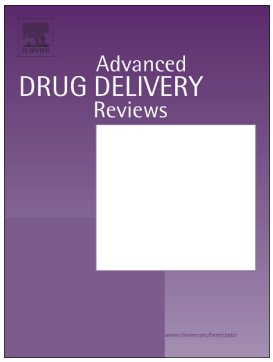

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The apparent competitive action of ECM proteases and cross-linking enzymes during fibrosis: applications to drug discovery

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Abstract: Progressive loss of organ function in most organs is associated with fibrosis, a tissue state associated with abnormal matrix buildup. If highly progressive, the fibrotic process eventually leads to organ failure and death. Fibrosis is a basic connective tissue lesion defined by the increase in the amount of fibrillar extracellular matrix (ECM) components in a tissue or organ. In addition, intrinsic changes in important structural cells can induce the fibrotic response by regulating the differentiation, recruitment, proliferation and activation of extracellular matrix-producing myofibroblasts. ECM enzymes belonging to the family of matrix metalloproteinases (MMPs) and lysyl oxidases (LOXs) play a crucial role in ECM remodeling and regeneration. MMPs have a catalytic role in degradation of ECM, whereas LOX/LOXLs mediate ECM, especially collagen, cross-linking and stiffening. Importantly, enzymes from both families are elevated during the fibrotic response to tissue injury and its resolution. Yet, the apparent molecular competition or antagonistic activities of these enzyme families during the various stages of fibrosis is often overlooked. In this review, we discuss the diverse roles of MMPs and LOX/LOXL2 in chronic organ fibrosis. Finally, we review contemporary therapeutic strategies for fibrosis treatment, based on neutralization of MMP and LOX activity, as well as the development of novel drug delivery approaches.

Keywords: fibrosis, extracellular matrix enzymes, matrix metalloproteinases, lysyl oxidases, drug delivery, pharmacological targeting

Abbreviations: ADAMs, a disintegrin and metalloproteinases; ADAMTS, ADAMs with thrombospondin motifs; BALF, bronchoalveolar lavage fluid; BAPN, β-aminopropionitrile; CD, Crohn's disease; ECM, extracellular matrix; EMT, epithelial to mesenchymal transition; EndoMT, endothelial cells to mesenchymal; FGF, fibroblast growth factor; HSC, hepatic stellate cells; IBDs, inflammatory bowel diseases; IGFBP3, insulin-like growth factor binding protein-3; IPF, idiopathic pulmonary fibrosis; LOX/LOXL, lysyl oxidase/lysyl oxidase-like; MMPs, matrix metalloproteinases; MT1-MMP, membrane type I MMP; PDGF, platelet-derived growth factor, PMNs, polymorphonuclear neutrophils; TNFα, tumor necrosis factor; TGF-β, transforming growth factor-β, TIMPs, tissue inhibitors of metalloproteinases; UC, ulcerative colitis; UUO, unilateral ureteral obstruction;