Control of T cell responses by accessory receptors revealed by phenotypic modelling

Nguyen, J.[1], Gaglione, S.[1], Pettmann, J.[1], Kruger, P.[1], Trendel, N.[1], Kutuzov, M.[1], Dushek, O.[1]

[1]Sir William Dunn School of Pathology, Oxford, UK

1. Abstract

T cells are important immune cells that are routinely being exploited for a number of different therapies. They are activated to respond when ligands bind to various receptors on their surface. This binding initiates signalling pathways that ultimately induce responses important for clearing infections and cancers. A key open question is how ligation of different surface receptors quantitatively control their responses. To address this, we have been systematically stimulating T cells with different combinations of ligands (input) and measuring their responses (output). Using systematic mathematical inference algorithms, we identify effective pathway models that intuitively explain how inputs are converted to outputs ('causal inference'). Here, we show that T cell response outputs to constant antigen ligand input induces perfect adaptation and that ligation of different accessory receptors (CD2, CD28, LFA-1, CD27, 4-1BB, GITR, and OX40) control this phenotype differently. Initial results with the inference algorithm suggest that an incoherent feedforward coupled to a digital switch can explain perfect adaptation along with the different phenotypes observed by the different receptors. The work offers a new way to infer effective signalling pathways directly from quantitative cellular response data.