In recent years, significant progress has been made in understanding the structure, function, and regulation of gene expression of secreted metalloproteinases that participate in the degradation of the mammalian extracellular matrix. Metalloproteinases of this class have been shown to be structurally related, and comprise a novel secreted proteinase gene family which includes interstitial collagenase, stromelysin, 72-kDa type IV collagenase (genatinase), 92-kDa type IV collagenase (gelatinase) and several other proteases whose functions have not yet been well defined. Both the 72 and 92-kDa type IV collagenases contain a fibronectin-like collagen binding domain. In addition, the 92-kDa type IV collagenase has a unique 54 amino acid long collagen-like domain. The structure of these metalloproteinases is the result of recruitment of the functional units from structural macromolecules into an enzyme protein in the process of evolution. The expression of genes coding for these enzymes is cell-type specific and most are regulated by growth factors, oncogenes, mediators of inflammation, and tumor promoters.

The extracellular activity of these enzymes is modulated by proenzyme activation and by interaction with the specific tissue inhibitor of metalloproteinases (TIMP). The possible pathway of activation of interstitial collagenase is better understood than that of the other members of this gene family and may involve a cascade of proteolytic events involving plasmin in the initial step and a second step requiring plasmin activated stromelysin. The 92-kDa and 72-kDa type IV procollagenases form a non-covalent complex with inhibitors which is activatable by organomercurials. The 92-kDa enzyme forms a stoichiometric complex with TIMP, while the 72-kDa enzyme type IV collagenase, purified from the same starting material, contains a novel 24-kDa inhibitor, TIMP-2.

The possible role of these metalloproteinases in disease processes will be discussed.