Survivin IPF: Targeting Cellular Metabolism to Promote Apoptosis in IPF Fibroblasts

Idiopathic pulmonary fibrosis (IPF) is a multifactorial disease characterized by progressive accumulation of activated fibroblasts (myofibroblasts) in the lungs, which leads to sustained deposition of extracellular matrix and loss of organ function (1). Although the causes that contribute to the abnormal accumulation of myofibroblasts in the IPF lungs are not fully understood, the acquisition of a sustained apoptosis-resistant phenotype has been recognized as one of the key pathological features of these disease-effector cells (2). Apoptosis is finely regulated by a cascade of complex and interconnected molecular events that culminate in the activation of cysteine proteases (also known as caspases), which are the final effectors of this process (3). Both apoptosis activators and suppressors play a critical role in promoting cell death or survival, respectively, and altered expression of these regulators leads to dysfunctional cell responses (3). For example, altered expression of apoptosis suppressor genes by epigenetic mechanisms has been shown to facilitate tumor growth and invasion of cancer cells (4). Additionally, epigenetic alterations associated with several key apoptotic genes have been observed in fibroblasts isolated from patients with IPF, thereby driving apoptosis resistance in these cells (5, 6). Thus, identification of signaling pathways that promote apoptosis resistance in myofibroblasts during lung fibrosis progression may provide a promising strategy to improve patient therapy.

During the last decade, aberrant epigenetic regulation of gene transcription has been increasingly recognized as an important mechanism promoting myofibroblast differentiation and lung fibrosis progression (6–9). Epigenetic modifications, such as covalent modifications to DNA and histones, play important roles in regulating gene transcription. Pathological modification of epigenetic states can have profound effects on gene expression (10). Post-translational modification of histones is an important epigenetic mechanism involved in promoting or repressing gene expression. Histone modifications are mediated by specific chromatin-interacting enzymes whose activities are sensitive to the availability of specific substrates derived from metabolic pathways, including the tricarboxylic acid cycle, β oxidation, and glycolysis (11). Given that IPF is characterized by aberrant cellular metabolism (12, 13) as well as altered epigenetic programs (9), there is growing interest in understanding how altered cell metabolism directly influences the epigenetic state of myofibroblasts to promote and maintain their disease-contributing phenotype.

In this issue of the *Journal*, Bai and colleagues (pp. 49–57) provide novel information linking glutamine metabolism (glutaminolysis) to epigenetic regulation of apoptosis in IPF-derived fibroblasts (14). Glutaminolysis is the metabolic process that converts the amino acid glutamine to glutamate by glutaminase and then to α-ketoglutarate (α-KG) by glutamate dehydrogenases to enter the tricarboxylic acid cycle (11). In addition to its energetic function, α-KG is the substrate of a subset of histone demethylases, also known as Jumonji domain-containing (JMJC) enzymes, including JMJD3 (also known as KDM6B) and UTX (ubiquitously transcribed tetratricopeptide repeat, X chromosome). Both of these histone demethylases are specifically responsible for the removal of methyl groups from lysine 27 on histone 3 (H3K27), an epigenetic mark implicated in gene silencing (15).

In their paper, Bai and colleagues demonstrate for the first time that enhanced glutamine metabolism in IPF-derived fibroblasts leads to increased expression of the apoptosis inhibitors XIAP and survivin, and that the demethylase JMJD3 is directly responsible for the transcriptional alterations of these genes. Both XIAP and survivin are known to block apoptosis by directly binding and inhibiting the enzymatic activity of caspase-3, caspase-7, and caspase-9 (3). Interestingly, the expression of these genes has been reported to be elevated in IPF fibroblasts (16, 17) and shown to promote apoptosis resistance in lung myofibroblasts, suggesting that they play important roles in the aberrant myofibroblast persistence observed in IPF.

Bai and colleagues demonstrate that α-KG potentiates the binding of JMJD3 to the promoter of XIAP and survivin genes in IPF-derived fibroblasts, leading to reduced H3K27 methylation levels. Intriguingly, although exogenous α-KG enhances JMJD3 binding to both XIAP and survivin gene promoters, this metabolite only promotes expression of XIAP, with no effect seen on the expression of survivin. As other epigenetic regulators involved in DNA and histone methylation can be affected by glutamine metabolism and can directly regulate survivin expression (5, 18, 19), these observations suggest that glutaminolysis-regulated apoptotic gene expression may involve additional epigenetic regulators beyond JMJD3.

Although this study provides a novel insight into how altered metabolism in IPF fibroblasts epigenetically alters apoptotic gene expression, many questions remain. The authors show that glutaminolysis epigenetically regulates XIAP and survivin expression; however, other antiapoptotic genes may be regulated by the same mechanism in IPF-derived fibroblasts. In addition, further investigations aimed at understanding how JMJD3 specifically targets apoptotic genes to promote apoptosis resistance in IPF fibroblasts will provide a broader perspective on how cellular metabolism epigenetically controls gene expression during lung fibrogenesis.

Given the emerging crucial role of aberrant metabolism in numerous fibrogenic disorders (12, 13, 20), these findings strongly suggest that targeting specific metabolic nodes may have beneficial

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effects in promoting myofibroblast apoptosis and ultimately slowing or reversing the progression of IPF. ■

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