How do keratinocytes count melanocytes and plant them in just the right places in the epidermis?

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In normal human skin, melanocytes lie adjacent to the basal lamina, interspaced between the basal keratinocytes. Meanwhile, melanocytes project dendrites through keratinocyte layers and interact with keratinocytes in a tightly regulated fashion. Research indicates that one melanocyte contacts approximately 36 keratinocytes to form the so-called epidermal melanin unit, which is achieved by a series of coordinated efforts by different keratinocytes and melanocytes responding to a complex array of signals produced by different types of cells in the skin (Pelc & Nordlund 1993). While there is growing knowledge of how individual cells respond from the genome through to the proteome and metabolome, it is difficult for biologists to integrate this growing body of new data and regenerate a holistic view of the organism (Rashbass, 1996). Computational modelling provides a powerful tool to handle this complexity, as it is capable of processing and organizing a huge amount of complex biological data, connecting experimental results to fundamental biological principles, thus improving our understanding of a complex biological system such as tissue morphogenesis and pathogenesis.

In addition to the massive literature about the complex interactions between these two types of cells, the following *in vitro* and *in virtuo* findings in our lab might help the modelers to establish a computational model.

1. The epidermal melanin unit can be reproduced beautifully using our *in vitro* tissue engineered 3D model (Figure 1a), which can be used to validate or test computational models.
2. Research from several groups including this one indicates that there is a mechanism for keratinocytes to control the number of melanocytes when the two types of cells are co-cultured in either 2D or 3D *in vitro* models-essentially the number of melanocytes are always down regulated by keratinocytes to a certain " pre-ordained "level no matter how many melanocytes are used initially (Eves et al, 2008).
3. Both 2D and 3D *in vitro* models indicate that the melanocytes can only survive when they attach to the culture surface (Figure 1b) or 3D dermal scaffold, suggesting the importance of the interactions between melanocytes with basal keratinocytes, and melanocytes with the ECM or scaffold.
4. Keratinocytes form very regular colonies due to an auto-regulation mechanism. The cell-cell bonds between keratinocytes change as the cells differentiate.

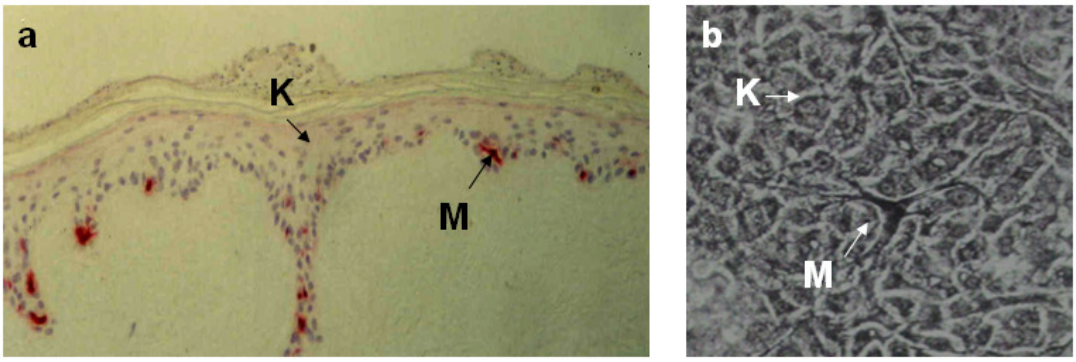

Figure 1: Appearance of keratinocytes (K) and melanocytes (M) in (a) an in vitro 3D model and (b) a 2D coculture model.

In summary, our research indicates that cell-cell and cell-substrate bonds might play a very important role in the formation of the epidermal melanin unit.

The problem proposed involves developing further existing agent based keratinocyte colony formation models (Sun et al, 2007) or developing new mathematical models to describe the complex interactions between keratinocytes and melanocytes at multi-cellular, cellular and sub-cellular levels, which should be accessible to biologists and can be linked directly with experimentation in the lab. Another aim is to produce a computational model that will be considerably less computationally expensive than existing agent based approaches.

References

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