NEW PHARMACOLOGICAL STRATEGIES FOR COPD

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Understanding the cellular and molecular mechanisms of COPD will lead to new approaches to therapy in the future, and in particular to drugs that will prevent progression of the disease. Many mediators are involved in COPD, although much less is known about the role of individual mediators than in asthma. Leukotriene B_4 is elevated in COPD and is a potent neutrophil chemoattractant, so that specific inhibitors of LTB_4 receptors are now being investigated. Interleukin-8 and other CXC chemokines are also neutrophil chemoattractants and antagonists of these mediators have been developed. Several new therapies are aimed at blocking TNF-α secretion or receptors, particularly in patients with cachexia. Oxidative stress may be very important in COPD in amplifying inflammation, increasing proteolysis and induction of steroid resistance. More effective antioxidants are needed in the future. Phosphodiesterase-4 inhibitors may be effective in neutrophilic inflammation, in contrast to corticosteroids. Nuclear factor-κB, p38 MAP kinase and phosphoinositide-3 kinase(PI3K)-γ inhibitors may also be effective anti-inflammatory treatments, and are in the early stages of clinical development. The lung destruction in COPD is due to release of proteases, including neutrophil elastase, suggesting that enzyme inhibitors might be effective. There is particular interest in matrix metalloproteinases (particularly MMP-9) that are released from macrophages and neutrophils and selective MMP inhibitors are in development. The possibility that the lung destruction of emphysema may be reversed by retinoic acid and its analogues (RARγ agonists) is under active investigation.

Theophylline appears to have a unique action of stimulating histone deacetylase (HDAC) activity and thereby "resensitising" cells that are rendered steroid-resistant by oxidative stress. This mechanism is independent of PDE inhibition and adenosine antagonism and therefore it may be possible to develop analogues that have the beneficial effects of theophylline without side effects. Theophylline restores HDAC via inhibition of PI3K-δ inhibition and selective inhibitors are now in clinical development. There may be other strategies to reverse the corticosteroid resistance in COPD and this might be a more effective and safer approach than developing new anti-inflammatory treatments that are likely to be limited by side effects.