Cleavage of Metastasis Suppressor Gene Product KiSS-1 Protein/Metastin by Matrix Metalloproteinases.

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A human placenta cDNA library was screened by the expression cloning method for gene products which interact with matrix metalloproteinases (MMPs), and we isolated a cDNA whose product formed a stable complex with pro-MMP-2 and pro-MMP-9. The cDNA encoded the metastasis suppressor gene *KiSS-1*. KiSS-1 protein was shown to form a complex with pro-MMP. KiSS-1 protein is known to be processed to peptide ligand of a G-protein-coupled receptor (hOT7T175) named metastin, and suppresses metastasis of tumors expressing the receptor. Active MMP-2, MMP-9, MT1-MMP, MT3-MMP and MT5-MMP cleaved the Gly^{118}-Leu^{119} peptide bond of not only full-length KiSS-1 protein but also metastin decapeptide. Metastin decapeptide induced formation of focal adhesion and actin stress fibers in cells expressing the receptor, and digestion of metastin decapeptide by MMP abolished its ligand activity. Migration of HT1080 cells expressing hOT7T175 which harbor a high level MMP activity was only slightly suppressed by either metastin decapeptide or MMP inhibitor BB-94 alone, but the combination of metastin decapeptide and BB-94 showed a synergistic effect in blocking cell migration. We propose that metastin could be used as an anti-metastatic agent in combination with MMP inhibitor, or MMP-resistant forms of metastin could be developed and may also be efficacious.

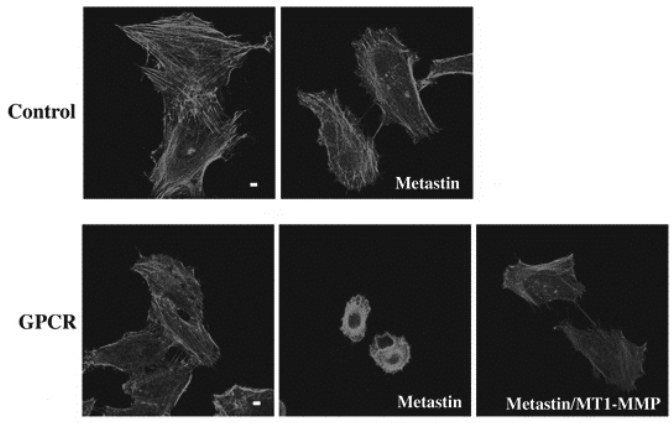

Fig. 1 Inactivation of Metastin by MMP. HeLa cells co-transfected with GFP and control plasmids (panels Control) or hOT7T175 cDNA (GPCR) were treated with vehicle (-), 100 nM metastin 112-121 peptide (Metastin) or metastin 112-121 peptide pre-incubated with MT1-MMP (Metastin/MT1-MMP) at 48 hr after transfection for 1 hr, and then stained with rhodamine-phalloidin.

Reference: Takino, T., Koshikawa, N., Miyamori, H., Tanaka, M., Sasaki, T., Okada, Y., Seiki, M., and Sato. H.: Cleavage of Metastasis Suppressor Gene Product KiSS-1 Protein/Metastin by Matrix Metalloproteinases. Oncogene (in press)