COMMENTARY
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Cell Movement in the Hair Follicle Dermis – More Than a Two-Way Street?

Colin A. B. Jahoda
University of Durham, UK

Since the pioneering work of Oliver (1980) the hair follicle dermal papilla, the specialized body of dermal cells at the base of the structure, has been recognized as having a governing influence on follicle epithelium. As the key signaling center, the papilla is responsible for maintaining the growth of hair and orchestrating events during the hair cycle, and the cells of the papilla have a developmental gene expression profile that reflects this complex role (Stenn and Paus, 2001). Recently, however, considerable interest has switched to the adjacent dermal sheath, the other main dermal component of the follicle. Anatomically, sheath cells connect with the base of the dermal papilla and then form a sleeve around the epithelium along the length of the follicle. Papilla and sheath cells have the same embryological origin, and sheath cells can replace the dermal papilla in experimentally amputated follicles (Oliver, 1966a); therefore, perhaps unsurprisingly, they possess many common features. However, sheath cells have generally been regarded as a reserve population, not normally recruited into undamaged papillae, and lacking some of the inductive properties of the papilla cells.

In this issue, McElwee *et al* (2003) have revisited the relationship between follicle dermal papilla and dermal sheath cells. Using GFP labeled mice they show that cells from the dermal sheath population immediately adjacent to papilla bulb termed the dermal sheath cup (DSC), can induce follicle formation when transplanted into the ear or footpad skin. They conclude that cells in this DSC compartment are functionally similar to the DP cells, and different from dermal sheath cells located higher up the follicle. In addition, DSC and DP cells both express alkaline phosphatase *in vivo* and *in vitro*, leading the authors to suggest that this might be a marker of inductive follicle dermis. Here, the significance of these findings is examined in the context of the older dogma, other recent studies, and some new thoughts about dermal stem cells in the hair follicle.

DERMAL CELL RECRUITMENT INTO FOLLICLES

One of the intriguing observations to emerge from the study in this issue (McElwee *et al*, 2003) is that labeled dermal papilla and dermal sheath cells were incorporated into the papillae of local hair follicles, causing their enlargement and apparently altering their growth characteristics. Recruitment of papilla cells is a phenomenon that has been speculated on in previous implantation experiments (Jahoda *et al*, 1993). In related work, it was recently shown that labeled DS cells implanted into skin wounds homed to, and became incorporated into, intact follicles some distance from the wound margins (Gharzi *et al*, 2003). These new findings have particular significance for those interested in hair follicle restoration by transplantation of cultured follicle dermal cells, since up to now, the attempts to translate animal work to a human context has focused on the creation of completely new follicular structures. The fact that follicle dermal cells can be recruited into existing follicles suggests the possibility of augmenting the size of existing follicles rather than creating new ones. In androgenetic alopecia, it raises the prospect of being able to convert small vellus follicles into large terminal structures, or perhaps more realistically of halting the reduction of follicle size during the terminal to vellus transition, by the judicious local addition of appropriate cells.

DERMAL SHEATH – DERMAL PAPILLA TRANSITION

McElwee *et al* look beyond their experimental study and suggest that DSC cells may also be a source of cells for the dermal papilla via migration during the normal hair cycle. The idea that there is movement of cells between the dermal sheath and dermal papilla during the normal hair cycle is not new (Oliver, 1991; Jahoda, 1998). Upward follicle regression at catagen and downward extension in early anagen have previously been identified as likely points for cell movements since these are when follicle reorganization is at its most mobile/labile. However, in this regard another recent study (Tobin *et al*, 2003a) is of crucial significance because, for the first time, the authors provide direct evidence that dynamic interconversion between the dermal sheath and dermal papilla does take place, and that the DP population is not as stable as previously thought. Specifically, the work provides evidence that dermal sheath cell division contributes directly to the recruitment of cells into the dermal papilla in early anagen, and that migration of cells into the dermal sheath (rather than apoptosis) causes the reduction in size of the papilla during catagen. The implications of these findings are discussed further in a related article (Tobin *et al*, 2003b). By demonstrating experimentally that cultured bulb dermal sheath cells can be incorporated into existing follicle dermal papillae, McElwee *et al* (2003) add to evidence from regeneration experiments that sheath cells can supplement papilla cell numbers or indeed replace a complete papilla (Oliver, 1966b). Conversely, where new follicles have been induced by the interaction of intact papillae with skin epithelium, it appears that the new dermal sheath is derived from the dermal papilla (Jahoda, 1992).

