COLCHICINE PREVENTS THE DEVELOPMENT OF BLEOMYCIN-INDUCED PULMONARY FIBROSIS AND INHIBITS COLLAGEN SYNTHESIS IN VIVO AND IN VITRO.

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Colchicine, a compound that disrupts microtubule formation, has been well known to inhibit the secretion of many proteins and has been widely used in human for the chronic treatment of gout and Familial Mediterranean Fever without any significant side effect. Recently, evidences have been presented that colchicine has an inhibitory effect on the synthesis and accumulation of collagen as well as a stimulatory effect on collagenase expression in vivo and in vitro. More recently, colchicine has been known to suppress the release of fibronectin and alveolar macrophage derived growth factor, well-known growth factors for fibroblast, from alveolar macrophage in vitro. Thus, we suggested that colchicine, a well-tolerated agent with numerous in vivo and in vitro effects including inhibition of extracellular deposition of collagen, could be used as an antifibrotic drug for the treatment of pulmonary fibrosis.

Single intratracheal administration of bleomycin caused marked increases of the steady-state levels of mRNAs for procollagen and fibronectin in lung tissues, and elicited significant lung damage as evidenced by marked elevated levels of several parameters including protein, albumin, hydroxyproline, N-acetyl-D-glucosaminidase, and angiotensin converting enzyme in bronchoalveolar lavage fluids. In contrast, animals treated with colchicine (100 ug/day) demonstrated a marked reduction in both mRNAs levels in lung tissues and biochemical evidence of lung damage.

In a parallel in vitro study, bleomycin stimulated collagen biosynthesis in a dose-dependent manner while colchicine showed a reverse effect in human lung fibroblast cultures. Colchicine inhibited collagen synthesis rather than only inhibition of secretion as confirmed by the measurement of collagen radioactivity in both medium and cell layer. In addition, colchicine led to selective inhibition of collagen formation with negligible effects on non-collagen protein synthesis and reversed the stimulatory effect of bleomycin on collagen synthesis by fibroblasts.

These data suggest that colchicine has a specific effect on synthesis of collagen in vivo and in vitro and has a protective effect on lung damage induced by bleomycin, and may, therefore, be useful in modulating pulmonary fibrosis.