

Allosteric regulation of the pH-dependent Ca(II)-binding affinity in langerin

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The dendritic C-type lectin receptor langerin plays an important role for the inert immune response of humans and other mammals. Through a high specificity towards mannose, it captures invading pathogens like e.g. HIV, to release them after endocytosis for degradation. For this purpose, the protein needs a calcium(II)-cofactor. The binding affinity to this cofactor is pH-dependent and already sensitive for a change from 7 to 6. The calcium binding pocket is, however, formed by aspartic and glutamic acids, which are not significantly protonated at pH 6. So the question is, how the observed sensitivity of the calcium binding is regulated. In a mutational study the side chain of a histidine (H294) was identified before as a partial pH-sensor, which is interesting because there is no direct contact with the binding-site. Thus, the effect of the additional proton has to be transported via an allosteric mechanism. We aim on explaining this mechanism on the atomic level by the analysis of microsecond long molecular dynamics simulations of the involved langerin species in different protonation states. In particular we use kinetic Markov state modelling for the identification of relevant long lived protein conformations. Furthermore, we use steered-MD setups to simulate the calcium-cofactor release event.

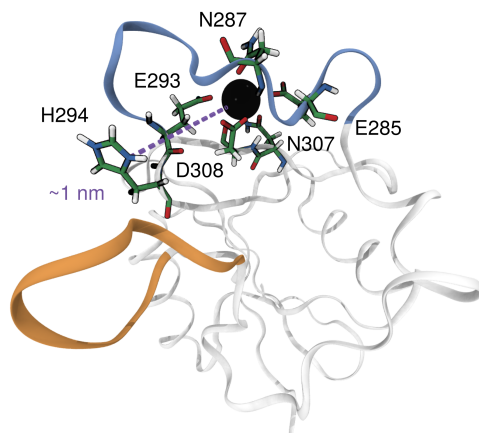


Figure 1: Structure of langerins carbohydrate recognition domain.

References

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