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Hair-follicle dermal papilla and sheath fibroblasts provide a supportive microenvironment for human skin regeneration

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Hair-follicle dermal papilla and sheath fibroblasts provide a supportive microenvironment for human skin regeneration

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This issue of *BJD* includes a paper from Higgins *et al*.,[1] reporting an important advance in skin regeneration, demonstrating that human hair-follicle-associated dermal cell populations can provide the necessary signals for complete human epidermal tissue regeneration. These data are valuable given that replacing extensive skin tissue loss resulting from injuries, burns or genetic defects remains a challenge, particularly in the face of restrictions on the use of animal products imposed by regulatory agencies. The most widely used technique for skin replacement is autografting from another body site – an option that is not always available to patients with extensive skin loss – and also one

that does not yield an aesthetically pleasing outcome. For patients where skin loss encompasses much of the body surface, the patient's remaining healthy skin is harvested, and the keratinocytes isolated from it for expansion in culture, prior to autografting, as epithelial sheets.

The best technique for clonal human keratinocyte expansion remains co-culture with an irradiated or mitomycin C-treated feeder layer of the J2 strain of Swiss 3T3s – a 'fibroblastic' cell line derived from mouse embryos – developed by Rheinwald and Green.[2] This technique and subsequent work in 3D organotypic models provides strong evidence that mesenchymal cell-derived secreted factors are critical for skin regeneration.[3,4] A thorough evaluation of alternatives to murine Swiss 3T3s in both 2D monolayer cultures and 3D organotypic cultures has not been undertaken. However, it has been demonstrated that human skin-derived dermal fibroblasts,[5,6] particularly those originating from the papillary dermis located adjacent to the interfollicular epidermis, were better at promoting epidermal regeneration than those from the deeper reticular dermis.[7] Dermal pericytes[8] and adipose-derived mesenchymal stem cells[9] can also support skin regeneration in organotypic cultures. Notably, dermal pericytes were capable of conferring improved skin regenerative capacity on interfollicular keratinocytes that were already committed to differentiate, when combined with dermal fibroblasts.[8]

The team of Jahoda and colleagues previously reported that hair follicle-associated mesenchymal cells, specifically the hair-inductive dermal papilla fibroblasts and dermal sheath fibroblasts, promote greater keratinocyte colony-forming efficiency than dermal fibroblasts in 2D culture.[10] In the current study, this group[1] advances this knowledge further, demonstrating that dermal papilla and dermal sheath fibroblasts – normally associated with hair follicle regeneration – can also support interfollicular skin regeneration in organotypic cultures. Moreover, the full programme of epithelial proliferation and differentiation was observed as judged by the presence of a $Ki67^{+}/K5^{+}$ basal layer and suprabasal expression of the keratinocyte differentiation markers K1 and loricrin. Further, the quality of the regenerated interfollicular epithelium obtained with these heterotypic fibroblasts was substantially improved with respect to basement membrane assembly compared with the results obtained with homotypic interfollicular dermal fibroblasts. Consistent with this, Cho *et al*. have reported improved α6 integrin expression in organotypic cultures containing dermal sheath vs. interfollicular skin-derived dermal fibroblasts.[11] Importantly, Higgins *et al*.[1] provide conclusive evidence that hair follicle-associated fibroblasts could be utilized in clinical applications to generate 3D skin reconstructs for transplantation without compromising skin integrity.

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