Mechanisms regulating expression of MMP-9 and TIMP-1 genes and their disorder in malignant tumor cells

Motoharu SEIKI
Department of Molecular Virology and Oncology, Cancer Research Institute, Kanazawa University, Takara-machi, Kanazawa, 920

92kDa Type IV collagenase, a member of matrix metalloproteinases, is believed to play a critical role in physiological tissue-remodeling processes and also in many pathological conditions such as tumor invasion. We analyzed the 5'-flanking sequence of the 92kDa type IV collagenase gene that controls the expression of the gene by ligating it to the chloramphenicol acetyltransferase gene. Deletion and mutation analysis revealed that three motifs, homologous to the binding sites for AP-1, NF-κB, and Sp-1 proteins, contributed positively to induction by 12-O-tetradecanoyl-phorbol-13-acetate (TPA) and tumor necrosis factor α (TNF α). The AP-1 site was indispensable but not sufficient for the induction and required synergistic cooperation with either the κB or the Sp-1 site. In OST cells, a nuclear factor which bound to Sp-1 was constitutively expressed, and those bound to AP-1 and κB elements were rapidly induced by TNF α treatment. Comparison of the findings with those for the promoters of other TPA-inducible matrix metalloproteinases, interstitial collagenase and stromelysin 1, revealed that the signal to the AP-1 sites is common for the TPA-inducibility of the genes but that the signals to the κB or Sp-1 sites, which are not present in interstitial collagenase and stromelysin 1 promoters, are the unique determinant for the inducibility of the 92kDa type IV collagenase gene.