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Mathematical modelling of Natural Killer Intracellular Mechanisms

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Background

Natural killer (NK) cells play a role in host rejection of aberrant cells – for example, by inducing apoptosis of tumour cells, or virally infected cells.

NK function is achieved via a balance of activation and inhibition, in response to proteins expressed on 'target cells'.

The balance between activation and inhibition can be perturbed, depending on the localisation of the NK cell within the body. Of particular interest is pregnancy, where expression of uterine NK cell receptors is significantly different to circulating peripheral NK cells. This may play a role in mum's immune tolerant response to the fetus, but the role of NK cells in this process is not yet fully understood.

A modular approach to understanding NK cell function

Mathematical models enable complex signaling pathways to be interpreted by physical laws governing reaction kinetics. Curated models of numerous pathways exist, including a number of components of NK cell intracellular signaling (models.physiomeproject.org).

To manage the complexity of NK cell intracellular signaling, and to allow reuse of existing models from the literature, we simplify the system into smaller modules that can be solved and validated against biological data alone or within a larger system (Fig 1).

Pathway construction

A comprehensive qualitative description of the intracellular signalling pathways leading to chemokine and cytotoxin release from pNKs is available from the KEGG database (https://www.genome.jp/kegg-bin/show_pathway?hsa04650). Using this database and a keyword searches on This collection of pathways is also based on keyword searches for 'NK cell receptors', 'NK cell signalling pathways' and, 'expression of natural killer signalling pathways molecule' the key pathways relevant to NK cell signalling from cell surface receptor to cytokine release were identified (Fig 2).

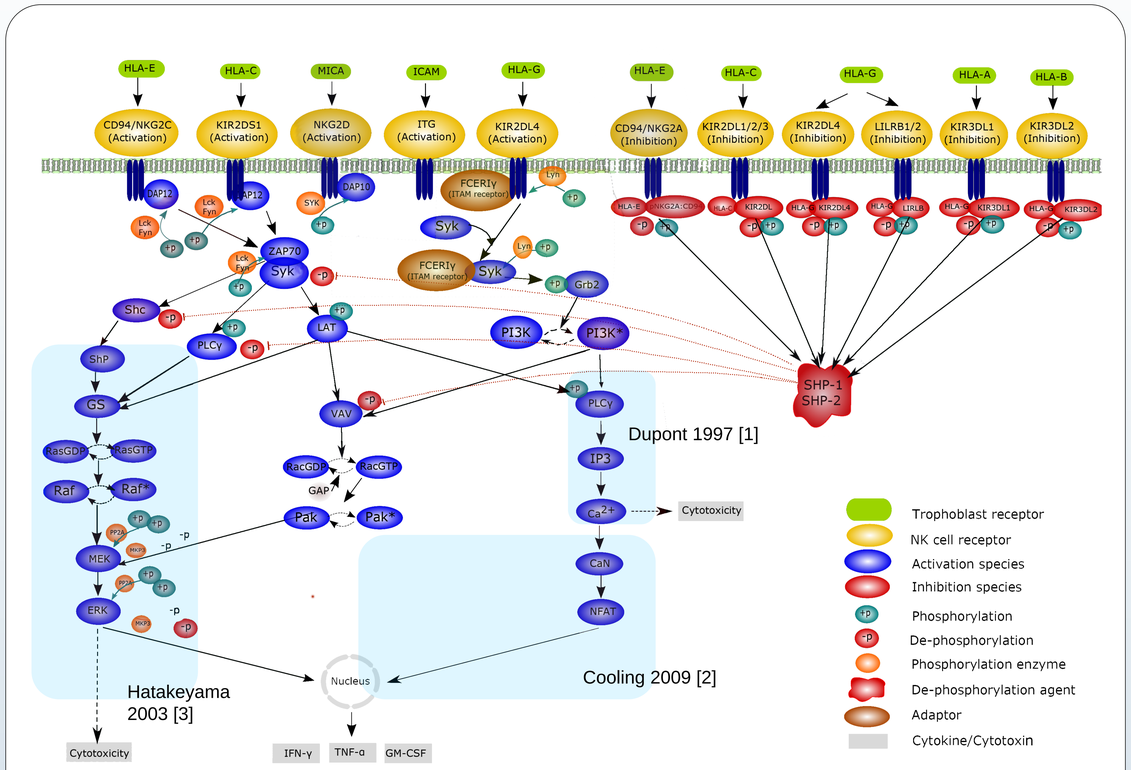

Fig 2: Complete NK cell signaling pathway created based on KEGG database and literature survey.

