Remission of fibrosis: rage to the rescue

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Abstract

Idiopathic pulmonary fibrosis (IPF) is characterized by a progressive and permanent decline of lung function that eventually leads to expiry. A study published in 2017 performed by Kumar et al. revealed that the disease may not be as irreversible as was once believed. The research discovered a novel role for the receptor for advanced glycation end-products (RAGE) in which it acts as a master regulator for DNA double-strand break repair. In doing so, Kumar et al. may have made a breakthrough that could redefine the translational approaches of IPF.

Keywords RAGE · DNA repair · Fibrosis · Nucleus · RAGE knockout

Idiopathic Pulmonary Fibrosis (IPF) is a fatal chronic disease characterized by a progressive and permanent decline of lung function (Kim et al. 2006). Its incidence is increasing with a mortality rate of approximately 50% in 4–5 years after onset. IPF is fixing to be one of the most critical chronic diseases society will face in the coming years, and yet, despite the severe threat posed by IPF, the complex mechanisms involved in its formation remain unknown (Kim et al. 2006). Lungs are frequently exposed to oxidative stress and reactive oxygen species (ROS), causing higher levels of DNA defects in pulmonary cells (Rodier et al. 2009). Evidence shows that an accumulation of defects in DNA exacerbates IPF; therefore, an efficient method of DNA repair could be essential for proper lung function (Rodier et al. 2009).

A 2017 study by Kumar et al. examined a novel DNA damage response in which the nuclear isoform of the Receptor for Advanced Glycation End-products (nRAGE) is a key regulator of double-stranded break (DSB) repair (Kumar et al. 2017). Historically, RAGE has been studied in the context of its role as a membrane-bound receptor (Neeper et al. 1992). As a pattern recognition receptor, it induces multiple pro-inflammatory pathways, including

the MAP kinase and NF- κ B pathways (Chavakis et al. 2003; Xie et al. 2013). Exploring the physiological relevance of nRAGE in the context of IPF is unprecedented, and demonstrates the ingenuity of this work.

Kumar et al. utilized RAGE-knockout mice, which results in pulmonary fibrosis, to explore the roles RAGE plays in mice lungs (5). The morphology of the RAGE^{-/-} mouse lungs displayed cellular senescence, accumulation of fibrotic tissue, and an increased, age-dependent incidence of lung carcinomas. Cultured pulmonary fibroblasts displayed a nuclear accumulation of RAGE, and RAGE^{-/-} pulmonary fibroblasts had significantly higher levels of broken DNA compared to wildtype and wildtype positive controls. These same authors induced DNA damage through laser microirradiation, bleomycin treatment, and camptothecin in pulmonary fibroblasts and human lung adenocarcinoma cells. They found that RAGE co-localizes and interacts with the Mre11-Rad50-Nbs1 (MRN) complex through binding with the double-strand break repair protein MRE11. To further validate their findings, Kumar et al. placed MRN alone, MRN with RAGE, and RAGE alone in the presence of single-stranded circular DNA. In a concentration-dependent manner, RAGE increased the nucleolytic processing of circular DNA by MRE11.

Among the most interesting finds made by this work is that reconstituting RAGE in RAGE^{-/-} mice normalized pulmonary function and caused a remarkable reduction in lung tissue fibrosis after four weeks. The importance of RAGE in this context is further evidenced by the fact that the non-phosphorylatable mutant of RAGE showed no changes in

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the mouse RAGE^{-/-} phenotype. While the authors admit that it is unknown if this dramatic reversal of IPF is due solely to the interaction between MRE11 and RAGE, they nevertheless showed that RAGE is a key determinant in the development of pulmonary fibrosis, and possibly its remission. Since RAGE is mostly researched as a membrane receptor, the discovery of its DNA repair role creates a refreshing paradigm shift in the field and makes RAGE a far more intricate target for future studies (1, 2, 9).

The complex interactions involved in the pathogenesis of IPF are becoming better understood, but many aspects are still shrouded in mystery. With the discovery of the importance of RAGE in the development of this disease, we now see that pattern recognition receptors are multifaceted regulators of disease induction. We still need more information to understand the inner workings of nuclear RAGE: what causes its translocation, what substrates and proteins does it interact with, and how is it regulated? It is still unknown if nuclear RAGE is the cause of the dramatic remission observed in this study. A mitochondrial isoform of RAGE has been identified, and it has recently been revealed that mitochondria may play a major role in the progression of IPF (Kang et al. 2014; Mora et al. 2017). Future studies are needed to determine how exactly RAGE and its multiple isoforms contribute to the remission of pulmonary fibrosis. Perhaps such studies will be the pivotal point in our understanding of IPF; a new hope for characterizing this severe chronic disease as reversible and survivable.

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