Dynamic regulation of Ca^{2+} binding to Langerin carbohydrate recognition domain by an allosteric network

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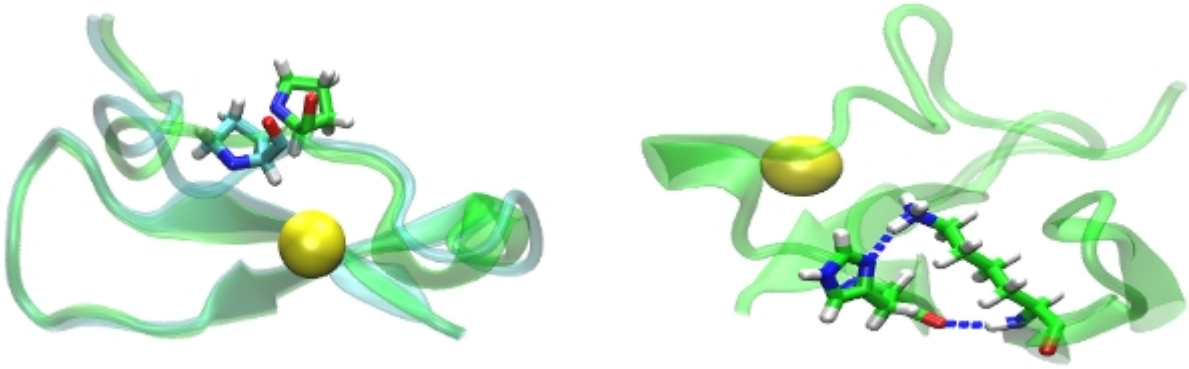

C-type lectin Langerin is a receptor of mucosal dendritic cells expressed as a trimer. Langerin facilitates endocytotic uptake of HIV viral particles through glycan recognition and in a Ca^{2+} dependent fashion. Endosomal Ca^{2+} channels open to reduce the effective concentration of Ca^{2+} , resulting in release of the cargo in endosome. The loss of Ca^{2+} ion causes a change of the conformational dynamics of Langerin. [1] We present a study on the Ca^{2+} binding to the Langerin carbohydrate recognition domain (CRD) investigated by NMR and all atom Molecular Dynamics (MD) simulations.

Residue P286 in Ca^{2+} binding loop undergoes slow cis/trans isomerization to accommodate the Ca^{2+} ion. Ca^{2+} binds only to the cis-P286 form of Langerin CRD. Chemical shift pertubation data suggested the existence of an allosteric network upon binding of the Ca^{2+} ion. We investigated the possibility of inter-residue communication in Langerin CRD by employing mutual information (MI) theory, and we confirmed, that the allosteric network existed. The hub residues of the allosteric network were mutated, and NMR data on the mutants showed the robustness of the allosteric network. H294 is an important residue, that couples the movement between the Ca^{2+} binding site, and β2-β2' loop (the region of the highest backbone flexibility). It establishes two hydrogen bonds with K257 of β2-β2' loop. H294A mutant has greater affinity towards Ca^{2+} ion compared to wild type Langerin. We also observed the decoupling in the movement of two loops in this mutant. Though, the allosteric network was still present. H294 was partially protonated in the acidic environment of the endosome, and lacked the hydrogen bond with the sidechain of K257.

In conclusion, the role of the allosteric network comprises cis/trans isomerization of P286 residue (tremendous conformational change in the binding pocket), and coupling of the movement between Ca^{2+} binding site, and β2-β2' loop.

[1] H. Feinberg, A. Powlesland, M. Taylor et al., The Journal of biological chemistry, **2010**, vol. 285, pp. 13285-13293 (2010)