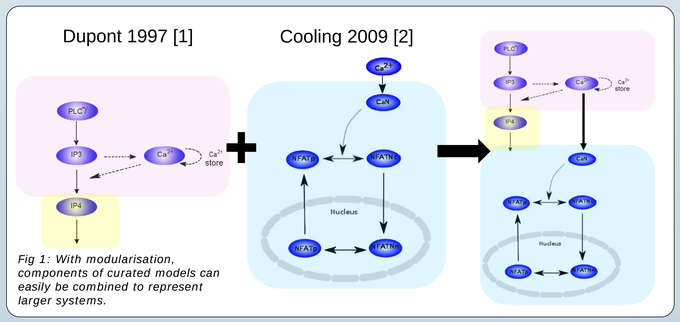

Fig 1: With modularisation, components of curated models can easily be combined to represent larger systems.

Reusing existing models

Three curated published models were available [1,2,3], highlighted in blue in Fig 2. These models were modularised to facilitate reuse, and tested for accuracy in the published system before incorporating into the NK cell network (Fig 3).

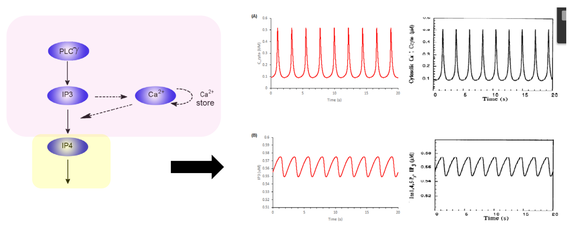

Fig 3: Models were modularised, and compiled to be tested against published results, prior to reuse of modules. Here the model of Dupont and Erneaux [1] is shown.

Novel modules

The literature was surveyed for data that could be used to parameterise key components of the intracellular signaling pathways in NK cells. For each new module, rate constants were fitted to ensure consistency with experimental data (Fig 4).

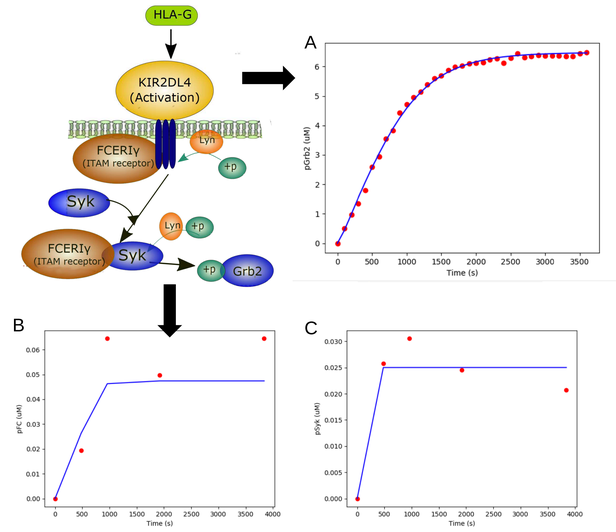

Fig 4: Unknown parameters in new modules (or combinations of modules representing components of the NK cell intracellular signaling pathway) were fitted to literature data, where available. For example, a model was compiled to represent the biology of FCERIγ (ITAM receptor) interactions with Syk and Grb2. The model was compared to data from Tsang et al. [4] (A) and Faeder et al. [5] (B,C).

Summary

A comprehensive model of NK cell intracellular signaling in response to activation and inhibition receptor interactions with target cells was constructed. This model is freely available, and provides a framework for investigating perturbations in NK cell receptor expression (e.g. in promoting immune response in pregnancy).

References

[1] Dupont and Erneux. Cell Calcium, 22(5):321–331, 1997.
[2] Cooling, Hunter, Crampin. Biophysical Journal, 96(6):2095–2104, 2009.
[3] Hatakeyama et al. Biochemical Journal, 373(2):451–463, 2003.
[5] Tsang et al. Journal of Biological Chemistry, 283(47):32650–32659, 2008.
[6] Faeder et al. The Journal of Immunology, 170(7):3769–3781, 2003.

Acknowledgements

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