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Commentary

Putting the brakes on age-related idiopathic pulmonary fibrosis: Can Nox4 inhibitors suppress IPF?

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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fatal lung disease that primarily affects patients over fifty years of age. These individuals present with a variety of symptoms of respiratory failure, including worsening dyspnea, cough, and decreased exercise tolerance. Additionally, these patients often present with bilateral, inspiratory crackles and demonstrate finger clubbing (Raghu et al., 2011). As idiopathic pulmonary fibrosis progresses, the patient's lung compliance becomes increasingly compromised, resulting in respiratory failure and death. Between 50% and 80% of patients die within five years of their initial diagnoses (Bjoraker et al., 1998; King et al., 2011). Additionally, annual mortality attributable to IPF is higher than that due to several cancers (Jemal et al., 2007). While risk factors like cigarette smoking have been associated with idiopathic pulmonary fibrosis, none have consistently presented with IPF to suggest a causative effect (King and Nathan, 2013; Camelo et al., 2014).

Although IPF is of great clinical significance, few treatment modalities currently exist for these patients. At present, evidence-based guidelines for the management of IPF state that medications that can usually treat fibrotic diseases are ineffective for the most patients with IPF (Raghu et al., 2011). In fact, the only method that can cure patients with IPF is a direct lung transplant (Raghu et al., 2011).

Despite IPF's great clinical significance, its pathogenesis still remains unexplained. Recent research has suggested that aberrant wound healing in response to a variety of irritants may ultimately cause pulmonary fibrosis (King and Nathan, 2013). At present, the lesions of pulmonary fibrosis are believed to stem from the senescence of lung epithelial cells, which then deregulate and activate lung fibroblasts. Under pathologic conditions, coupled with high concentration of TGF-β, the fibroblasts become activated and can differentiate into myofibroblasts, which then overproduce extracellular matrix (ECM) proteins (Camelo et al., 2014). Histologically, IPF presents with patches of fibroblastic foci with temporal heterogeneity (King et al., 2001). These foci are comprised of myofibroblasts, which damage the alveolar epithelium through continuous fibroblastic proliferation and ECM production (Camelo et al., 2014; King et al., 2001). Between these islands of myofibroblasts are areas of dense fibrosis and chronic inflammation (Katzenstein and Myers, 1998).

A recent study by Hecker et al. compared the development of lung pathology in both young and aged mice (2 months and 18 months, respectively) after undergoing pulmonary injury and has proposed a mechanism to explain the increased prevalence of IPF and persistent fibrosis in older patients (Hecker et al., 2014). Furthermore, they have demonstrated that pharmacological silencing of Nox4 (NADPH oxidase-4), an enzyme that generates reactive oxygen species, can reverse the persistent fibrosis that presented in older mice.

When Hecker et al. first began to examine young and aged mice's responses to lung injury, they compared the severity of fibrosis in response to an intratracheal exposure to bleomycin, a chemotherapy medication that induces alveolar epithelium injury. Both groups of mice exhibited similar levels of collagen deposition three weeks after the injury, which demonstrated that the initial, fibrogenic, healing response was intact and of similar magnitude for the young and the aged. However, after the primary fibrotic response, the older mice presented an impaired capacity for fibrosis resolution, as they failed to return to normal body weights and still had myofibroblasts present in the fibrotic regions two months after the original injury. Additionally, these myofibroblasts still expressed p16INK4A, a senescence marker. The lung tissue of aged mice showed a lower level of apoptosis than the tissue of younger mice. Furthermore, the cells from older mice proved to be resistant to apoptosis induced by staurosporine.

