Development and validation of an agent-based computational model of normal human keratinocytes organisation *in vitro*

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Abstract: An agent-based computational model was developed to describe the dynamic multicellular morphogenesis of normal human keratinocytes (NHK) in monolayer culture at low (0.09mM) and high (2mM) exogenous Ca++ environments. *In silico* hypothesis testing indicated that cell-cell contact, cell-substrate contact, and differentiation of transit amplifying (TA) cells were major mechanisms, whereas cell cycle times of both stem and TA cells had no obvious effects on the pattern of NHK distribution. The model suggested that the limited divisional capability of TA cells wasn't an internal cell property but a statistical phenomenon. By deliberately omitting the rules for the stem cell colony autoregulation and for cell differentiation mechanism, the population growth of a transformed keratinocyte cell line (HaCat cells) was also successfully described. The model of NHKs was then used in a predictive sense. Simulation of scratch wounds made to NHK cells indicated that wound healing in low [Ca2+] media would be achieved mainly by migration and subsequent proliferation. In physiological [Ca2+] media, a stem cell position dependent wound closure pattern was predicted. Both were then validated by *in vitro* experiments designed to check the model's predictions. This work demonstrates that an agent-based model, incorporating rules relating to relatively few mechanisms, is sufficient to describe, explain and predict some biological phenomena seen when keratinocytes and transformed keratinocytes are cultured *in vitro*.

Key words: Computational modelling, keratinocyte, HaCat cells, calcium, wound healing