Dynamical modelling of T cell co-inhibitory pathways to predict anti-tumour responses to checkpoint inhibitors

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In recent years, T cells were recognized to often display a reduced ability to eliminate cancer cells, caused by the expression of co-inhibitors at their surface. Antibodies blocking these co-inhibitors (checkpoint inhibitors) have become standard treatment for metastatic melanoma (Simpson et al. 2013), thus leading to a revival in the study of T cell co-inhibitors. However, our understanding of their immunobiology and their harmful role during anti-tumour responses remains fragmentary. Particularly, a mechanistic understanding at the systems-level of T cell function modulation by co-inhibitors has remained elusive.

To overcome these limitations, we aim to delineate the mechanisms through which co-inhibitory molecules, such as PD-1 and CTLA-4, impede T cell functions at the systems-level. To reach this goal, we use computational methods to map and model TCR co signalling pathways, and ultimately predict cell responses to perturbations. First, we developed comprehensive annotated molecular maps (using the software CellDesigner, http://www.celldesigner.org) by curated scientific literature, automated queries to public databases and protein-protein graph reconstruction. Next, using the software GINsim (http://www.ginsim.org), these maps and protein networks were translated into a regulatory graph integrating current knowledge. The major challenge was then to properly model concurrent intracellular processes, along with feedback control mechanisms. To cope with this complexity, we explored network modules using a Rule-based formalism (Feret et al. 2009), in order to evaluate concurrent biological hypotheses and specify logical rules that recapitulate observed component behaviour into the logical model. The resulting integrative model will be used to predict cell response to single or multiple perturbations, thus paving the way to delineate novel experiments, which in turn will be used to refine the maps and model. This integrated systems-level view of the action mechanisms of key T cell coinhibitors will provide a further rationale for designing and evaluating drugs targeting T cell co-inhibitory pathways in anti-cancer immunotherapy.