New Insights on the Structural Features of the Different Interleukin 15/Receptor Interfaces Using Molecular Dynamics Simulations

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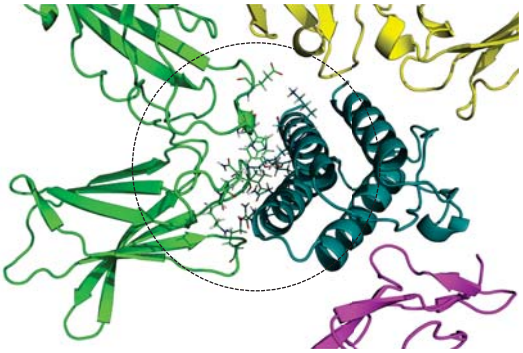
Introduction

- Interleukin 15 (**IL-15**): a tightly regulated pleiotropic cytokine involved in a plethora of different cellular functions. (1)
- **IL15 structure**: based on a quaternary complex between **IL-15** and its α (**IL-15Rα**), β (**IL-15Rβ**) and γ (**IL-15Rγ**) receptors. (2, 3)



The design of ligands targeting IL-15 interfaces requires a deep knowledge of their structure and behavior

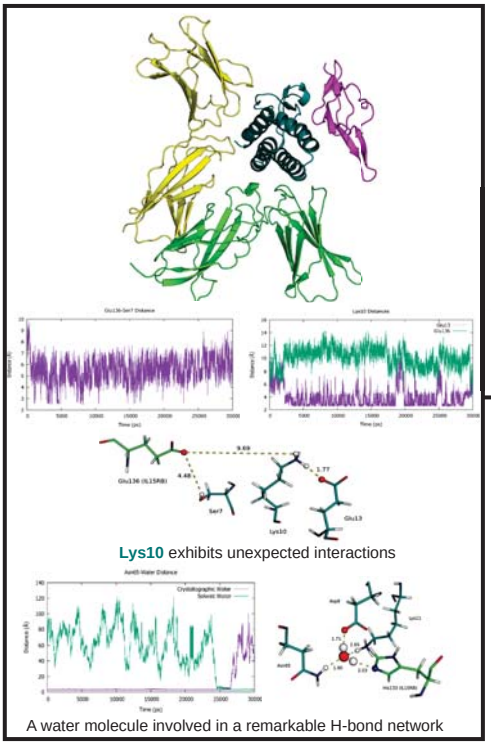
Objectives

- Investigate the time related behavior of the **IL-15**/**IL-15Rβ** interface through MD simulations
- Determine the **key amino acid components** of the interface and their **interactions**.

Methods

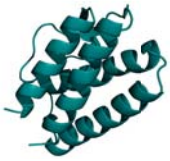
- MD simulations – NAMD (CHARMM3)
- 200 ps equilibration (NVT) followed by 30 ns production (NPT), on the different multimeric models

Results

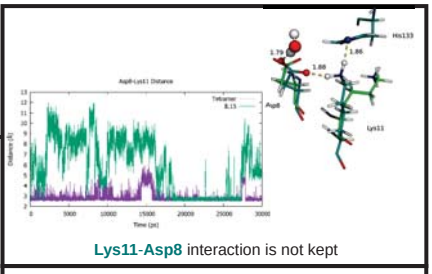


Lys10 exhibits unexpected interactions

A water molecule involved in a remarkable H-bond network

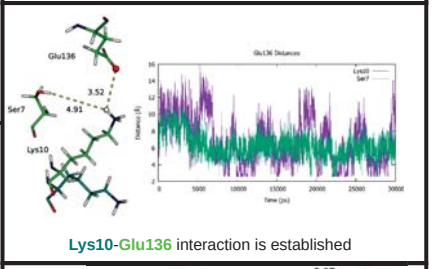


IL-15



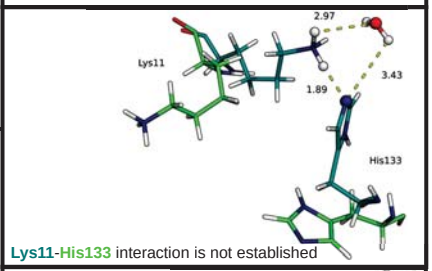
Lys11-Asp8 interaction is not kept

IL-15/**IL-15Rβ**

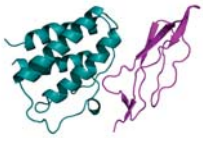


Lys10-Glu136 interaction is established

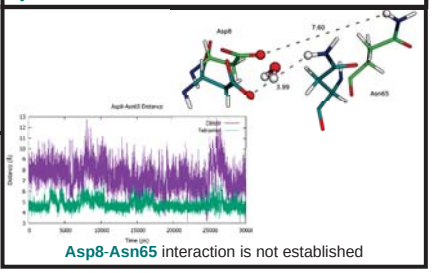
IL-15/**IL-15Rα**/**IL-15Rβ**



Lys11-His133 interaction is not established



IL-15/**IL-15Rα**



Asp8-Asn65 interaction is not established

Conclusions

- MD simulations allow the identification of key features not previously observed.
- The presence/absence of receptor chains directly or indirectly influences the structural features of the **IL-15**/**IL-15Rβ** interface.

Work in progress

- Analyses of the other IL-15/receptor interfaces.
- Study of relevant mutants to probe the influence of key residues in the features of the different interfaces.

References

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(2) Chirifu M., Hayashi C., Toma S. et al. (2007), Crystal structure of the IL-15-IL-15Ralpha complex, a cytokine-receptor unit presented in trans. Nat. Immunol., 8(9):1001-7.

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