NOX4 implicated in fibrosis

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Genkyotex, a developer of selective NOX enzyme inhibitors, announced today the publication of data showing that GKT137831, a first in class NOX1 and 4 inhibitor, was able to reverse lung fibrosis associated with aging in a new model of idiopathic pulmonary fibrosis. Collaborators led by Professor Victor Thannickal at the University of Alabama at Birmingham published the results in the April 9, 2014 issue of *Science Translational Medicine*. Genkyotex is investigating GKT137831 in a Phase II trial in patients with diabetic nephropathy, another progressive fibrotic disease.

The incidence of mortality and morbidity associated with fibrotic disorders is increasing worldwide, and aging is an important risk factor. Idiopathic pulmonary fibrosis (IPF) is a rapidly progressive and fatal lung disease, with no effective treatment or cure. The incidence of IPF also increases with age and is characterized by clusters of myofibroblasts, which cause remodeling and scarring of the alveoli.

Data from these studies show that in contrast to young mice, aged mice developed irreversible lung fibrosis in response to injury. In aged mice, myofibroblasts (the key effector cell type and a central mediator of fibrosis) acquired a senescent phenotype and resistance to the natural cell death mechanism, apoptosis. These changes were mediated by NOX4 and could be reversed by genetic or pharmacological inhibition of NOX4.

"Our results provide preclinical data supporting the potential role for therapeutic agents that inhibit NOX4 for age-associated fibrotic

disorders and provide new insights into redox mechanisms that control profibrotic effects of fibroblast senescence," explained Victor J. Thannickal, MD, Professor of Medicine and Pathology, Director, Division of Pulmonary, Allergy, and Critical Care, University of Alabama (USA). "Specifically, we were able to demonstrate that established fibrosis in lungs of aged mice is partially reversed by administration of GKT137831, a new NOX inhibitor from Genkyotex."

Details of the Studies

The capacity for fibrosis resolution following bleomycin-induced lung injury was investigated in young (2 months) and aged (18 months) mice. Persistent fibrosis in lungs of aged mice was characterized by the accumulation of senescent and apoptosis-resistant myofibroblasts. These cellular phenotypes were sustained by alterations in cellular redox homeostasis resulting from elevated expression of the enzyme NOX4 and an impaired capacity to induce Nrf2 (NFE2-related factor 2)-mediated antioxidant responses. Moreover, lung tissue taken from human subjects with IPF also demonstrated this NOX4-Nrf2 imbalance.

Pharmacological targeting of NOX4 with GKT137831 in aged mice with established fibrosis attenuated the senescent, antiapoptotic myofibroblast phenotype and led to a reversal of persistent fibrosis. Mice treated with GKT137831 also showed improved survival.

"These data confirm previous positive results seen with GKT137831 in a range of preclinical models of fibrotic diseases in the lung, liver and kidney," noted Ursula Ney, CEO of Genkyotex. "The role of NOX enzymes in fibrotic disorders is beginning to be unraveled and we believe our first in class NOX inhibitors have broad potential in a range of fibrotic diseases."

More information: "Reversal of Persistent Fibrosis in Aging by

Targeting Nox4-Nrf2 Redox Imbalance" Louise Hecker, Naomi J. Logsdon, Deepali Kurundkar, Ashish Kurundkar, Karen Bernard, Thomas Hock, Eric Meldrum, Yan Y. Sanders, and Victor J. Thannickal
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