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RESEARCH NEWS

New Hope for the Treatment of Pulmonary Hypertension: Novel Approaches to a Complex Disease

A review of: Cowan KN, Heilbut A, Humpl T, Lam C, Ito S, Rabinovitch M 2000 Complete reversal of fatal pulmonary hypertension in rats by a serine elastase inhibitor. Nat Med 6:698–702

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UNTIL THE RECENT dramatic findings reported by Cowan *et al.*, there was little evidence to suggest that severe chronic pulmonary hypertension was reversible. Most previous experiments evaluating therapies for pulmonary hypertension had been designed such that the therapeutic agent of interest was given concomitantly with the agent or stimulus used to cause the pulmonary hypertension. While a number of pharmacologic studies utilizing this approach were demonstrated to "prevent" or attenuate pulmonary hypertension, few experiments had demonstrated that established severe pulmonary hypertension could be completely reversed. This study should put to rest the idea that severe chronic pulmonary hypertension, associated with significant structural change in the vascular bed, is not amenable to therapy.

Pulmonary hypertension can occur idiopathically or can complicate a wide variety of pulmonary and cardiac disorders. It is known to be associated with abnormalities of vascular tone as well as of vascular structure, with the relative contribution of these components differing based on the etiology of the pulmonary hypertension and on its chronicity (1). Most currently available treatments have been directed primarily at alleviating the vasoconstrictive component of the disease. In certain situations, for example treatment of the newborn with persistent pulmonary hypertension with inhaled nitric oxide (iNO), this therapeutic approach has been tremendously successful (2). However, in cases of longstanding pulmonary hypertension where significant structural changes are believed to be major contributors to obstruction of pulmonary blood flow, right heart failure and ultimately death, treatment with vasodilators is often ineffective. Thus therapies capable of reversing the structural changes either used alone or in conjunction with vasodilators could aid in the treatment of a vast number of patients.

The fact that the serine elastase inhibitors proved so effective in the treatment of chronic pulmonary hypertension was not a serendipitous observation. The Rabinovitch group, along with others, has productively worked for years to elucidate the molecular mechanisms that drive the process of structural change in the hypertensive pulmonary vascular bed. They have suggested that endothelial injury and loss of barrier function may induce elastase or protease activity, which is critical for the initiation and progression of pulmonary hypertension (3). This increase in elastase activity causes degradation of essential growth inhibiting extracellular matrices, release of stored growth factors within this matrix, and induction of new extracellular matrix proteins such as tenascin-C and osteopontin which can act as amplifiers of SMC growth or migration through beta-3 integrin-dependent intracellular signaling mechanisms (4). Inhibition of elastases, through the use of serine elastase inhibitors, could arrest ongoing collagen or elastin degradation, prevent the beta-3 integrin-dependent signal which induces tenascin-C (potentially a survival factor in phenotypically altered SMC) and thus initiate an apoptotic cascade leading to regression of the hypertrophied vessel wall. Thus, the therapeutic advances described in this study are the result of a long series of studies that have begun to elucidate the pathophysiologic mechanisms of vascular remodeling in pulmonary hypertension.

There are certain caveats that should be taken into account when considering this work in the context of human disease. First, the rodent system used to test the hypothesis has not always proved to be a reliable predictor of the success of pharmacologic treatments in human vascular disease. This has been most consistently observed in balloon-catheter induced injury and restenosis trials in rats versus humans. Secondly, monocrotaline-induced pulmonary hypertension, while an excellent system to evaluate pathophysiologic mechanisms, does not have an exact human counterpart and does not exhibit the same vascular pathology (*i.e.* intimal thickening) observed in many fatal cases of primary and secondary pulmonary hypertension in humans. Lastly, as the authors point out, no reversal of the abnormal alveolar to arterial ratio (perhaps an index of cross-sectional vascular area in the lung) caused by the monocrotaline was noted, raising the possibility that new vessel growth, which might be important for a return to normal lung function, is inhibited by serine-elastase inhibitor treatment. Nonetheless, the observations are so dramatic and important that they should stimulate immediate investigations in other model systems. Successful use of the drug in these settings either alone or in combination with vasodilator treatment could lead to hopeful new strategies to treat a devastating human disease entity.

1. Stenmark KR, Mecham RP 2000 Cellular and molecular mechanisms of pulmonary vascular remodeling. Annu Rev Physiol 59:89–144
2. Kinsella JP, Abman SH 2000 Clinical approach to inhaled nitric oxide therapy in the newborn with hypoxemia. J Pediatr 136:717–726
3. Cowan KN, Jones PL, Rabinovitch M 2000 Elastase and matrix metalloproteinase inhibitors induce regression and tenascin-C antisense prevents progressive vascular disease. J Clin Invest 105:21–34
4. Jones PL, Boudreau NJ 1999 Extracellular matrix and integrin signalling: the shape of things to come. Biochem J 399:481–488

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