Modelling Atopic Dermatitis using Petri Nets

Marta E Polak

Clinical and Experimental Sciences, University of Southampton, Faculty of Medicine, Mailpoint 825, Level F, South Block, Sir Henry Wellcome Laboratories, Southampton General Hospital, Southampton, SO16 6YD, United Kingdom,
m.e.polak@soton.ac.uk

1 Background

Atopic dermatitis (AD) is a disorder of inflammation in the skin and is strongly associated with other inflammatory epithelial atopic conditions (asthma, allergic rhinitis and food allergy). The pathogenesis of AD results from complex interactions between susceptibility genes encoding skin barrier molecules and markers of the inflammatory response, host environments, infectious agents, and specific immunologic responses [1-3]. Despite the long-held knowledge about the multiple immunological processes involved in AD pathogenesis (including role of dendritic cells, kerationocytes and T lymphocytes, interactions between different cell types, effect of allergen exposure, trauma and infection with Staphylococcus Aureus on the AD exacerbations) the precise reason for the bias towards a cutaneous Th2 response in AE still remains obscure. It seems likely that understanding of the complex cross-talk between different components of the cutaneous immune network is fundamental to understanding of the Th2 polarised inflammation in AD.

To gain in-depth understanding and be able to predict the behavior of the system, we sought to create an integrated in silico model compositionally from relatively simple individual components that are amenable to detailed mathematical analysis. The simple, initial model described in this contribution will serve as a high level architectural specification of AD skin and immune system interactions. In the future we plan to harness data from microarray analysis in order to refine the individual model components by incorporating the reconstructed signal transduction pathways within cellular components.

2 Model description

Petri nets have been widely used in modelling biochemical, genetic, signaling and metabolic networks [7-9]. We however feel that the modelling of AD requires a multistep approach, embedding the investigations of the internal genetic or metabolic signaling cascades within the detailed analysis of the interactions between the cellular components of the cutaneous immune system. The preliminary model of cell-to-cell signaling in AD exposed to allergen and infected with S.A. incorporates three cell types (KC, DC and T cells), where KC and T cells are

simplistically represented as places. The signaling within DC is represented by two independent pathways, TNF-α–NFκB-dependent IL-12p70 initiating Th1 responses and TSLP-STAT3-OX-40L pathway inducing Th2 responses. The signaling proteins are represented as places and are connected by activating (black arrows) and inhibiting (red diamond arrows) edges.

The model was constructed using yEd graphical software, and BioLayout Express3D [10] was used to simulate the signal flow allowing investigating the dynamic behaviour of the network dependently on presence/absence of inhibition edges, conservation or consumption of the tokens at the transitions, and the value of initial stimulation given by the number of tokens. To represent healthy skin and AD skin firings via TNF-α or TSLP were inhibited, respectively, and the simulation for altered number of tokens at each starting place was repeated as for the initial state of the network. Similarly, the effect of S.A. infection (0-1000 tokens) and combined effect of Der-p-1 and S.A. in exclusive Th1/Th2 or both pathways enabled models was investigated.

As assumed, stimulation with der-p-1 in AD model induced only Th2 responses, which were greatly enhanced in the presence of Staphylococcal infection. While in normal skin model infection with SA led to induction of both Th1 and Th2 responses, stimulation of AD model resulted in Th2 skewing. Induction of Th2 polarisation depended on blocking of the Th1 signaling, rather than enhancing Th2 signaling.

Acknowledgements

I am very grateful to Dr. Mike Ardern-Jones and Dr. Pawel Sobocinski for critical review of the manuscript. I would also like to thank Prof. Tom Freeman for advice on Petri nets and model construction. This study has been funded by British Skin Foundation.

References

1. Boguniewicz M, Leung DY. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. Immunol Rev. 242(1):233-46.(2011)
2. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med. 365(14):1315-27 (2011)
3. Hamid Q, Boguniewicz M, Leung DY. Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. J Clin Invest. 1994 Aug;94(2):870-6.
4. Niebuhr M, Werfel T. Innate immunity, allergy and atopic dermatitis. Curr Opin Allergy Clin Immunol. 10(5):463-8. (2010)
5. Zaba LC, Krueger JG, Lowes MA. Resident and "inflammatory" dendritic cells in human skin. J Invest Dermatol. 129(2):302-8 (2009)
6. Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, Gilliet M, Ho S,Antonenko S, Lauerma A, Smith K, Gorman D, Zurawski S, Abrams J, Menon S,McClanahan T, de Waal-Malefyt Rd R, Bazan F, Kastelein RA, Liu YJ. Human epithelial cells trigger dendritic cell mediated allergic in-flammation by producing TSLP. Nat Immunol. 3(7):673-80 (2002)

7. Ruths D, Muller M, Tseng JT, Nakhleh L, Ram PT. The signaling petri net-based simulator: a non-parametric strategy for characterizing the dynamics of cell-specific signaling networks. PLoS Comput Biol. 29;4(2):e1000005 (2008)
8. Heiner M, Koch I, Will J. Model validation of biological pathways using Petri nets–demonstrated for apoptosis. Biosystems. 75(1-3):15-28 (2004)
9. Moore JH, Boczko EM, Summar ML. Connecting the dots between genes,biochemistry, and disease susceptibility: systems biology modeling in hu-man genetics. Mol Genet Metab. 84(2):104-11. (2005)
10. Theocharidis A, van Dongen S, Enright AJ, Freeman TC. Network visualization and analysis of gene expression data using BioLayout Express(3D). Nat Protoc. 4(10):1535-50 (2009)