Whisker growth induced by implantation of cultured vibrissa dermal papilla cells in the adult rat

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SUMMARY

Retention of the capacity to induce the growth of hair by cultured adult rat vibrissa dermal papilla cells has been investigated. Small pellets of serially cultured papilla cells were implanted into the bases of the exposed follicular epidermis of amputated adult rat vibrissa follicles. Amputated follicles that received no cell implants or implants of cultured dorsal skin fibroblasts were used as controls. Over 50% of follicles implanted with cultured papilla cells in the passage range 1–3 grew hairs. In contrast none of the follicles that received late passage cells (range 6–15) produced hairs; and spontaneous regeneration of hair occurred in only 3% of the control follicles. These results demonstrate that cultured papilla cells of early passage numbers retain their ability to induce hair growth. Histological examination confirmed that the implanted papilla cells interacted with follicular epidermis to organize the development of new, hair-producing bulbs, each containing a discrete dermal papilla. An important observation was that aggregative behaviour leading to papilla formation was only manifested by early passage papilla cell implants. This persisting embryonic characteristic appears to be an essential functional component of papilla cell activity which operates to regulate the profound morphogenetic changes that occur during the hair growth cycle.

INTRODUCTION

Mammalian hairs are formed by the differentiation and keratinization of cells produced in the germinative epidermal component at the base of the hair follicle. This epidermal matrix invests the dermal papilla, a discrete population of specialized fibroblasts. The importance of the dermal papilla in the growth of hair has been established in a series of experimental studies using the comparatively large rat vibrissa follicle, a model first used by Cohen (1961). Transplantation experiments have shown that freshly dissected papillae can induce hair growth when implanted into vibrissa follicles (Oliver, 1967; Ibrahim & Wright, 1977), and induce the development of new hair follicles when associated with ear or scrotal sac epidermis (Oliver, 1970). More recently it has been demonstrated that wounding of the dermal papilla in situ can lead to the production of longer hairs and extended growth cycles (Jahoda & Oliver, 1984b,c).

Key words: hair growth, dermal papilla, cell culture, vibrissa, whisker, implantation, fibroblasts, rat.
While postembryonic dermal papilla cells apparently remain mitotically quiescent (Pierard & de la Brassinne, 1975), it has now been shown that this intriguing population of cells can be grown in culture (Jahoda & Oliver, 1981, 1984a; Messenger, 1984). When compared with skin fibroblasts, cultured vibrissa papilla cells display unique morphological and behavioural characteristics and in particular tend to form discrete cell aggregates even after extended serial cultivation (Jahoda & Oliver, 1984a). This approach has opened up the possibility of analysing cultured papilla cells to determine their hair-growth-promoting characteristics. In this respect, it was important to establish whether the papilla cells also retained their ability to induce the growth of hair.

It has been shown that permanent cessation of hair growth occurs following removal of more than the lower third of the vibrissa follicle (Oliver, 1966a, b, 1967). This finding has been exploited in the present work where retention of the functional capacity of cultured papilla cells was investigated by implanting serially cultured papilla cells into the bases of amputated follicles. The early fate of the implanted cells was followed by introducing papilla cells that had been labelled with \[^{3}H\]thymidine while growing in culture. As controls, follicles received implants of cultured skin fibroblasts. Here we amplify and present new findings to a preliminary account reported elsewhere (Jahoda, Horne & Oliver, 1984).

**MATERIALS AND METHODS**

Inbred hooded PVGC rats (colony, Dundee University) aged 3–6 months and of either sex were used to provide dermal papillae and skin fibroblasts for culture.

