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Commentary

Prospective Cell-Based Strategies for Hair Follicles (HF) Regenerative Therapy

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DESCRIPTION

Hair loss (alopecia) is a disease that affects a growing range of individuals worldwide and impacts physical, psychological, and social well-being. Patients with hair loss or disorders suffer from emotional stress, embarrassment, and depression that severely compromise their life. Up to this point, treatments embrace medicine and surgical (autologous hair transplant) interventions. Though hair restoration surgery these days is the foremost effective method, donor Hair Follicles (HFs) scarcity is usually its major limitation. Besides, medical treatments still do not totally satisfy the patient's desires and entail drastic facet effects. Thus, the restricted effectiveness and side effects of these treatments have fostered the exploration of various therapeutic solutions, capable of generating an unlimited range of HFs. Noteworthy, stem cell-based tissue engineering is rising because the most thriving approach, reaching to reconstruct HFs *in vitro* to exchange lost or damaged HFs as a consequence of disease, injury, or aging. HF technology approaches are supported by the accumulated knowledge on reciprocal Epithelial-Mesenchymal (EM) interactions controlling embryonic organogenesis and postnatal HF cyclic growth. However, despite recent progress within the field, clinical applications of tissue engineering methods for hair loss are still missing [1]. Neogenesis of human follicles derived from cultivated HF dermal cells has not been with successfully achieved.

Hair follicles are a mini-organ that forms throughout embryonic skin development. Its functional and cycling activities depend on a coordinated communication between the various cell populations from epithelial, mesenchymal, and neural crest somatic cell origin, which regulates adult skin homeostasis and wound repair. So, understanding the HF anatomy, as well as the stem-cell populations in operation throughout postnatal cyclic regeneration, is crucial for tissue engineering-based solutions. Follicular dermal stem cells exist within the dermis (skin-derived precursors, SKP) ready to regenerate Dermal Sheath (DS), and populate the Dermal Papilla (DP) at each growth cycle. Both dermal papilla and dermal sheath comprise mesenchymal cells with multi-lineage differentiation capability. Within the mature HF, the dermal papilla is adjoined to connective tissue sheath (DS), forming the dermal component of the mature hair follicles [2]. The dermal papilla is assumed to be a master regulator of hair follicles cycling, which consists of serial phases of growth (anagen), apoptotic-driven regression (catagen), and rest (telogen).

On the human scalp, anagen lasts 1-5 years and it involves the entire regeneration of the cycling portion of the hair follicle. At the telogen-to-anagen transition, dermal papilla stimulates epithelial Hair Follicle Stem Cells (HFSC) from the bulge regions, which are adult potent cells holding self-renewal capability and kept quiescent within their niche enclosed by the Sebaceous Gland (SG) in the outer root sheath. Once dermal papilla stimulatory signaling overcomes the threshold imposed by the repressive bulge microenvironment, HFSCs divide generating a replacement pool of progenitors at the bulging base referred to as the secondary germ cells that survive catagen-driven apoptosis [3]. These primed hair germ cells migrate to the bulb, whereas increasing and differentiating into Hair Follicle Transit-Amplifying Cells (HF-TACs) that attach to the basement membrane closes the dermal papilla's lower half. HF-TACs likely sit in place throughout abundant anagen to fuel HF growth by differentiating into eight distinct epithelial lineages (eg, shaft, inner root sheath, and companion layer cells).

Stem cell-based regenerative drugs are rising because the most thriving approach for hair loss treatment by holding the potential of HF cloning, that is, the production of bioengineered instructive germs from human HF cells expanded *in vitro* to generate totally functional HFs upon transplant into the patient's bald scalp. Rationally, such a regenerative therapy could only be possible if combining receptive-epithelial and inductive-mesenchymal populations to mimic the well-orchestrated interactions controlling lifelong hair follicle cycles, which are deeply affected throughout hair loss. Ideally, a cell-based regenerative drug therapy would be autologous, that is, resort to patients' cells derived from little amounts of tissue biopsies [4]. Thus, researchers within the field are primarily focused on developing therapeutic technology solutions using dissociated HFSCs and Dermal Papilla Cells (DPCs) isolated from HF biopsies. HFSCs and DPCs retrieved from nonbalding scalp follicles should to 1st be swollen in culture to provide bioengineered structures *in vitro* with hair regenerative therapy.

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Still, an allogeneic cell supply might be used for HF regenerative therapy.

Comprehensive knowledge of HF growing and cyclic regenerative regulation, along with optimized protocols for HF/stem cell isolation and culturing has boosted the creation of a large variety of technology solutions reaching to cure hair loss [5]. However, future efforts are still required to bridge such knowledge into a translational tissue engineering solution. Significantly, the development of *in vitro* human HFs will definitely suit major biological applications far after the hair loss cure. The conception of biologically improved skin replacement therapies (whose usage has been restricted by the absence of HF), or perhaps their application as a research model for skin drug development or cosmetic product testing, flip the HF technology into a knowhow seeker by many medical and pharmaceutical industries.

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