Altered extracellular matrix of linitis plastica (scirrhous gastric carcinoma): aberrant tissue remodeling as possible therapeutic targets

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Linitis plastica (LP) is characterized by an abundant deposition of extracellular matrix components and has a very poor prognosis. Altered synthesis of extracellular matrix components as well as angiogenesis, degradation by proteolytic enzymes contribute equally to the formation of the tumor stroma, which would affect various cell functions and in finally, determine the biologic behavior of the tumor. Recent studies demonstrated that altered extracellular matrix (ECM) caused by cancer invasion could modify not only host cell functions but various tumor cell phenotypes. Thus, far from being an inactive scaffold around cells, ECM actively participates in the key steps of cancer invasion and metastasis. Therefore, an intimate involvement of ECM in aspects of the aberrant tissue remodeling prompts us to elucidate the fibrotic mechanisms and the roles of desmoplasia and angiogenesis in LP, which are largely unknown to date.

To elucidate the fibrotic mechanism in gastric carcinoma tissue, we evaluated collagen synthetic and degrading activity in gastric carcinoma tissue. Although collagen synthetic activity, as determined by P4H activity, was generally elevated in gastric carcinoma tissue, collagen degrading activity against type I and IV collagens was significantly decreased in tissue samples of LP. Moreover, abundant expression of tissue inhibitor of metalloproteinases-1 (TIMP-1) was observed in the collagenous stroma of LP. We also found that the level of TIMP-1 in the sera of patients with diffuse type gastric carcinoma (including LP) was significantly higher than that in intestinal type gastric carcinoma and the control subjects. It was suggested that decreased collagenase activity and an elevated level of TIMP-1 would result in the tissue fibrosis observed in patients with gastric carcinoma, in particular, LP. Inhibition of desmoplasia as a therapeutic potential for LP is yet to be elucidated.

Expression of angiogenic molecules such as vascular endothelial growth factor (VEGF) and its receptor KDR were observed in tissue of LP. To target tumor angiogenesis, we have successfully isolated human phage antibodies against KDR, which recognized endothelial cells in the stroma of LP representing a therapeutic potential of these antibodies.