**Cell culture**

**Dermal papilla cells**

Dermal papillae were dissected from the bulb regions of vibrissa follicles excised from the upper lips of freshly killed rats and stored in Eagle’s minimal essential medium (MEM) as previously described (Jahoda & Oliver, 1981, 1984a). Each papilla was cut into several pieces and the cut pieces of between 5 and 30 papillae were either grown on the glass coverslips of Cruickshank tissue culture chambers (Sterilin) and subcultured onto 35 mm plastic Petri dishes or grown directly in dishes at 37 °C in an atmosphere of 5 % CO₂–95 % air. The culture medium consisted of Eagle’s MEM containing 1 % L-glutamine (20 mm), 15 % foetal calf serum (changed to 10 % at passage 1), penicillin (50 i.u. ml⁻¹) and streptomycin (50 μg ml⁻¹), all components from Gibco. The medium was changed every 3 or 4 days and when the cells started aggregating (Fig. 1) they were either prepared for implantation or subcultured. Cell dissociation was obtained using a solution of 0.25 % trypsin in phosphate-buffered saline EDTA (0.2 mg ml⁻¹). A maximum dose of 2 μCi of \[^{3}H\]thymidine (specific activity 45 Ci mm⁻¹; Radiochemical Centre, Amersham) was added over a 2 week period to passage 1 cells to provide labelled cells for implantation.

**Skin fibroblasts**

Skin fibroblasts were obtained from dorsal skin of rats of the same age range as those used to provide dermal papillae. Small pieces of dermis were dissected out and squashed under coverslips in 35 mm Petri dishes. When fibroblast outgrowth was established (Fig. 2), the coverslips and explants were removed. The same culture conditions and subculturing procedures used with papilla cells were employed.
In vivo implantation

Preparation of follicles

Anaesthesia was induced by the intraperitoneal injection of Sagatal, 0.044 ml 100 g⁻¹ body weight. Since the major vibrissa follicles on the upper lip of the rat are arranged in a constant pattern of dorsoventrally and anteroposteriorly aligned rows, individual follicles can be surgically treated and subsequently identified. In this study all operations were performed on the three most posterior dorsoventral rows and the follicles were exposed as previously described (Oliver, 1966a; Jahoda & Oliver, 1984b). The follicles selected for operation were identified and a record was made of the length of the vibrissae present in the follicles.

Lengths of follicle were removed with a transverse cut, attempting to leave half or less of the upper region of the follicle in situ. The cut vibrissa shafts were plucked from the upper segments which were then available to receive cultured cell implants or to act as nonimplanted controls.

Implantation of cultured cells

Prior to implantation dermal papilla cells and fibroblast cultures were washed with phosphate-buffered saline (Oxoid Dulbecco ‘A’) and reincubated in medium containing 10% rat serum. When the recipient follicles were prepared, the cells were harvested with a rubber policeman then divided into small pellets containing approximately 2000–5000 cells. Using watchmaker’s forceps a pellet was positioned within and around the opening of the follicular epidermis at the transected base of each follicle, essentially as described for the implantation of intact, freshly dissected dermal papillae (Oliver, 1967), and the lip stitched back in position. From 3–4 weeks postoperatively the follicle sites were examined under a stereoscopic microscope for evidence of fibre production, and the lengths of any hairs present were recorded.
Design of experiments

283 follicles in 45 rats were exposed to one of the four procedures employed. Details of the long-term experiments, in which follicles were biopsied from 28–162 days after operation, are shown in Table 1.

To study the early response of follicles to the procedures employed 30 follicles were used: 2 amputated, but nonimplanted, follicles (biopsied at 11 days), 6 follicles that had received cultured fibroblasts (biopsied at 5 or 7 days) and 22 follicles that were implanted with cultured papilla cells and biopsied from 1 h up to 11 days after operation.

To determine the level of amputation, all of the operated follicles were fixed at biopsy for gross reconstruction with their removed lower portions which had been fixed after operation. In addition the exact level of cut was confirmed at histological examination of the biopsied follicles and, in 17 of the follicles that had received low passage number papilla cells, by histological examination of the removed lower portions.

Histology and autoradiography

Biopsied follicles and removed lower regions were fixed in formal saline, processed and embedded in paraffin wax before being serially sectioned at 8 μm parallel to the long axis of the follicle. Sections were stained in a combination of Weigert's haematoxylin, alcian blue and Curtis' Ponceau S.

For autoradiography, slides with serial sections were taken to distilled water and dipped in Ilford Nuclear Emulsion Type K2. The sections were exposed for 14 days at 4°C and after developing and fixing were stained with haematoxylin and eosin.

RESULTS

Control experiments

Nonimplanted controls

An essential aspect of the study, that surgical removal of the lower third or more of the follicles would reliably ensure permanent cessation of hair growth, was clearly demonstrated. 87 of the 90 follicles in this control group did not produce hairs (Table 1). This was confirmed by histological examination of 40 of the biopsied follicles. With the exception of the three follicles that had produced hairs, there was no evidence of spontaneous regeneration of dermal papillae. The epidermal cells of the lower outer root sheaths had formed solid columns which terminated just above the level of the original cut (Fig. 3).