COMPARTMENTS IN THE HAIR FOLLICLE DERMIS

The cumulative evidence suggests that, within the follicle, DS cells are a reservoir or stem cell source for the papilla. In this regard, there are distinctive parallels with the epithelial outer root sheath of the follicle, an anatomically distinct subpopulation of which (the bulge cells) are believed to contribute to the matrix during the cycle (Cotsarelis *et al*, 1990). This brings up the question of whether there are also specific DS cell compartments. If McElwee *et al* are correct, the close phenotypic and functional relationship between the DSC cells and the DP segregates them from the rest of the DS. But what is the evidence that this is a

specialized DS cell compartment? In work using microinjected dyes to investigate compartmentalization within rodent follicles, no clear evidence was found for a junctional link between the papilla and adjoining dermal sheath cells (Kam and Hodgins, 1992; Choudhry *et al*, 1997). However, in a recently published paper in which the location and density of gap junctions was investigated in human hair follicles using EM and antibody staining, clear evidence of gap junctions was found within separate DP and DP compartments (Iguchi *et al*, 2003). Moreover, a particularly strong line of expression of gap junction proteins was observed at the base of the follicle exactly at the junction between the DP and the DS cells. Indeed, the authors postulated that these may "form a sort of functional syncytium through the gap junctions by which they may play a pivotal role in controlling hair growth and its cycle". Nevertheless there is evidence that, functionally, dermal sheath cells from above the DSC are not dissimilar to those in the bulb region. For example, Oliver (1967) showed that dermal sheath cells from the middle of the follicle were able to regenerate a DP within implanted follicle sections. Moreover, another group have shown that dermal sheath cells from the upper half of follicles can regenerate when transplanted ectopically into the kidney capsule (Matsuzaki *et al*, 1996). Therefore, there are circumstances in which other follicle DS cells can become papilla cells. These discrepancies may be explained by proximity of the DSC cells to the germinative epithelial cells, insofar as these cells may be "primed" by contact with epidermal cells to be inductive. Generally speaking, it suggests that the nature and role of the cells is influenced, as in most progenitor populations, by location.

