

Healing the scars of life—targeting redox imbalance in fibrotic disorders of the elderly

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Organ fibrosis is a leading cause of death in developed countries with effective treatments still missing (1). Fibrotic disorders, affecting major organs like lungs, heart, liver or kidneys, account for up to 45% of all deaths in the United States, and aging is considered as their most important universal risk factor (2).

In order to unravel new therapeutic options for fibrotic diseases, the concept of ‘core’ and ‘regulatory’ pathways to fibrosis was introduced (3). This concept suggested that core pathways in fibrosis, like the onset of fibrogenesis, are more evolutionary conserved than regulatory pathways being more organ-specific. Thus, new therapeutic approaches should preferentially aim at targeting such core pathways. As a consequence, initial positive results from a specific intervention in a specific organ should be confirmed rather in another organ type than with another stimulus in order to improve chances to show efficacy of a drug in subsequent clinical trials (3). The response to cellular oxidative stress, which is especially impaired in older people, might represent such a core pathway to organ fibrosis with promising therapeutic implications, as suggested by a recent hallmark publication by Hecker and colleagues (4).

Oxidative stress resulting from an inappropriate redox balance was shown to induce fibrosis in different organs like the liver (5) or the lung (6). Members of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) family catalyze the formation of reactive oxygen species (ROS). The ROS-forming enzyme NOX4 was shown to mediate myofibroblast differentiation in lung injury thereby supporting tissue fibrogenesis (7). In liver fibrosis a possible role for NOX1 and NOX4 was suggested as well (8). A small molecule inhibitor targeting both NOX1 and NOX4, GKT137831 (Genkyotex S.A. Geneva, Switzerland),

showed promising results in two different models of liver fibrosis (8) and is currently investigated in patients with diabetic nephropathy (ClinicalTrials.gov NCT02010242).

In a very elegant approach Hecker and colleagues addressed the efficacy of this inhibitor in a mouse model of idiopathic pulmonary fibrosis (IPF) (4). IPF is a chronic and ultimately fatal lung disease with increasing incidence and prevalence in elderly patients (9). The authors raised the assumption that the inability to translate the effectiveness of numerous drug candidates from bench to bedside owes to the predominant usage of young mice for pre-clinical trials that have a high capacity for recovery from injury (4). In fact, in a model of liver fibrosis induced by repetitive injections of carbon tetrachloride for 6 weeks, young (6-12 weeks old) mice recover as early as 4 days after cessation of injury and completely resolve hepatic fibrosis after 7 days (10). To circumvent this issue in the model of IPF, both young mice (2 months) and aged mice (18 months) were subjected to bleomycin-induced lung-injury (4). Two to three weeks after treatment with bleomycin, an antibiotic and anticancer drug, a peak of fibrosis was observed in the mouse model. A very important finding was that the resolution of fibrosis throughout a period of four months after onset was impaired in aged mice, which could be attributed to the acquisition of a senescent and apoptosis-resistant myofibroblast phenotype. Following up former results from the same group (7) the investigators described an increased expression of NOX4 in fibroblasts isolated from human IPF lung tissue (4). Furthermore, the antioxidant transcription factor NRF2 was induced in fibroblasts isolated from young mice but decreased in aged fibroblasts, an observation which also correlated with mRNA expression of NRF2-responsive

genes. The resulting NOX4-NRF2 imbalance is thought to mediate the senescent and apoptosis-resistant phenotype of aged myofibroblasts. By the use of the NOX1/4 inhibitor GKT137831 a role of NOX4 for this phenotype was demonstrated. Both genetic and pharmacological targeting of NOX4 at the peak of fibrosis resulted in an attenuation of the senescent, anti-apoptotic phenotype and reversal of persistent fibrosis. Moreover, survival of aged fibrotic mice was ameliorated by curative treatment with GKT137831.

The strength of the present study is the detailed mechanistic insight, spurring further investigations on the therapeutic potential of the NOX inhibitor GKT137831 for IPF or other (age-related) fibrotic disorders. As NOX enzymes were shown to be relevant for fibrosis of several organs (4,8,11), this component seems to be part of a core pathway to fibrosis. This study also highlights the importance of investigating such core pathways in the context of aging, as balance of pro-oxidative and anti-oxidant mechanisms strikingly varied with the age of the animals.

While the work by Hecker and colleagues clearly supports to target oxidative stress responses in myofibroblasts for fibrotic disorders, other core pathways may also hold promising therapeutic potential. For instance, blocking α_v integrin on myofibroblasts was demonstrated to effectively ameliorate fibrosis progression in different organs (12). Moreover, inflammation is recognized as a driving force of fibrogenesis in several organs and crucial for fibrosis resolution (13). Thus, targeting critical pathways of inflammatory cell recruitment may also work in different fibrotic diseases (14). In a recent study we have shown that in liver fibrosis the C-C motif chemokine ligand 2 (CCL2)-dependent recruitment of the pro-inflammatory Ly-6C⁺ monocyte subset counteracts fibrosis resolution in mice (10). Administration of a pharmacological inhibitor of CCL2, mNOX-E36 (Noxxon Pharma AG, Berlin, Germany), accelerated regression from liver fibrosis after toxic or metabolic liver injury in mice (10). The human 'counterpart' NOX-E36 is already being tested in a phase II clinical trial in diabetic nephropathy (ClinicalTrials.gov NCT01547897). In addition, an inhibitor of the CCL2-receptor CCR2, cenicriviroc (Tobira Therapeutics Inc., San Francisco, USA), is currently explored in patients with non-alcoholic steatohepatitis and liver fibrosis (ClinicalTrials.gov NCT02217475).

In conclusion, several interesting studies revealed novel perspectives in addressing fibrotic disorders, which justify further investigation in clinical trials. In order to maximize the chances for successful new drug development in organ

fibrosis, promising new therapeutic avenues should target core pathways of fibrogenesis such as the imbalance of ROS generation and antioxidant mechanisms affecting apoptosis or senescence in myofibroblasts. Importantly, preclinical models for early antifibrotic drug testing should not only have similar histological features and molecular characteristics (e.g., NOX4 induction in IPF) as the human disease, but should also consider aging as an important factor in fibrogenesis.

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