Of the three follicles that had produced hairs two, biopsied at 49 and 162 days, had grown recognizable vibrissae following removal of their lower halves. In the third follicle, biopsied at 44 days and from which the lower two thirds had been removed, histological examination revealed the presence of two pelage-like follicles which were growing fine hairs, located just below the sebaceous gland. Apart from the size and anatomical similarity with pelage follicles (Fig. 14), the hairs had compartmentalized medullae in contrast with vibrissae which have an open, continuous medulla.

Cultured fibroblast-implanted controls

Of the 61 follicles that were implanted with cultured skin fibroblasts (35 receiving cells in the passage range 1–3 and 26 passage 4 or passage 5 cells), two produced hairs (Table 1). The 6 short-term follicles and 35 of the long-term
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follicles were examined histologically. Except for the two follicles that had produced hairs, these follicles were indistinguishable in appearance from non-implanted controls, showing the presence of a thin layer of fibroblastic scar tissue over the base of the follicular epidermis (Fig. 4).

One follicle, from which just the lower third had been excised and which was therefore within the level of expected spontaneous regeneration, had produced vibrissae. In the second follicle, where the lower two thirds had been removed, histology revealed a pelage-like follicle extending below the vibrissa sebaceous gland.

Cultured papilla cell implants

The results obtained from the 98 follicles that had received implants of cultured dermal papilla cells are shown in Table 1. None of the 42 follicles implanted with cells of high passage numbers (6–15) were observed to produce hairs. The follicles resembled control follicles, as shown in Figs 3 and 4, with no histological evidence of the presence of dermal papillae.

In contrast 30 (53%) of the 56 follicles that were implanted with cells in the passage range 1–3 were observed to have produced hairs either during routine observations (24 follicles) or at histology (6 follicles).

Induced hair growth

27 of the 30 hair-producing follicles had grown vibrissae and a further three were found to be producing pelage-like hairs on histological examination. Vibrissae were first seen to emerge at 4 weeks after operation and the majority of those kept under extended observation produced hairs in the normal cyclic fashion. However, 5 follicles that had initially produced emergent vibrissae were revealed

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Biopsy time in days</th>
<th>Passage number of cultured cells</th>
<th>Number of follicles</th>
<th>Number growing vibrissae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonimplanted controls</td>
<td>30–162</td>
<td>—</td>
<td>90</td>
<td>2+1P</td>
</tr>
<tr>
<td>Intact papilla implants</td>
<td>153</td>
<td>—</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Cultured fibroblast implants</td>
<td>30–162</td>
<td>1–3</td>
<td>35</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td>4,5</td>
<td>26</td>
<td>1+1P</td>
</tr>
<tr>
<td>Cultured papilla cell implants</td>
<td>28–120</td>
<td>1</td>
<td>9</td>
<td>6</td>
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<td></td>
<td>36–119</td>
<td>2</td>
<td>33</td>
<td>17+2P</td>
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<td></td>
<td>44–142</td>
<td>3</td>
<td>14</td>
<td>4+1P</td>
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<tr>
<td></td>
<td>62–120</td>
<td>6–9</td>
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<td></td>
<td>120</td>
<td>10,15</td>
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<td>0</td>
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P = number producing pelage-like hairs.
on biopsy to have subsequently formed intrafollicular cysts containing coiled vibrissae (Fig. 13).

Because of the varying biopsy times and the intermittent observations few definitive club or terminal hair lengths were obtained. However, hairs ranging in
length from 10–21 mm were observed growing from 14 of the follicles. This represented 25–57% of the expected hair length for the follicle positions.

Analysis of the preimplantation level of follicle amputation revealed that 12 follicles had grown vibrissae after removal of between the lower third and lower half of the follicles and that 13 follicles had grown vibrissae after removal of more than the lower half (Fig. 5). Of the five follicles that had produced hairs after removal of the lower two thirds, two had grown vibrissae and three had developed as pelage-like follicles.

