Angiotensin II: tapping the cell cycle machinery to kill endothelial cells

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IDIOPATHIC PULMONARY FIBROSIS (IPF) is an insidious and progressive disease that has devastating consequences on affected individuals and their families (4, 22). Approximately 50,000 individuals in the United States have this disease and most will develop respiratory failure within 3 to 5 years of being diagnosed. Patients with IPF typically present with reduced exercise tolerance, restrictive lung function, and interstitial lung infiltrates in the parenchyma. It was thought for a long time that chronic inflammation in the lung was responsible for the maturation of fibrotic foci that restricted alveolar compliance and hence impaired gas exchange. However, anti-inflammatory therapies have done little to alter the rate of disease progression. Instead, experimental animal models suggest that repetitive or severe epithelial injury and dysfunction lead to an abnormal wound repair response that ultimately manifests as a fibrotic scar (1, 14). Consistent with this new hypothesis, hyperplastic bronchiolar-like epithelial and alveolar epithelial type II cells have been found lining the surface of mature honeycombed fibroproliferative foci in lungs of people with IPF (2). Apoptotic alveolar epithelial type II cells are also seen in the most active areas of fibroblast growth and maturation. Hence identifying and manipulating pathways controlling the proliferation and apoptosis of lung parenchymal cells may provide new therapeutic opportunities for treating people with IPF.

There is growing appreciation that angiotensin II, a protein controlling blood pressure homeostasis, and angiotensin type 1 (AT1) and type 2 (AT2) receptors are significant mediators of fibrotic organ disease, including lung fibrosis (19). Angiotensin II is an octapeptide derived from sequential cleavage of angiotensinogen by renin and angiotensin converting enzyme (ACE). Increased levels of angiotensin II or AT1 and AT2 receptors have been observed in lungs of people with IPF or in the mouse model of bleomycin-induced lung fibrosis (9, 11). In vitro studies reveal angiotensin II stimulates proliferation and activation of myofibroblasts, while inducing apoptosis of alveolar epithelial type II cells and pulmonary arterial endothelial cells. These opposing cell specific responses are mediated by the two different angiotensin receptors. Angiotensin II stimulates fibroblast proliferation and myofibroblast maturation through AT1 and AT2 receptor-dependent activation of mitogen-activated kinases p38 and p42/44 (ERK) (9). In contrast, angiotensin II-mediated apoptosis of alveolar epithelial cells is dependent on expression of AT1 and activation of protein kinase C (16). Administration of the ACE inhibitor captopril or the AT1-specific inhibitor losartan, or genetic loss of the AT1 receptor, attenuates bleomycin-induced lung fibrosis in mice (12, 13, 21). However, another study found that losartan did not protect against bleomycin-induced lung fibrosis, which the authors speculated could be related to strain differences in the mice being used or the route of drug administration (7). Moreover, a retrospective analysis of patients receiving ACE inhibitors for treatment of scleroderma renal disease failed to demonstrate efficacy in reducing pulmonary fibrosis (15). These differences were the subject of an editorial review in this journal by Budinger (3), who referred to a paper by Uhal (20) showing how processing of angiotensin II to ANG1–7 by angiotensinogen converting enzyme 2 (ACE2) could inhibit JNK activation and bleomycin-induced lung fibrosis. This suggests strategies that enhance angiotensin metabolism might be more efficacious than strategies that block angiotensin signaling. So the quest goes on to better understand how angiotensin II regulates the proliferation and apoptosis of different types of parenchymal cells involved in pulmonary fibrosis.

In a recent issue of this journal, Kim and Day (8) reveal how angiotensin II promotes apoptosis of pulmonary arterial endothelial cells using the same pathway required for cell proliferation. They provide novel and compelling evidence that angiotensin II stimulates phosphorylation and activation of 5′-AMP-activated protein kinase (AMPK), which results in disassociation of cyclin-dependent kinase 4 (Cdk4) from AMPK. Cdk4 then phosphorylates the retinoblastoma (Rb) gene product, thereby releasing E2F1, which stimulates transcription of proapoptotic Bim and thus apoptosis. Interestingly, the same Cdk4-Rb-E2F1 pathway used to activate Bim also drives cell cycle progression from G1 into S phase (6). The findings extend earlier work by these investigators showing how angiotensin II also stimulates apoptosis through AMPK-dependent suppression of antiapoptotic Bcl-XL (10). Taken together, these two studies show how angiotensin II uses AMPK and the cell cycle machinery to shift the balance of pro- and antiapoptotic members of the Bcl-2 family to cause endothelial cell apoptosis.

The relevance of these findings to pulmonary fibrosis still needs to be determined because the studies were performed on cultured pulmonary arterial endothelial cells, whose role in that disease is unclear. Even if apoptosis of endothelial cells plays little role in pulmonary fibrosis, knowing that angiotensin II uses the cell cycle machinery to kill endothelial cells may provide insight into why alveolar epithelial cell hyperplasia and apoptosis are seen in the same disease. Perhaps angiotensin II uses the same pathway discovered in pulmonary arterial endothelial cells to promote apoptosis of alveolar epithelial type II cells. If confirmed, the activation of Cdk4-Rb-E2F1 might be responsible for promoting hyperplasia of alveolar epithelial type II cells or the proliferation of fibroblasts. Although forced overexpression of E2F1 is often sufficient to drive premature S phase entry and hence sensitivity to apoptotic signals (17), overexpression of E2F1 alone was not sufficient to stimulate a Bim promoter luciferase reporter in pulmonary arterial endothelial cells (8). This implies that addi-
tional factor(s) were needed for E2F1 to activate the Bim promoter in response to angiotensin II. Identifying the missing factor(s) might provide a way to block the apoptotic effects on the alveolar epithelium or switch the angiotensin response in fibroblasts from proliferation to apoptosis. Additionally, the activation of AMPK by angiotensin II provides ATP required for apoptosis of pulmonary arterial endothelial cells (5). Since DNA replication is an energy-expensive process, modulating AMPK activity might diminish the proliferative effects of angiotensin II on alveolar epithelial cells or fibroblasts. It is equally important to mention that angiotensin II signaling and in particular its metabolism by ACE2 can also affect experimental models of pulmonary vascular permeability or hypertension (for review see Ref. 18). Whether the findings in the present study help clarify how angiotensin signaling modulates these vascular diseases also remains to be determined.

In summary, Kim and Day’s research identified an unforeseen mechanism by which angiotensin II uses the cell cycle machinery to activate apoptosis of pulmonary arterial endothelial cells. Given the overwhelming evidence linking angiotensin II signaling and pulmonary fibrotic disease, I have chosen to speculate on how these findings in pulmonary arterial endothelial cells might extend our understanding of how angiotensin II affects alveolar epithelial cells or fibroblasts. But this is certainly a limited view of the field, and I apologize to those investigators whose work was not cited or who might view the significance of the Kim and Day paper differently. Nonetheless, I hope that this review catalyzes discussion and experiments that further clarify how angiotensin II controls normal lung homeostasis and disease.

GRANTS

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