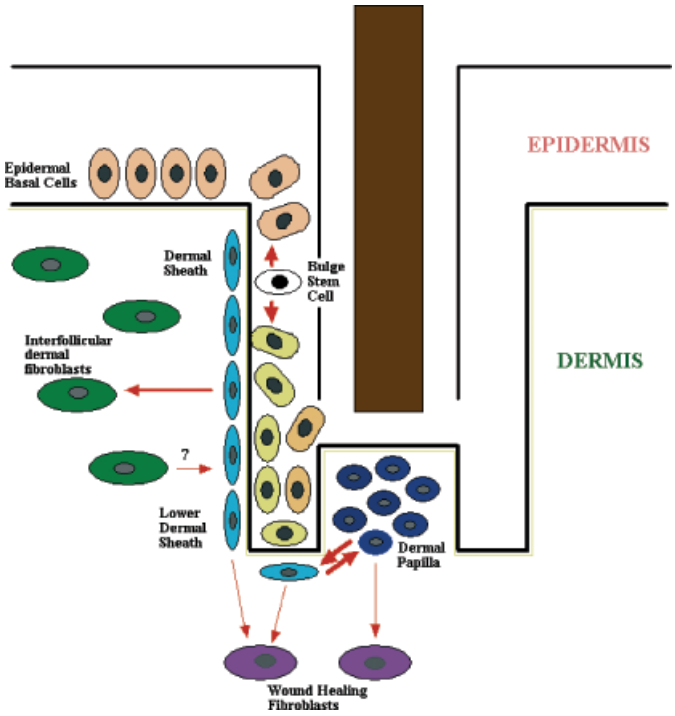

Figure 1. Speculative diagram illustrating movements of dermal cells between the dermal papilla and dermal sheath within the follicle, and also into the skin dermis.

HAIR FOLLICLE DERMIS AND SKIN DERMIS

The papers by McElwee *et al* and Tobin *et al* both reinforce the stem cell role of dermal sheath cells within the follicle; however, recent findings suggest that this may only be part of the story. McElwee *et al* point to the fact that DSC cells and DP cells both express alkaline phosphatase expression *in vivo* and *in vitro*, as a marker of inductive follicle dermis. However, we now know that follicle dermal papilla and sheath cells can be differentiated into bone and adipose tissue (Jahoda *et al*, 2003). Therefore, the expression of alkaline phosphotase, a marker of osteocyte differentiation, could reflect the broader stem cell capabilities of these populations, or indeed could just be incidental.

Possibly the most intriguing observation made by Tobin *et al* (2003a) is the bi-directional flow of follicle dermal cells. Not only are DS cells recruited into the DP, but there is also a loss of DP cells into the DS at catagen. But is this cellular exchange limited to the follicle? It is long established that epithelial cells of the follicle ORS are crucial in the regeneration of wounded interfollicular epidermis. We have hypothesized that in the same way that ORS cells are recruited into wounded follicles, the DS/DP cells play a parallel role as stem cells in dermal wound repair (Jahoda and Reynolds, 2001), and have shown that DS cells can incorporate into healing wounds (Gharzi *et al*, 2003). Therefore, there is some evidence that follicle dermal stem cell activity extends to the interfollicular dermis in the context of trauma. The perception of the relationship between follicle epithelium and skin epidermis underwent a major revision when labeling experiments showed that follicle stem cells in the epithelial bulge region contribute to normal undamaged skin (Taylor *et al*, 2000). If the parallels between the DS and ORS were to be extended further, then one could envisage that, in a similar way, dermal sheath cells could contribute to the interfollicular skin fibroblast population. An exciting observation described in the work of Tobin and colleagues, but whose significance is not considered, further is the "release" of dermal sheath cells from the follicle during catagen. From my perspective this could well be the first evidence of the follicular dermis contributing to the interfollicular dermis in undamaged skin. Some of these ideas are summarized in **Fig 1**. This is a highly simplified model diagram because the exchange of cells between the papilla and sheath occurs at specific and different times of the hair cycle, as may the loss of cells from the follicle dermal sheath into the dermis. However, what it attempts to illustrate is the idea that movement of dermal cells may occur not only within the follicle but to the skin dermis as well, and that this may occur both in trauma situations and during the dynamic migratory phases of the hair cycle. Whether there is movement in the reverse direction, from the skin dermis to the dermal sheath, cannot be completely ruled out. However, this would seem unlikely since the follicle dermis appears to have unique developmental properties. Thus, McElwee's paper, having raised the prospect of being able to augment follicle size by recruitment, is balanced by Tobin's evidence of movement of dermal cells not only within the follicle, but outside to the dermis. In skin undergoing androgenetic alopecia, there is the possibility that the balance of migration is altered and incontinence of dermal sheath cells to the skin dermis leads to reduction in size of the dermal papilla, and in turn to miniaturization of the follicle structure. If this leakage is the result of signals from a dermal environment unique to this region of skin, then addition of cells by recruitment might only be postponing the inevitable.