**Histological observations**

To determine the early fate of implanted papilla cells, 22 follicles were examined at intervals after operation. Shortly after implantation a variable number of papilla cells was seen located within the base of the outer root sheath where the cells appeared to be held in position by an underlying blood clot (Fig. 6). Papilla cells were also seen more diffusely spread within and outside the transected collagen capsule, sometimes associated with detached portions of the outer root sheath.

Evidence that the implanted papilla cells formed the new papillae was provided by autoradiographic examination of follicles that had received papilla cells labelled with [3H]thymidine. At 11 days labelled papilla cells were present within an indentation at the base of the otherwise now solid column of lower outer root sheath cells (Fig. 7). By 28 days, when whisker growth was occurring (Fig. 8), there was a new bulb at the site of papilla cell implantation, with an epidermal matrix containing active melanocytes organized around a discrete dermal papilla. Labelling of the dermal component of the follicle was strictly confined to cells within the body of the papilla and the papilla stalk (Fig. 9). Unlabelled cells were associated with the capillary network now established within the papilla.

Examination of the 27 follicles that had produced vibrissae, and that were biopsied 28–142 days after operation, showed that the majority of the follicles had lengthened and either projected below the level of the cut collagen capsule or

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**Fig. 3.** Nonimplanted control vibrissa follicle biopsied at 104 days after amputation of the lower one third of the follicle. The follicular epidermis (fe) has formed a solid cord of cells which terminates above the transected rim of the collagen capsule (c). ×30.

**Fig. 4.** Detail of the base of a control follicle, biopsied at 35 days, from which the lower one third had been removed and which had received an implant of passage 2 skin fibroblasts. A thin layer of fibroblastic scar tissue has formed immediately below the follicular epidermis (fe) which displays the characteristic appearance of outer root sheath cells. ×570.

**Fig. 5.** Macrograph of two follicles (A and B) biopsied at 117 days after implantation of passage 2 papilla cells. The arrows indicate the original level of cut through the collagen capsule on the implanted upper segments. The removed lower portions are shown to the right. Follicle A, following a midfollicular amputation, was growing the curled whisker at left, which measured 11 mm in length at the time of biopsy. The associated bulb can be seen as a pigmented area just below the cut capsule (see Fig. 10). Follicle B had the lower two thirds removed. An epithelial cyst projects below the cut capsule and histology revealed the presence of a large papilla and epidermal matrix high in the cyst wall and a coiled whisker within. ×13.
showed lateral displacement of the bulb (Figs 10, 12, 13). Nineteen follicles showed the characteristic anatomy of vibrissa follicles with prominent and, generally, large dermal papillae. Seventeen of these follicles were in the mid-anagen phase of the hair growth cycle, one was in very early anagen (Fig. 11) and one was in telogen or the resting phase.

Of particular interest was a follicle that had formed three separate bulbs at the base of the follicle (Fig. 12), each of which was producing its own whisker, 10 mm long when biopsied at 44 days.

The remaining eight follicles, from which the lower half or more of the follicle had been removed, had formed epithelial cysts containing coiled vibrissa shafts. Five of these follicles had previously grown emergent hairs, but then hair growth continued below the skin surface. Two of these follicular cysts contained multiple bulbs. One contained two small bulbs (Fig. 13). In the second, four papilla/matrix associations had formed and a small, isolated clump of papilla cells was enclosed within the capsule.

The three follicles that had produced pelage-like hairs were identified at histology (Fig. 14). As in the two similar follicles observed in control follicles, the lower two thirds of the follicles had been removed at operation.

As with some of the control follicles, a further phenomenon revealed at histology was the presence, in five follicles, of sebaceous gland cells within the upper root sheath as apparent extensions of the sebaceous glands located within the collagen capsule. These sebaceous cells were seen in association with two of the pelage-like follicles (Fig. 14) and as additional histological features in three follicles growing vibrissae.

**Intact dermal papilla implants**

Three of the four follicles into which freshly dissected dermal papillae had been implanted produced generations of vibrissae ranging in length from 15–21 mm. This represented 33–40% of the expected lengths for the follicle positions.

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**Fig. 6.** Upper region of a follicle biopsied 1 h after implantation of a pellet of cultured papilla cells in the base. The implant (i) is located within the proximal end of the follicular epidermis (fe) and a retaining blood clot (bc) has formed at the site of amputation. ×30.

