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Mimicking normal tissue architecture and perturbation in cancer with engineered micro-epidermis

Julien E. Gautrot [a,b,c], Chunming Wang [a,b], Xin Liu [a], Stephen J. Goldie [d], Britta Trappmann [a], Wilhelm T.S. Huck [a,e,*], Fiona M. Watt [b,d,**]

[a] Melville Laboratory for Polymer Synthesis, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK
[b] Wellcome Trust Centre for Stem Cell Research, University of Cambridge, Tennis Court Road, Cambridge, CB2 1RE, UK
[c] School of Engineering and Materials Science, Queen Mary, University of London, Mile End Road, London, E1 4NS, UK
[d] Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, Robinson Way, Cambridge, CB2 0RE, UK
[e] Radboud University Nijmegen, Institute for Molecules and Materials, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands

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ABSTRACT

Correct tissue architecture is essential for normal physiology, yet there have been few attempts to recreate tissues using micro-patterning. We have used polymer brush micro-engineering to generate a stratified micro-epidermis with fewer than 10 human keratinocytes. Epidermal stem cells are captured on 100 μm diameter circular collagen-coated disks. Within 24 h they assemble a stratified micro-tissue, in which differentiated cells have a central suprabasal location. For rings with a non-adhesive centre of up to 40 μm diameter, cell–cell and cell–matrix adhesive interactions together result in correct micro-epidermis assembly. Assembly requires actin polymerization, adherens junctions and desmosomes, but not myosin II-mediated contractility nor coordinated cell movement. Squamous cell carcinoma cells on micro-patterned rings exhibit disturbed architecture that correlates with the characteristics of the original tumours. The micro-epidermis we have generated provides a new platform for screening drugs that modulate tissue assembly, quantifying tissue stratification and investigating the properties of tumour cells.

1. Introduction

Recent advances in micro-patterning technology have made it possible to identify key microenvironmental cues that regulate stem cell behaviour at single cell resolution [1,2]. However, the architectural and functional complexity of tissues is essential for their physiology [3,4], yet there have been few attempts to use micro-patterning to recreate tissues *in vitro* [5,6]. This is an important goal because it opens the way for designing screens for small molecules that modulate tissue physiology and a platform for uncovering disease mechanisms that operate at the level of groups of cells rather than at the single cell level.

Human epidermis is an obvious tissue to engineer at the micro-scale. The interfollicular epidermis is a multi-layered epithelium in which the basal layer of cells is attached to an underlying extracellular matrix (ECM), known as the basement membrane, and the suprabasal layers comprise cells that undergo terminal differentiation, culminating in formation of the barrier that protects the body from water loss and penetration by micro-organisms. As the outermost cells are shed from the surface of the epidermis they are replaced by proliferation of stem cells in the basal layer. There are well-characterised markers of the terminal differentiation process, including involucrin and transglutaminase 1 (Fig. 1a) and a number of markers that enrich for stem cells, including β1 integrins, Lrig1 and Dll1. Cultured epidermis is used to provide long-term autologous grafts for burns victims, providing evidence that stem cells persist in culture. In addition, cells can be cultured from tumours of the epidermis and other multi-layered epithelia, such as the oral cavity, and these can be used to study changes in cell behaviour linked to cancer.

We, and others, have previously used micro-patterning techniques to culture single cells on ECM-coated islands of defined shape and size [1,2,7,8]. Here, we used micro-patterned

* Corresponding author. Radboud University Nijmegen, Institute for Molecules and Materials, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands. Tel.: +44 1223 334370; fax: +44 1223 334866.
** Corresponding author. Wellcome Trust Centre for Stem Cell Research, University of Cambridge, Tennis Court Road, Cambridge, CB2 1RE, UK.
E-mail addresses: w.huck@science.ru.nl, wtsh2@cam.ac.uk (W.T.S. Huck), fiona.watt@cancer.org.uk (F.M. Watt).

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