Phenotypic models of T cell activation

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T cells are white blood cells that play an important role in immunity. While much progress has been made in discovering what molecules constitute the signaling network within the T cell, the functional relationship between these molecules remains unclear. We take the approach of generating a phenotypic model in order to understand this network, informed from a quantitative dataset generated by stimulating T cells expressing a high affinity therapeutic receptor with ligands that have a million-fold range in affinity. This modelling approach can explain the entire dataset, the majority of published data and help elucidate the signaling network.

Phenotypic models, T-cell signaling, systems biology, signal transduction, immunology

I. INTRODUCTION

T cells are important immune cells that initiate and regulate the adaptive immune response to infections and cancer. Much progress has been made in molecular immunology to identify the molecules that form the signaling network inside the T cell [1]. However, this network is complicated and it is unclear how these molecules functionally interact with each other. Numerous experimental studies have shown that it is the binding parameters between T cell receptors and their ligands that determine the functional response of the T cell [2-5]. Knowledge of the relationship between stimulation strength and response can offer insight into the structure of the signaling network. Despite extensive study, there is still no mathematical model that can explain this relationship consistently with the published data [6]. We have taken the approach of developing a phenotypic model inferred by a quantitative dataset in order to elucidate this signaling network.

II. RESULTS

We present a phenotypic model of T cell activation that has been inferred from a quantitative dataset. The dataset has been generated by stimulating T cells expressing a therapeutic high affinity T cell receptor with ligands that span a million-fold range in affinity. The phenotypic model consists of kinetic proofreading with limited signaling [6] coupled to an incoherent feed-forward motif [7]. The model is able to explain all key features of the dataset: ligand discrimination, an optimal ligand binding time and an inhibition in the response at high doses. It is also able to explain the majority of published data [2-5,8]. Furthermore, we can show how the model can inform where molecules lie in the signaling network. By comparing perturbations of the model with knock-down experiments, the role of a molecule within the signaling network can be found.

III. CONCLUSION

We have shown how the approach of generating a phenotypic model of T cell activation can yield a tractable model that can explain the experimental data and provide information on the structure of the underlying signaling network. It is an approach that can be applied to signaling networks more broadly.

M.L. is supported by a Doctoral Training Centre Systems Biology studentship from the Engineering and Physical Sciences Research Council (EPSRC). O.D. is supported by a Sir Henry Dale Fellowship that is jointly funded by the Wellcome Trust and the Royal Society (grant number 098363).

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