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MATRIX METALLOPROTEINASES-MEDIATED ENDOTHELIAL CELL PROTEOLYSIS INDUCED BY THYMOSIN β4

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Angiogenesis, the formation of new blood microvessels from preexisting network, is essential during organ development, wound healing, tissue repair, inflammation as well as under various pathological processes, such as tumor growth and metastasis, diabetic retinopathy and arthritis. In the early stages of angiogenesis endothelial cell growth, proliferation and migration, as well as vascular permeability take place allowing leakage of plasma proteins such as fibrinogen/fibrin and vitronectin to create a temporary matrix for migrating epithelial cells, leukocytes, and endothelial cell. To invade fibrin networks, migrating endothelial cells are believed to mobilize proteolytic enzymes, particularly belonging to u-PA/plasmin and matrix metalloproteinase (MMPs) systems. It has been shown quite recently, that endothelial cell angiogenesis is enhanced by thymosin β4 (Tβ4) but its angiogenic potential is still poorly elucidated. In order to further characterize Tβ4 angiogenic activity, we produced series of mutants that were deprived of the N-terminal tetrapeptide AcSDKP ($T\beta4_{(AcSDKPT/4A)}$), the actin binding sequence KLKKTET ($T\beta4_{(KLKKTET/7A)}$) and with the nuclear localization sequence damaged by a point mutation Lys16Ala ($T\beta4_{(K16A)}$). Our data demonstrate that increased intracellular expression of Tβ4 and its mutants is necessary and sufficient to induce expression of PAI-1 gene, as well as expression and release of MMP-1, -2, and -3 in endothelial cells. Furthermore, Tβ4 promotes migration, invasion and capillary-like tubular structures formation in a three-dimensional fibrin matrix by MMP-dependent mechanism.