The authors found that within fibroblastic foci of IPF lungs, the cells expressed p16INK4A and p21Cip1, two senescence markers, and also exhibited apoptosis resistance. However, only cells on the periphery

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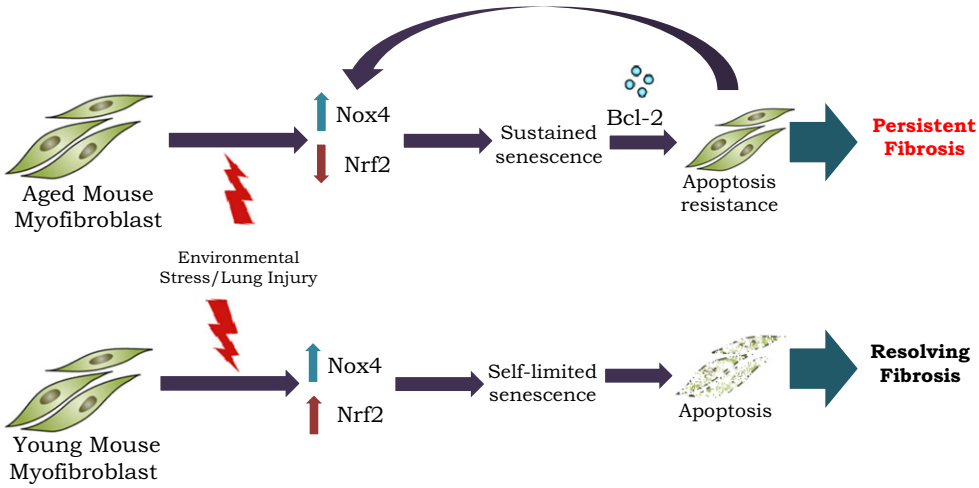

Fig. 1. Comparative proposed mechanisms for pulmonary fibrosis in young and aged mice after lung injury.

expressed cell proliferation markers. Tissue samples from mice with IPF expressed higher levels of Nox4, an enzyme involved in producing hydrogen peroxide, a reactive oxygen species that in this case, likely induces signaling cascades to convert cells into a myofibroblast phenotype. Additionally, the antioxidant transcription factor Nrf2 is only present in low levels in fibroblastic foci. Because most of the Nrf2 protein was localized in the cytoplasm and was deficient in the nucleus of senescent cells, the authors suggested that the decreased Nrf2 response is due to a defect in this protein's nuclear trafficking. Together, the imbalanced expression of Nox4 and Nrf2 promotes the production and maintenance of ROS-mediated damage.

Normally, the antioxidant activities of Nrf2 maintain homeostasis by opposing the ROS production mediated by Nox4. However, the authors presented data indicating that in IPF, this delicate balance shifts in favor of Nox4, especially in aged lung fibroblasts. After inducing lung injury in young and aged mice, the authors compared the levels of Nrf2 activation between the two groups. While the lungs from young mice showed Nrf2 induction, lung tissue from older mice demonstrated significantly diminished levels of Nrf2 expression. Consequently, these older mice also showed significantly increased hydrogen peroxide levels within their fibroblasts. Similar results were exhibited by fibroblasts from non-IPF, aged mice, as well as by IMR90 lung fibroblasts in a replicative senescence model. Taken together, these results show that Nrf2 induction is deficient in older cells, which could further exacerbate the oxidative stress present in the lungs affected by IPF.

The authors present data supporting that inhibition of Nox4 by siRNA knockdown or treatment with the pharmacological agent GKT137831 can reverse senescence and apoptosis resistance in IPF fibroblasts, as well as in mice from both age groups. With in vivo experiments, mice treated with GKT137831 recovered their normal body and lung weights, and histological samples from their lungs showed fewer fibroblastic foci, as well as a decreased amount of senescence marker expression.

Taken together, these results indicated that with increased age, myofibroblasts that developed in response to an injury persist for an excessive amount of time because they do not undergo apoptosis normally. Instead, the altered homeostasis of Nox4 and Nrf2 allows oxidative damage to induce the persistence of myofibroblasts and prevents the clearance of these cells and their associated ECM proteins (Fig. 1).

The publication by Hecker et al. represents a major and much-needed advance in the understanding of idiopathic pulmonary fibrosis. Their proposed mechanism provides several targets for further research, as well as possible targets for therapy. Because idiopathic pulmonary fibrosis is such a severe disease with a bleak prognosis, the authors' preclinical data for GKT137831 provides great hope for the development of effective therapeutic means of managing and potentially reversing the progress of this illness.

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