**Fig. 7.** Autoradiograph of the base of a follicle 11 days after implantation of papilla cells that had been labelled with [3H]thymidine. Follicular epidermis (fe) is becoming organized around the labelled papilla cells (i) which have remained at the site of implantation. ×400.

**Fig. 8.** Follicle biopsied 28 days after implantation of passage 1 papilla cells labelled with [3H]thymidine following removal of the lower half of the follicle. A new bulb with a discrete dermal papilla (dp) and investing epidermal matrix (em) has developed at the site of implantation. A pigmented whisker (w) was being produced. ×30.

**Fig. 9.** Autoradiograph showing detail of the bulb in Fig. 8. Labelling, not to be confused with pigment in the melanocytes (me) in the epidermal matrix (em) at right, is restricted to dermal cells within the papilla (dp) and its basal stalk. Unlabelled endothelial cells of the capillary network that has migrated into the papilla are also present. ×550.
DISCUSSION

Fulfilment of experimental requirements

An essential requirement of this study was to demonstrate the validity of using amputated vibrissa follicles to evaluate the inductive capacity of cultured dermal papilla cells. This was necessary because while permanent cessation of hair growth has been observed following removal of more than the lower third of vibrissa follicles, removal of less is associated with spontaneous papilla regeneration and renewed whisker growth (Oliver, 1966a,b, 1967; Ibrahim & Wright, 1982).

The present results showed clearly that amputation of more than the lower third of vibrissa follicles reliably prevents further vibrissa growth. Only 3% of the control follicles grew hairs (5 out of 151 follicles) and this included two follicles that produced fine, pelage-like hairs rather than vibrissae. This presence of hairs in the control follicles was found on histological examination subsequent to our earlier report (Jahoda et al. 1984).

Induction of hair growth

A major limitation of most culture systems is that the activities of cells grown in culture can rarely be related to their in situ function. Here we have demonstrated that cultured vibrissa cells of early passage numbers retain their functional capacity to induce the growth of hair. Over 50% of follicles that were implanted with cultured papilla cells in the passage range 1–3 subsequently grew hairs (30 out of 56 follicles), 27 producing vibrissae and three pelage-like hairs.

Histological studies of follicles biopsied at early intervals after implantation, in conjunction with the autoradiographic experiments, confirmed that the implanted papilla cells formed the new papillae responsible for vibrissa growth. The papilla cells interacted with follicular epidermis at the site of implantation to organize the development of new, hair-producing bulbs each containing a discrete dermal papilla. The majority of the follicles subsequently biopsied showed follicle lengthening and various stages of the growth cycle expected in follicles producing generations of hairs.

Fig. 10. Section through follicle A in Fig. 5 showing the displaced bulb with its dermal papilla (dp) and epidermal matrix (em) projecting just below the cut capsule (c). ×30.

Fig. 11. Follicle biopsied 117 days after implantation of passage 2 papilla cells. This early anagen follicle is entering a new hair growth cycle with an epidermal matrix (em) developing around the papilla (dp). ×30.

Fig. 12. Follicle biopsied 44 days after implantation of passage 3 papilla cells. Three separate bulbs had formed (two of which can be seen in this section), each of which had produced a whisker 10 mm above the skin surface. ×30.

Fig. 13. Detail of base of a follicle biopsied 119 days after implantation of passage 2 papilla cells. Two bulbs, located within the cut edge of the capsule (c), were growing whiskers (w) within an intrafollicular cyst. ×75.

Fig. 14. Detail of the upper region of a follicle that had received a passage 3 papilla cell implant. This follicle had developed a hyperplastic sebaceous gland (sg) and a pelage-like follicle. The small bulb of this follicle (lower right) was producing a fine hair (h). ×195.
In all of these respects the cultured papilla cells behaved like freshly dissected papillae which previous work has shown induce whisker growth when implanted into similarly amputated vibrissa follicles (Oliver, 1967), a finding confirmed in this study by the three out of four follicles that produced vibrissae after implantation of intact papillae.

