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Review

Hair follicle stem cells

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Abstract

The increasing use of the hair follicle as a stem cell paradigm is due in part to the complex interplay between epithelial, dermal and other cell types, each with interesting differentiation potential and prospective therapeutic applications. This review focuses on research into the environmental niche, gene expression profiles and plasticity of hair follicle stem cell populations, where many recent advances have come about through novel technological and experimental approaches. We discuss major developmental pathways involved in the establishment and control of the epithelial stem cell niche, and evidence of plasticity between stem and transit amplifying cell populations.
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1. Introduction

The identification, characterisation and transplantation of adult stem cells is currently one of the most intensively investigated areas of biological and biomedical research. Cells with stem cell properties have recently been described in many integumental appendages including feathers [1] and teeth [2] but the hair follicle stands out as one of the best model systems for studying adult stem cells. Hair follicles are accessible, well-defined in terms of their developmental biology, and their stem cell populations are located in discrete compartments or niches. However, it is their unique cycling activity, influenced by many of the common developmental signalling pathways [3] that makes hair follicles so intriguing. During each cycle (Fig. 1), follicles undergo extremely rapid epithelial cell division and execute exquisitely timed differentiation programmes when in the growing (anagen) phase. Then, as growth stops (catagen),

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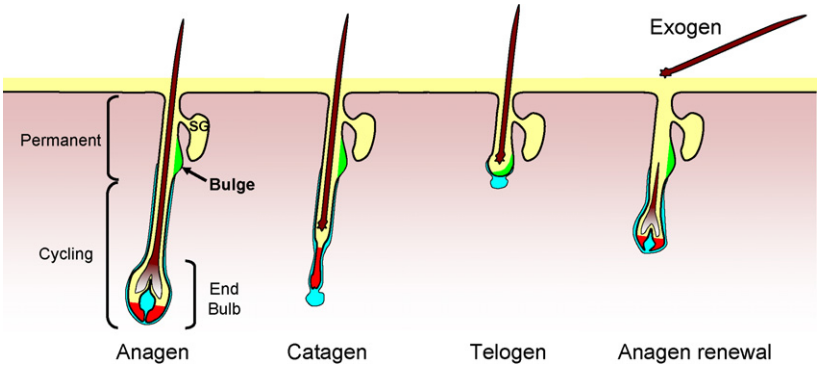

Fig. 1. Hair follicle cycle. The different stages of the adult hair follicle are divided into three main categories known as anagen, catagen, telogen, which continually cycle throughout the life of the follicle. During anagen the cells of the germinative epithelium at the base of the follicle (red) rapidly proliferate and differentiate to produce the lengthening hair fibre and layers of the inner root sheath. As the mitotic activity in the end bulb slows and eventually ceases, the hair follicle enters catagen which is characterised by apoptosis of the epithelial cells of the lower, transient, section of the follicle and the formation and anchorage of the club fibre. The dermal papilla (blue) moves up to the base of the permanent section of the follicle, in close proximity to the bulge (green). A latent phase known as telogen then occurs before the renewal of a subsequent anagen phase. A less regulated aspect of the hair follicle cycle is exogen which describes the removal of the remaining club fibre. A key question revolves around how the bulge epithelial stem cells maintain the germinative epithelium at the follicle base during prolonged anagen periods. SG – sebaceous gland.

most follicles regress into structures that resemble immature developing follicles, after which they go into a period of mitotic quiescence (telogen). Stem cells are at the core of these dynamic events that includes a new burst of activity and further morphogenetic remodelling as the follicle grows again at the start of a new anagen phase.

For epithelial stem cells in particular, questions about where they are located, how they are maintained, what they can become, and the interchangeable nature of the stem and transit amplifying state are central topics of current research. Stem cells from the mesenchymal or dermal compartment of the follicle will also be reviewed, along with other reports of follicle-derived stem cells being able to differentiate into a broad range of cell types outside of the skin or its appendages. The successful clinical application of adult stem cell therapies, such as bone marrow and cornea transplantation, has been the driving force for stem cell research in many systems. Thus, a better understanding of hair follicle stem cells and their differentiation potential may lead to treatments of skin injury, inherited skin diseases and cancers, hair loss, and even haematopoietic and neuromuscular diseases.

2. Epithelial stem cells

Since the landmark paper of Cotsarelis et al. [4] highlighted the bulge as an important anatomical niche for hair follicle epithelial stem cells in mice, much work directed at refining the location of stem cell compartments has been ongoing. Aside from their location, the focus has been on three different aspects of their biology. The first is aimed at discovering specific markers for these cells, the second has examined their potential to contribute to and/or reconstitute hair follicles, skin, and other tissues, while the third and more recent question concerns the cellular and molecular microenvironment surrounding them, asking essentially, what maintains this population as stem cells?

2.1. Embryonic origin and regulation of follicular epithelial stem cells – skin versus hair and lineage control in developing and adult follicles

Hair follicle embryogenesis is underpinned by a sequential series of epithelial–mesenchymal interactions. The signalling cascade that controls the diverse cellular activities required for a follicle to form has been relatively well described [5] and involves secreted ligand members of many common developmental pathways including BMP's, FGF's, Wnt's, Shh, and TNF. In relation to epithelial lineage determination, two groups (Fuchs, Watt) in particular have used mouse models to show that Wnt/β-catenin is crucial. This work has been comprehensively reviewed elsewhere [6]. In brief, inducible forms of active β-catenin in postnatal skin have demonstrated that new follicles can be formed from most regions of the follicle epithelium [7], emphasising its plasticity. The Notch pathway may be acting downstream as recent work has shown that deletion of jagged-1 results in postnatal follicles switching to an interfollicular phenotype, while the induction of new hair follicles by β-catenin is prevented by blocking Notch signalling [8]. As different epithelial components of the follicle are examined new regulatory elements are appearing. For example, the transcriptional repressor Blimp1 appears to govern cellular input into the sebaceous gland [9]. Attention is now being paid to events preceding morphogenesis, by defining the transcriptional events that determine lineage from the ES cell state.

An emerging approach for isolation of tissue-specific stem cells is to derive cues from the transcriptional program that dictates their lineage restriction. Several strategies have recently been utilised to determine the origin of stem cells of the epithelial compartment, and to examine what controls restriction to the stem cell cohort during development. Tcf3, which is expressed in the slow cycling cells of the adult hair follicle, was first shown to be able to act independently of its β-catenin interacting domain and Wnt signalling to suppress epidermal differentiation and promote features of stemness [10]. Inducing Tcf3 postnatally

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