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Attenuation of Radiation-Induced Lung Fibrosis by Inhibition of Platelet-Derived Growth Factor in a Mouse Model

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Progressive irreversible fibrosis is one of the most clinically significant consequences of ionizing radiation in normal tissue. Fibrotic diseases can occur in many organs, especially in lungs. Pulmonary fibrosis is a progressive condition, associated with a gradual loss of tissue architecture and normal cell activities, leading to end-stage organ dysfunction. However the pathogenesis of the pulmonary fibrosis is complex and poorly understood. Several cytokines were shown to play important roles in the fibrotic process, including platelet-derived growth factor, transforming growth factor beta, tumor necrosis factor alpha and interleukin-1. In the present study we focused on platelet-derived growth factor, because the importance of this pathway in the pathogenesis of pulmonary fibrosis is supported by a number of findings. We established a mouse model for ionizing radiation induced lesions. The fibrotic development was monitored directly with non-invasive radiological morphological characterization (high resolution computed tomography), histology, immunohistochemistry, and indirectly with overall survival and clinical criteria. It is demonstrated that 1) high-resolution computed tomography is a suitable technique to monitor radiation-induced lung fibrosis in the mouse model; 2) direct intervention of the fibrogenic cytokines/growth factors cascade with a potent and selective PDGF-receptor tyrosine kinase inhibitor, SU9518, attenuated radiation-induced pulmonary fibrosis. However, it is unlikely that single pathway inhibition can completely prevent lung fibrosis in humans, considering the intricate genetic networking. Nevertheless the PDGF RTKIs that are undergoing clinical studies or are approved for certain oncological indications (e.g., SU11248 or Gleevec [STI571/Imatinib]) may have appropriate potency, selectivity, and safety profiles for the treatment of fibrosis-related diseases. This could be of benefit for lung cancer patients to enhance the therapeutic efficacy by simultaneously reducing the radiation-induced undesired side effects.