ALCAM Makes It All Calm by Inhibiting Apoptosis

Alveolar type 2 (AT2) epithelial cells are important stem cells in the distal lung compartment necessary for proper repair. Maladaptive responses by AT2 cells play a pivotal role in the pathogenesis of idiopathic pulmonary fibrosis (IPF) (1). Central to this concept is the depletion of AT2 cells through death and exhaustion, which is prohibitive for proper repair after injury and promotes fibroproliferation (2–4). In particular, fibrotic lungs have a predominance of apoptotic AT2 cells that are induced by several established fibrogenic stimuli (e.g., TGF-β1, endoplasmic reticulum stress) (2, 5, 6). However, programmed cell death has multiple levels of checks and balances that limit the induction of executioner caspases, which upon activation leads the cell down an apoptotic path of no return (7). Thus, loss of antiapoptotic signals could be just as damaging as the accumulation of proapoptotic signals in the fibroproliferative microenvironment.

In this issue of the *Journal*, Kim and colleagues (pp. 415–427) offer strong evidence that activated leukocyte cell-adhesion molecule (ALCAM; CD166) has antiapoptotic properties, and its reduced expression in human IPF lungs and in murine lung fibrosis models promotes fibrosis through AT2 cell apoptosis (8). ALCAM is a cell surface protein that is part of the immunoglobulin superfamily of surface receptors (9). Widely expressed by many different hematopoietic and nonhematopoietic cells, ALCAM can bind with itself or engage in heterotypic binding with CD6 to facilitate cell–cell adhesion. ALCAM has several homeostatic roles, including regulation of cell differentiation, proliferation, and migration, but also is pathologically expressed in various malignancies, where it confers oncogenic properties. To determine the functional role of suppressed ALCAM expression, the authors induced fibrosis using two models (bleomycin injury and an inducible TGF-β1 overexpression transgenic), which provides strength to the observations of more lung fibrosis in ALCAM-deficient mice compared with wild-type conditions. This effect in ALCAM-deficient mice was abrogated when bleomycin-injured mice were concurrently treated with the pan-caspase inhibitor (Z-VAD-FMK) to block apoptosis, indicating that antiapoptotic properties of ALCAM conferred a protective effect in lung fibrosis. Mechanistically, the authors focused on an intertwined relationship between ALCAM and TGF-β1, a potent profibrotic cytokine that promotes lung fibrosis in part through the induction of AT2 apoptosis (2). Their data indicate not only that TGF-β1 causes downregulation of ALCAM but also that ALCAM-deficient compared with wild-type epithelial cells are more apoptotic in bleomycin-injured lungs and *in vitro* after induction by TGF-β1.

Although the role of AT2 cell apoptosis in lung fibrosis is well described, previous studies focused largely on proapoptotic signals (2, 5). The present results provide novel insights by demonstrating ALCAM as a cytoprotective signal that is reduced by TGF-β1, thus tipping the scale toward a proapoptotic environment. Consistent with prior studies, ALCAM appears to be mediating its antiapoptotic effects through the PIK3-AKT axis (10). In addition, ALCAM has been found to mediate its cytoprotective effects through Yes-associated protein (YAP). An interesting future line of investigation would be to determine if ALCAM effects on YAP signaling could also be regulating the antiapoptotic effects. Moreover, YAP has an important role in alveolar regeneration after injury (11). Accordingly, it is worthwhile considering if ALCAM regulates AT2 cell self-renewal and alveolar repair after injury. Another interesting function of YAP is its effect on mechanotransduction, which facilitates the cell sensing of the external environment and promotes alveolar regeneration in response to mechanical tension (12). Moreover, the stiffness of the fibrotic lungs increases sixfold, which can promote cellular reprogramming via Yap signaling (13, 14). As such, another interesting direction would be to determine if ALCAM regulates cell mechanosensing as an additional mechanism by which it modulates lung fibrosis.

Whether or not augmented ALCAM signaling can be used as a therapeutic in lung fibrosis is a matter of speculation. To further study this pathway for therapeutic purposes, we will need to define if the ALCAM signaling, or lack thereof, is via homotypic (ALCAM–ALCAM) or heterotypic (ALCAM–CD6) interactions. Understanding the nature of these upstream signals is necessary to determine the best method to target and restore the dysfunction resulting from the downregulation of ALCAM in lung fibrosis. Because ALCAM is not a secreted protein, restoring its function likely cannot be simply achieved through instillation of recombinant protein. Alternatively, determining how TGF-β1 (and other signals) downregulates ALCAM expression could provide novel avenues to therapeutically augment ALCAM expression. In addition, the investigators focused the effect on the AT2 cell. However, ALCAM is widely expressed in many different cell types and likely has additional effects that need to be considered. Defining the cellular targets and functional outcomes of ALCAM signaling would provide insight into the possible off-target effects that may limit the approaches for ALCAM signal modulation. For example, myofibroblast resistance to apoptosis is a contributor in lung fibrosis (15), and antiapoptotic effects of ALCAM on these mesenchymal cells in lung fibrosis may offset the benefit to the lung epithelium.

In summary, this work by Kim and colleagues adds to our knowledge base by identifying ALCAM as a novel antiapoptotic signal in the lungs. ALCAM reduction in lung fibrosis releases the brakes on programmed cell death and augments AT2 apoptosis as a fibrogenic signal. Future studies are needed to broaden our

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understanding of the anti-fibrotic functions of ALCAM, but the present study is intriguing because it urges us to consider ALCAM signaling as a potential therapeutic target in lung fibrosis. ■

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