STRUCTURAL ANALYSIS OF ENDOSTATIN N-TERMINAL FRAGMENT AND A PUTATIVE INTERACTION WITH AVB3 INTEGRIN

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Angiogenesis or neovascularization is a complex physiological process that culminates with the proliferation and migration of endothelial cells and the formation of new blood vessels. It is an important event in wound healing processes and in the formation of uterine endometrium, although it might be stimulated by certain pathologies like cancer, diabetic retinopathy and psoriasis. Many antiangiogenic compounds, amongst which is endostatin, exert part of their functions through the interaction with integrins, which plays a central role on the migration of endothelial cells and on new vessel formation. Recently, it was demonstrated that the antiangiogenic activity of endostatin might be carried out by a peptidic fragment (mP1), containing 27 residues, from the N-terminal region of the protein.

This study aims to contribute to the understanding of the mechanism of action of the mP1 peptide and a possible interaction with αvβ3 integrin, as well as to elucidate mechanisms involved in the activation of this integrin.

We employed, nuclear magnetic resonance, circular dichroism, molecular modeling and molecular dynamics techniques in the analysis of the mp1 peptide structure and mechanism of action.

The results suggest that the peptide reaches a β-hairpin conformation, capable of interacting with a cleft at the interface between the αvβ3 integrin subunits that exhibits steric and electrostatic complementarity to the peptide. We have also identified important regions for the maintenance of the inactive conformation of the integrin, such as a loop belonging to the 5th blade of the β-propeller domain and a hydrophobic cluster formed by residues of the EGF and Hybrid domains.

Thus, we have proposed that the peptide, as well as other antiangiogenic substances might exert their biological functions through an interaction not yet described in the literature and the exploration of those regions may, therefore be of relevance for the design of integrin inhibiting drugs.

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