A significant feature of the implanted papilla cells of early passage numbers was that they formed discrete cell masses which in turn formed associations with follicular epidermis. Presumably separate groupings of papilla cells occurred immediately after implantation in those follicles that produced multiple hairs. This aggregative property of papilla cells appears to be a fundamental characteristic related to their function. It is shown by the condensation of dermal cells to form papilla anlagen in the ontogenetic development of follicles (e.g. Wessells & Roessner, 1965); the tendency of adult papilla cells to form clumps in culture (Jahoda & Oliver, 1981, 1984a), and the fact that dermal papillae remain intact as discrete entities when transplanted into vibrissa follicles and a variety of ectopic sites, regardless of whether epidermal contact is made or not (Oliver, 1970; Young, 1977; Jahoda & Oliver, 1984c).

In contrast to follicles receiving early passage number papilla cells, none of the 42 follicles that received late passage cells (range 6–15) produced hairs. Histological examination of the follicles revealed that the implanted papilla cells (in common with implanted fibroblasts) did not form recognizable cellular aggregates in situ. The implanted cells may have migrated from the implantation site, as has been demonstrated with follicle dermal sheath cells labelled with $^{3}H$thymidine (Horne, unpublished observations), and/or contributed to the fibroblastic layer at the follicle base. These observations suggest that loss of inductive potential by papilla cells after extended culture may be associated with loss of aggregative behaviour in vivo.

The occasional development of pelage-like follicles (whether in the control or implanted groups) after removal of more than the lower two thirds of the follicle shows similarities to the reported regrowth of human axillary hair following amputation of the follicle up to the level of the sebaceous gland (Inaba, Anthony & McKinstry, 1979). A further regenerative phenomenon was the presence of sebaceous gland cells within the upper outer root sheath in some of the control and hair-growing follicles, a feature seen previously in a single amputated vibrissa follicle (Oliver, 1967).

Our demonstration that cultured papilla cells can induce hair growth after reimplantation warrants examination of papilla cell properties in vitro even though, in monolayer cultures, the cells are unlikely to display all of the activities they exhibit in situ. We have now shown, for example, that human papilla cells from scalp and pubic follicles are targets of both androgen and glucocorticoid action (Murad et al. 1985). This approach may reveal the intrafollicular link between hormones and their effects on hair growth.

By using clonal culture techniques it should also be possible to determine the number of divisions papilla cells will go through and still be competent to induce
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hair growth. While apparently postmitotic in situ (Pierard & de la Brassinne, 1975), the fact that papilla cells can divide in culture and yet subsequently perform normal functions demonstrates that they do not conform to the classical category of a postmitotic terminally differentiated cell type.

The involvement of dermal cells other than papilla cells in follicle development and function has also to be considered. It has been shown, for example, that cells from newborn mouse skin form hair follicle structures when reassociated in transplantation chambers (Worst, MacKenzie & Fusenig, 1982). However, it remains unclear whether follicular dermal cells simply reassembled or whether all newborn dermal cells can become the dermal component of hair follicles. Our results indicate that adult skin fibroblasts are incapable of replacing dermal papilla cell function in the hair follicle.

Papilla cells become distinct from surrounding mesenchyme as an apparently nondividing cell population early in follicle development (Wessells & Roessner, 1965). However, Oliver (1966a) and Ibrahim & Wright (1982) showed that cells from the follicular dermal sheath can form replacement dermal papillae after removal of the original papilla and up to one third of the lower follicle. Interestingly, dermal sheath cells from this regenerative region also display aggregative behaviour in culture while cells from the upper dermal sheath demonstrate normal fibroblast behaviour (Horne, unpublished). Thus, as suggested by Oliver (1980), it may be appropriate to consider the lower follicle dermis, including the dermal papilla, as the crucial dermal element for hair production. Furthermore, our observations reinforce the idea (Jahoda & Oliver, 1984a) that cells of this dermal element are 'embryonic' in nature. This retention of embryonic properties into adulthood enables the papilla to regulate the profound morphogenetic changes that occur during the hair cycle; events which have been compared to those taking place during follicle development (e.g. Chase, 1965). Thus mesenchymal cell aggregative behaviour, which is a feature of skin appendage development, has been retained by dermal papilla cells as a property necessary for their morphogenetic role, and possibly also for maintaining follicle size (Jahoda & Oliver, 1984c).

The important question now arises as to whether cultured papilla cells can induce hair follicle formation, an ability shown by intact adult papillae (Oliver, 1970). Experiments are now being performed to test this hypothesis.

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REFERENCES


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