Jorn M Werner et al., Biol syst Open Access 2016, 5:2 (Suppl)
http://dx.doi.org/10.4172/2329-6577.C1.005

MHC I and antigen selection: Immune system modeling integrates cellular function with structural plasticity

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The control of the immune system plays a key role in both healthy and diseased states and the presentation of peptides at the surface of most nucleated cells by major histocompatibility complex class I molecules (MHC I) is crucial for eliciting or evading an immune response. Since the pool of surface presented peptides only presents a small sample of all possible peptides understanding their selection process is crucial for the development of treatments such as vaccines, which rely on the selection of specific peptides. The peptide selection process is mediated primarily by a weakly interacting multi-protein peptide loading complex (PLC) at the centre of which is the modulation of MHC class I conformation. To gain a better understanding of the mechanisms of peptide selection by MHC I, we developed computational systems models encoding distinct mechanistic hypotheses of PLC function. Using *in vivo* biochemical data we were able to infer that the system is under kinetic control and that a conformational intermediate of MHC I is significant for peptide selection. We investigate the molecular determinants of peptide selection using a combination of X-ray, NMR and biophysical techniques together with molecular dynamics simulations. Using this approach we show that peptide selector function correlates with protein plasticity rather than structure. This in turn was tested experimentally *in vivo* and extended to the PLC resident chaperone tapasin. By combining computational systems models with in-cell biochemical data and structural methods we identify a previously undetected correlation between protein plasticity and *in vivo* peptide selector function of MHC I, with implications for host defense and immunotherapy.

Biography

Jorn M Werner has received his PhD in Biochemistry from the University of Oxford and established his own research group at the University of Southampton in 2003. His interdisciplinary research group integrates structural biochemistry with cellular function using systems model approaches. He has published over 50 peer reviewed papers and is serving as an Editor for *Science Reports* as well as *Frontiers in Structural Biology.*

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