Tumor suppressor may attenuate fibrotic disease

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New research reveals a critical cellular signaling pathway that is responsible for generating excess connective tissue in multiple organs, similar to what is seen in human patients with scleroderma. The study, published by Cell Press in the February issue of the journal *Developmental Cell*, also reveals an intriguing but unexpected regulatory role for a tumor suppressor gene in fibrotic disease.

Platelet derived growth factors (PDGF) regulate the proliferation, survival, migration and differentiation of cells and play a critical role during embryonic development. However, the consequences of excess PDGF signaling are not very well understood.

"Aberrant PDGF signaling has been implicated in diverse fibrotic conditions where connective tissue cells called fibroblasts proliferate and deposit excessive connective tissue, leading to progressive scarring and organ dysfunction," says senior study author, Dr. Philippe Soriano from the Mount Sinai School of Medicine in New York."For example, human scleroderma patients, who characteristically exhibit widespread fibrosis, possess antibodies that activate PDGF receptors."

Dr. Soriano and Dr. Lorin E. Olson, who conducted this work initially at the Fred Hutchinson Cancer Research Center in Seattle and then pursued it at Mount Sinai, developed a mouse model in which they could selectively activate the PDGF receptor alpha (PDGFR?) during embryonic development and in adult animals.

The researchers found that elevated PDGFR? signaling led to aberrant overgrowth of connective tissue. In adults, this led to a progressive fibrosis in multiple organs. Interestingly, loss of the tumor suppressor Ink4a/Arf dramatically accelerated the development of fibrotic lesions. This finding suggests that cells may attenuate the effects of PDGFR? signaling through an Ink4a/Arf-dependent mechanism.

The study provides insight into the signaling pathways involved in connective tissue disease and highlights a new role for tumor-suppressors in the regulation of fibrotic conditions. "Our findings provide direct evidence that increased PDGFR? signaling can be sufficient to drive systemic connective tissue disease in organ systems that are relevant to human scleroderma," concludes Dr. Soriano. "The work also establishes an excellent animal model for testing novel therapeutic approaches for blocking aberrant PDGFR? signaling in human disease."

Source: Cell Press