibrosis, how mature adipocytes modulate fibroblast function in the skin and whether the loss of adipocytes contributes to fibrosis is not well understood. Here, we show that bleomycin-induced fibrosis in mice depletes the adipocyte stem cell niche concomitant with expansion of dermal ECM. We explore the role of mature adipocytes on fibroblast function during fibrosis using mouse models that allow specific ablation of dermal adipocytes and in vitro assays. These studies are the first to define a functional role for secreted factors derived from mature adipocytes in maintaining collagen homeostasis in the skin and preventing fibrosis.











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