An *in silico* approach to aid in assessing the risk of chemical-induced skin sensitization

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Chemical-induced skin sensitization leading to allergic contact dermatitis is the most common manifestation of immunotoxicity in humans and an important occupational and environmental health issue. The need for alternative (i.e., non-animal) approaches in the human safety evaluation of this toxic endpoint has motivated the development of *in vitro* assays that aim to be predictive of skin sensitization induction [1-4]. However, the nature of such assays restricts their assessment to a few pathways of the overall biological response. Furthermore, understanding of how individual pathways contribute to the system level response is poorly understood. To address this knowledge deficit, we have developed an *in silico* model with which we analyze the relative contribution of individual pathways involved in the induction of skin sensitization.

We present a mechanistic mathematical model of skin sensitization induction. The model is constructed as a series of linked modules that express our current understanding of the cellular and molecular interactions involved in the epidermis and draining lymph node. The model includes a representation of the following key events: (1) chemical exposure in the epidermis; (2) epidermal cell activation and cytokine production; (3) chemical uptake and antigen processing by epidermal Langerhans cells (LCs); (4) LC traffic to the draining lymph node (LN); (5) antigen presentation and costimulation in the LN, and (6) the resulting CD4+ and CD8+ T cell response.

The model is constructed in a "top-down" manner to focus on the biological components and dynamics most relevant to skin sensitization induction. Both qualitative and quantitative information from papers in the contemporary literature were utilised. In order to calibrate the model, available quantitative data was incorporated such that the appropriate individual modules of model could reproduce key results from published experiments (e.g. Keratinocyte cytokine response to chemical stimulus). The entire model was then evaluated by using experimental data

taken from published papers (distinct from those used for calibration purposes) to ensure that the system-level behaviours (e.g., extent of T-cell proliferation) associated with chemical-induced skin sensitization were reproducible.

Interestingly, in order to explain LN cellularity data reported in the literature, the model requires the inclusion of enhanced cellular recruitment to the LN upon sensitizer exposure: a mechanism not previously appreciated in the context of skin sensitization. Furthermore, sensitivity analysis of the model reveals that non-antigen-specific and antigen-specific pathways are as significant as each other in the induction of skin sensitization. These results indicate that any collection of *in vitro* assays predictive of a chemical's potential for inducing skin sensitization will need to assess both non-antigen-specific and antigen-specific pathways.

Reference List

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