REFERENCES

Choudhry R, Pitts JD, Hodgins MB: Changing patterns of gap junctional intercellular communication and connexin distribution in mouse epidermis and hair follicles during embryonic development. *Dev Dyn* 210:417–430, 1997

Cotsarelis G, Sun TT, Lavker RM: Label-retaining cells reside in the bulge area of pilosebaceous unit: Implications for follicular stem cells, hair cycle, and skin carcinogenesis. *Cell* 61:1329–1337, 1990

Gharzi A, Reynolds AJ, Jahoda CAB: Plasticity of hair follicle dermal cells in wound healing and induction. *Exp Dermatol* 12:126–136, 2003

Iguchi M, Hara M, Manome H, Kobayasi H, Tagami H, Aiba S: Communication network in the follicular papilla and connective tissue sheath through gap junctions in human hair follicles. *Exp Dermatol* 12:283–288, 2003

Jahoda CAB: Cellular and developmental aspects of androgenetic alopecia. *Exp Dermatol* 7:235–248, 1998

Jahoda CAB: Induction of follicle formation and hair growth by vibrissa dermal papillae implanted into ear wounds: Vibrissa-type fibres are specified. *Development* 115:1103–1109, 1992

Jahoda CAB, Whitehouse CJ, Reynolds AJ, Hole N: Hair follicle dermal cells differentiate into adipocyte and osteogenic lineages. *Exp Dermatol*, 2003 (in press)

Jahoda CAB, Reynolds AJ: Hair follicle dermal sheath cells – Unsung participants in wound healing. *Lancet* 358:1445–1448, 2001

Jahoda CAB, Reynolds AJ, Oliver RF: Induction of hair growth in ear wounds by cultured dermal papilla cells. *J Invest Dermatol* 101:584–590, 1993

Kam E, Hodgins MB: Communication compartments in hair follicles and their implication in differentiative control. *Development* 114:389–393, 1992

Matsuzaki T, Inamatsu M, Yoshizato K: The upper dermal sheath has a potential to regenerate the hair in the rat follicular epidermis. *Differentiation* 60:287–297, 1996

McElwee KJ, Kissling S, Wenzel E, Huth A, Hoffmann R: Cultured peribulbar dermal sheath cells can induce hair follicle development and contribute to the dermal sheath and dermal papilla. *J Invest Dermatol* 121:1267–1275, 2003

Oliver RF: Dermal–epidermal interactions and hair growth. *J Invest Dermatol* 96:76S, 1991

Oliver RF: Ectopic regeneration of whiskers in the hooded rat from implanted lengths of vibrissa follicle wall. *J Embryol Exp Morph* 17:27–34, 1967

Oliver RF: Histological studies of whisker regeneration in the hooded rat. *J Embryol Exp Morph* 16:231–244, 1966b

Oliver RF: Local interactions in mammalian hair growth. In: Spearman RIC, Riley PA (eds). *The Skin of Vertebrates.* Academic Press: New York, 1980, p199–210.

Oliver RF: Whisker growth after removal of the dermal papilla and lengths of follicle in the hooded rat. *J Embryol Exp Morph* 15:331–347, 1966a

Stenn KS, Paus R: Controls of hair follicle cycling. *Physiol Rev* 81:449–494, 2001

Taylor G, Lehrer MS, Jensen PJ, Sun TT, Lavker RM: Involvement of follicular stem cells in forming not only the follicle but also the epidermis. *Cell* 102:451–461, 2000

Tobin DJ, Gunin A, Magerl M, Handijski B, Paus R: Plasticity and cytokinetic dynamics of the hair follicle mesenchyme: Implications for hair growth control. *J Invest Dermatol* 120:895–904, 2003b

Tobin DJ, Gunin A, Magerl M, Paus R: Plasticity and cytokinetic dynamics of the hair follicle mesenchyme during the hair growth cycle: Implications for growth control and hair follicle transformations. *J Investig Dermatol Symp Proc* 8:80–86, 2003a