The atomistic face of the human MHC-I peptide-loading complex

Olivier Fisette*†[1] and Lars Schäfer[1]

[1]Center for theoretical chemistry, Ruhr-University Bochum – Germany

Abstract

Antigens exposed at the cell surface by major histocompatibility complex class I (MHC-I) proteins enable self/non-self recognition by cytotoxic T cells, protecting the organism against viral infections and cancer-causing mutations. To perform their role, MHC-I must first be loaded with an antigenic peptide in the peptide-loading complex (PLC), a large multi-protein assembly whose atomic-level structure and dynamics are still poorly understood.
Using all-atom molecular dynamics (MD) simulations, we studied key elements of the human PLC, how they stabilise MHC-I and catalyse antigen selection, and how they assemble to form the PLC. By combining microsecond-timescale MD simulations with a recent 6-Å-resolution cryo-EM structure of the PLC, we obtained an atomistic model of the complete complex, in explicit solvent and in a membrane environment (1.5 million atoms). This model offers unprecedented insights into the structure and dynamics of the human antigen-loading machinery.

Our simulations explain how tapasin, a central component of the PLC, acts as both an MHC-I chaperone and a catalyst that accelerates the off-rate of low-affinity peptides to facilitate antigen triage (peptide editing). We also show how tapasin recruits the transporter associated with antigen processing (TAP) into the PLC via transmembrane interactions. Finally, truncating antigens or removing them from the MHC-I binding groove gives a spatially resolved map of MHC-I plasticity which reveals how peptide loading status affects key structural regions.
Taken together, our MD simulations explain experimental kinetics and mutagenesis data, and represent the first in-depth, atomic-level study of the mechanisms underlying the biological function of the PLC, an important step towards a better understanding of adaptive immunity.

Keywords: MD simulations, cryoEM, MHCI, PLC

*Speaker
†Corresponding author: olivier.fisette@rub.de