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Mechanism of Regulation of Tumor Angiogenesis and Tumor Growth by Hexastatin a Peptide Derived from Extracellular Matrix

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Peptides or short protein domains derived from the extracellular matrix are known to possess anti-tumor properties. One such molecule, hexastatin [α6(IV)NC1] was derived from the carboxy terminal non-collagenous domain of α6 chain of type (IV) collagen and was found to inhibit tumor growth, but the mechanism by which it inhibits the growth of solid tumors has not been reported yet. In the present study we identified that the biological functions of hexastatin are attributed to its binding to different cell surface integrins. We identified that hexastatin binds to 31, V3 and 51 integrins. Hexastatin competes with human vascular endothelial cells in binding to 11 integrins on type IV collagen, and or with 51/V3 integrins on fibronectin/vitronectin matrix, thus inhibiting endothelial migration and tube formation. Interestingly, p38-MAPK phosphorylation was not inhibited in α3 and β3 integrin null endothelial cells upon treatment with hexastatin which confirms that the antiangiogenic functions of hexastatin are possibly mediated through α3β1, V3 and 51 integrins. While both the integrins (α3β1 and α5β1) are required for the inhibition of tube formation by hexastatin in human vascular endothelial cells, only α3β1 integrin was found to regulate endothelial cells migration. In addition we also demonstrated that hexastatin inhibits tumor growth, tumor angiogenesis and circulating endothelial cells in-vivo. These in-vitro and in-vivo findings indicate that α3β1, V3 and 51 integrins are critical for hexastatin mediated inhibition of angiogenic signaling and tumor progression. Collectively, our findings demonstrate that hexastatin is a potent therapeutic agent for targeting tumor angiogenesis and tumor growth.