DETERMINATION OF THE BINDING MODES OF INTEGRIN ANTAGONISTS
BY MOLECULAR DOCKING AIMING TO ASSIST THE DESIGN OF NEW
SPECIFIC INHIBITORS

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Integrins are transmembrane cell surface proteins, which have the properties of adhesion, proliferation and migration of immune cells by recognizing, mainly, binding sites in extracellular matrix proteins. The integrins are heterodimeric molecules composed of two monomers, \(\alpha\) and \(\beta\), which comprise 24 subtypes formed out of 18 different \(\alpha\) and 8 \(\beta\) chains. There is a constant search for inhibitors and antagonists, due to the pharmacological interest in this protein. Three integrins (\(\alpha_4\beta_1\), \(\alpha_5\beta_1\), and \(\alpha_V\beta_1\)) have been analyzed by Molecular Dynamics and Docking. Objectives: Characterization of the binding modes of the integrins able to bind to fibronectin, with the aim of helping the rational design of new ligands.

Methods: The crystal structure of \(\alpha_4\), \(\alpha_5\), \(\alpha_V\) and \(\beta_1\) were obtained on PDB (Crystal id: 3V4P, 3VI3, 1JV2 and 3VI3 respectively). The complexes \(\alpha_4\beta_1\), \(\alpha_5\beta_1\) and \(\alpha_V\beta_1\) were created by aligning the monomers to their respective partner. The output was submitted to docking with Vina using PyRx software. Five families of non-peptide ligands were selected, according to the effectiveness described in several papers in the literature.

Results: The binding site characterization showed that the region around the MIDAS ion is highly electronegative, favoring the interaction of predominantly positive ligands. In addition, the mobility in the \(\beta\) subunit in the same region is higher than the \(\beta\)-propeller in the \(\alpha\) subunit, confirmed by the RMSF, RMSD and B-factor. The secondary structure was also analyzed along the 10ns of dynamics for the four receptors. Our simulations pointed the residues involved in the interaction with the best inhibitors. The lowest calculated affinity for the \(\alpha_4\beta_1\) was -8.6 kcal/mol for C2; \(\alpha_5\beta_1\) was -9.1 kcal/mol for C4; \(\alpha_V\beta_1\) was -9.2 kcal/mol for C1. Conclusions: These results may be helpful in the design of new and potent inhibitors of integrins, mimicking other peptide ligands with increased affinity and stability.

Key words: Integrin, Molecular Docking, Molecular Dynamics