Differential modulation of αvβ3 dynamics upon RGD-ligands

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Integrins are heterodimeric cell adhesion receptors composed of two non covalently bound α and β glycoproteins. On the cell surface these proteins exist in an inactive state. The tripeptide RGD has been identified as the common motif used by several endogenous binders to recognize and bind integrins, initiating biological and pathological processes and promoting allosteric changes in the ectodomain required for signal transduction.[1-3]

The study of conformational responses of protein receptors upon the binding of endogenous ligands may be a source of inspiration for the design of small molecule modulators that permit to control such biological processes.

Here we present molecular dynamics simulations of the multidomain receptor αvβ3 integrin bound to two different sequences of the endogenous ligand fibronectin: the wild type one, wtFN10, which acts as an agonist activating the receptor, and a high affinity mutant, hFN10, which acts as a true antagonist inhibiting the receptor.[4] Through the comparative analysis of several dynamic descriptors at different levels of resolution, from the residue to domain level, we shed light on the salient conformational dynamics differences determined by fibronectin sequence mutations: we show that it is possible to identify interaction hotspots in the integrin binding site that specifically respond to the fibronectin sequence variations, and allosterically drive conformational changes towards integrin activation (in the case of wtFN10 binding) or inhibition (hFN10 binding).[5]

Moreover, in recent years a wealth of linear or cyclic peptidic and peptidomimetic integrin ligands has been developed and few potent compounds are in different stages of clinical trials as anticancer drugs (e.g. Cilengitide) or in clinical use for antithrombotic therapy. By means of MD studies, we investigate a new class of cyclic peptidomimetic RGD-based integrin ligands containing bifunctional diketopiperazine scaffolds (cyclo[DKP-RGD] ligands) which showed low nanomolar IC50 values in competitive binding assays to the purified αvβ3 receptor.[6-8]

Different dynamic ensembles of the protein upon ligand-binding unveil the links between the fine atomic-scale protein-ligand interactions and the large-scale protein motions, enabling an allosteric model of integrin regulation that can be used in the design of small molecule integrin inhibitors or modulators.

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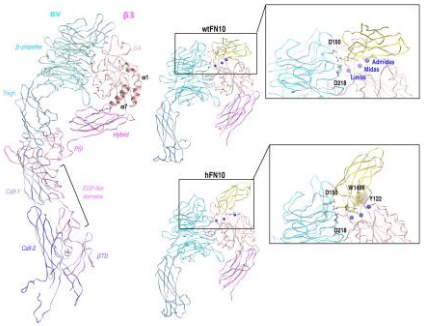

Figure 1. 3D-structure of integrin αvβ3 and αvβ3-FN10 complexes.

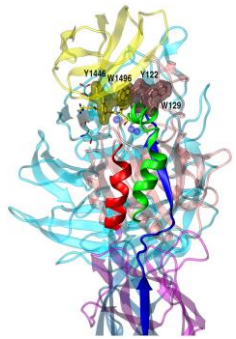

Figure 2. Close-up view of hFN10 complex.