Allosteric control of pH-sensitive Ca(II)-binding in langerin

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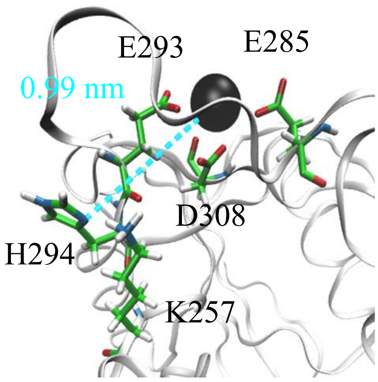

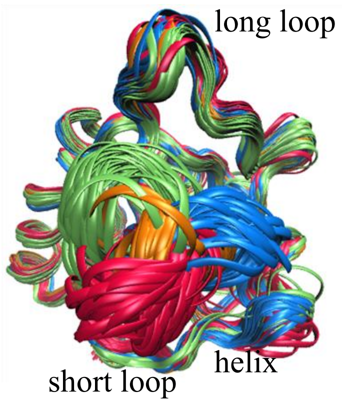

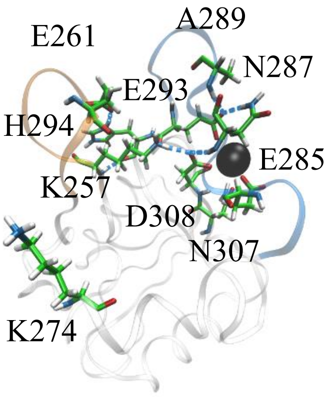

The dendritic C-type lectin receptor langerin plays an important part in the inert immune response of humans and other mammals by trapping invading pathogens like HIV. This is due to a high binding specificity for mannose that relies on the presence of a calcium cofactor. The calcium and therefore the sugar binding affinity itself is sensitive to a change in pH from neutral to weakly acidic. This pH-dependency was attributed to a H294 side chain protonation which is interesting, because this histidine residue has no direct contact to the calcium/sugar binding site (left figure). Hence the effect of the additional proton has to be transported to the binding site via some kind of allosteric mechanism that is currently under investigation.[1]

Several microseconds of MD simulation data of the holo- and apo-protein in different protonation states are analysed, compared and used for the construction of Markov state models. In particular principle component analysis and time-lagged independent component analysis are applied. Force distribution analysis proofed useful for the evaluation of long-lived conformations (centric figure) with respect to their calcium binding ability. Amongst others, a weakly binding conformation was discovered (right figure). However, no large domain involving conformational change can be observed upon protonation that would explain allosteric signal transportation. In contrast, so far a set of local structural variations have been identified that are distributed over the protein network, suggesting a rather *violin*-like model of dynamic allostery as proposed by Kornev and Taylor.[2] These structural elements cover a flexible, so called short loop, parts of the opposed long loop including the calcium binding site and a helix connecting both loops. Especially the short loop-long loop coupling over hydrogen bonded interactions is of interest.

[1]. J. Hanske, S. Aleksić, M. Ballaschk, M. Jurk, E. Shanina, M. Beerbaum, P. Schmieder, B. G. Keller, C. Rademacher, *J. Am. Chem. Soc.*, **2016**, *138*, 12176-12186.
[2]. A. P. Kornev, S. S. Taylor, *Trends Biochem. Sci.*, **2015**, *40*, 628-647.