PULMONARY FIBROSIS IS A DEVASTATING consequence of several distinct clinical and pathological pulmonary syndromes including the acute respiratory distress syndrome, connective tissue diseases, drug reactions, environmental and occupational exposures, and idiopathic pulmonary fibrosis (14). Much of our understanding of the mechanisms that underlie the development and resolution of lung fibrosis comes from careful studies conducted in rodents by several groups of investigators using the bleomycin model (11). The administration of a single dose of bleomycin to mice or rats results in the rapid development of acute lung injury followed by activation of the profibrotic cytokine TGF-β1, which is both required and sufficient for the subsequent development of fibrosis (5, 12). In the absence of additional doses of bleomycin, the lung fibrosis resolves over time. The use of mice lacking genes encoding key proteins in major cellular pathways in this model has provided a rough outline of the mechanisms that incite fibrosis after lung injury. Unfortunately, many of the therapies predicted to be effective on the basis of results of experiments conducted in the bleomycin model have failed to demonstrate efficacy in clinical trials (16).

The disconnect between efficacy in animal models and human disease might result from fundamental differences between the development of fibrosis in human and murine lungs or the activation of mechanisms unique to bleomycin that have limited importance in human fibrosis. Alternatively, these differences might result from our lack of a detailed understanding of the molecular events that lead to fibrosis in mice exposed to bleomycin. For example, most therapies and virtually all genetic abnormalities shown to be protective or sensitizing in the bleomycin model are present before the bleomycin is administered (10, 16). Therefore, it is unclear whether a protective phenotype in the bleomycin model is the result of inactivation of the bleomycin, protection against bleomycin-induced lung injury, inhibition of TGF-β1-mediated fibrosis, or acceleration of resolution. In addition, most genetic models and pharmacological agents target major pathways in all of the cells present in the lung. These pathways might have profoundly different effects in different cell types (3, 7). Finally, an incomplete understanding of the molecular effects of a drug or genetic strategy might confound the interpretation of these interventions in the bleomycin model.

In this issue of the Journal, Uhal and colleagues (17) provide an example of how a deeper molecular understanding of a pathway can generate new hypotheses about therapies for lung fibrosis. More than a decade ago, this group of investigators reported that the administration of captopril to rats beginning 2 days before the intratracheal administration of bleomycin provided significant protection against fibrosis (18). However, the continued development of lung fibrosis in patients with scleroderma receiving angiotensin-converting enzyme (ACE) inhibitors to prevent scleroderma renal crisis and retrospective analyses of patients with pulmonary fibrosis receiving ACE inhibitors argued against the clinical importance of these findings (13, 15). ACE converts the 10-amino acid peptide angiotensin I to an 8-amino acid peptide angiotensin II. Uhal and colleagues reported angiotensin II was present at high levels in mice treated with bleomycin and in patients with pulmonary fibrosis and that angiotensin II-induced alveolar epithelial cell apoptosis (8, 9, 18). Since activation of the intrinsic apoptotic pathway is required for the development of bleomycin-induced lung fibrosis downstream of the activation of TGF-β1, they suggested that the accumulation of angiotensin II might serve as a signal to activate apoptosis (2, 4). Angiotensin II can be removed by ACE-2, which cleaves its COOH-terminal amino acid to form a cleaved to a seven-amino acid peptide ANG1–7, which in turn can signal through its receptor, the mas oncogene (1). In their present report, Uhal et al. found that ANG1–7 acts through its receptor mas to inhibit bleomycin-induced fibrosis by inhibiting the activation of JNK, which is required for bleomycin and angiotensin II-induced apoptosis (6).

The results are limited by the use of in vitro systems and will require genetic and pharmacological confirmation in vivo. Nevertheless, this work suggests that strategies that enhance angiotensin II metabolism, particularly those that increase the abundance or activity of angiotensin converting enzyme II, may be effective against lung fibrosis. Alternatively, the activation of mas or inhibition of JNK signaling may prevent angiotensin II-induced apoptosis and ameliorate fibrosis. Since JNK signaling has also been implicated in the excess matrix deposition by fibroblasts in the bleomycin model, these results also suggest an alternative pathway by which angiotensin II might contribute to fibrosis (19). Perhaps most importantly, these results provide a potential explanation for the lack of observed effect of ACE inhibitors in clinical trials. In this case excessive signaling by angiotensin II appears to be the consequence of its impaired degradation and the loss of an inhibitory signal rather than increased synthesis of the protein. These results should serve as a cautionary note to investigators in interpreting the results of negative studies. In some cases, a deeper molecular understanding of why an intervention doesn’t yield the expected result might lead to important findings with implications for newer therapeutics.

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