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Hair Biology and Androgenetic Alopecia

Diagnosis, Neogenesis, and Management

Gordon H. Sasaki, MD*
Loma Linda Medical University, Loma Linda, CA, USA

KEYWORDS
• Hair follicle • Hair cycle • Stem cell niches • Diagnostic tests • Androgenetic alopecia
• FDA-approved and novel therapy

KEY POINTS
- Hair development, cycling, and androgenetic alopecia are believed to be significantly triggered by molecular and cellular stem cell activity.
- Typical normal hair characteristics define lanugo, vellus, intermediate, and terminal hairs.
- Complete personal, family history, diagnostic tests, and clinical presentations determine the type of alopecia and therapeutic alternatives.
- The precise etiology for the development of male and female pattern baldness, including telogen effluvium, are unknown, which is a challenge for directed therapies.
- A knowledge of medications approved by the Food and Drug Administration (FDA) and novel approaches that can provide safe and effective stand-alone or combined remedies in conjunction with surgical procedures.

INTRODUCTION

Scalp hair normally serves various physiologic roles that include protection against excessive exposure to ultraviolet radiation [1] and cold temperatures, as well as defining an individual's social, sexual, and health well-being [2]. The occurrence of androgenetic alopecia (AGA) in previously vibrant healthy individuals can produce devastating psychological impacts as thinning, shortening, or loss of hair progressively advances. Because male pattern hair loss (MPHL) and female pattern hair loss (FPHL) affect more than 50% of men and nearly 50% of women [3] by 50 years of age, concerned individuals often seek treatment advice from primary care physicians, dermatologists, or cosmetic surgeons. Physicians must be well-informed to recommend to their patients safe and effective therapies and avoidance of "miracle" cures. Fundamentals for hair loss counseling and management include a sophisticated understanding of the development, regulation, and dysregulation of hair follicles in both normal and diseased conditions.

Previous extensive investigations of hair development in both invertebrates [4] and in mice [5] have added clarity to the morphologic and cyclical transformations. Schofield [6,7] first proposed the term,

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*800 South Fairmount Avenue, Suite No. 319, Pasadena, CA 91105. *E-mail address:* ghsasakimd@drsasaki.com

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"niches," in hematopoietic tissues to describe slow cycling stem cells in specialized domains. Stem cells within similar domains have also been observed within human hair follicles and were found to leave their niches and evolve into rapidly dividing transit-amplifying to dynamically proliferate and commit to terminal differentiation.

MPHL, FPHL, and telogen effluvium (shedding) are believed to be affected by molecular and cellular disturbances during hair cycle regulation initiated by a variety of triggers; that is, hormones, stresses, drugs, metabolic and nutritional deficiencies, immunologic alterations, and diets. In general, the mechanism of action of these damaging factors is not fully understood or controllable. As investigators continue to identify more putative mediators and attempt to regulate the complex cross-communications within the stem cell hierarchy, new innovative therapeutic approaches may be possible to stimulate more effectively hair growth in MPHL/FPHL conditions, enhance follicular growth after transplantation, and treat other acquired diseased conditions.

The purpose of this article was to provide current information on the biology, potential stem cell–based pathophysiology, diagnostic tests, clinical presentation, Food and Drug Administration (FDA)-approved approaches, and novel non–FDA-approved treatments for patterned hair loss.

HAIR DEVELOPMENT

Hair follicles are organized into many heterogeneous cell types in stem cell habitats that interface with each other in a hierarchical manner during embryonic and postnatal cycling (Fig. 1). In a review by Schmidt-Ulrich and Paus [8], de novo initiation of follicle development in mice embryos was contingent on reciprocal cross-talk between single layered primitive epidermal cells (*placodes*) and dermal mesenchymal cells (*condensates*) regulated through canonical Wingless (Wnt) and Hedgehog (Hh) pathways via β-catenin transcription factors, receptors, ligands, and adhesion molecules. The undifferentiated *placode* cells (Stage 1) are transformed into *primary germ center* [9] *(Stage 2)*, composed of a population of quiescent histone label retaining cells (LRCs) with specified stem cell markers, such as Sox9 proteins. As epithelial hair germ cells plunge downward forming the hair peg and the outer root sheath (ORS), a trail of Sox9 LRC cells congregates into another niche, called the bulge (Stage 3–5). These specialized bulge LCR Sox9 stem cells are located subjacent to the ORS and positioned between the sebaceous gland units and opposite to the point of insertion of the arrector pili muscle. Progeny of the LRC Sox9-derived bulge stem cells are a requirement for formation of the sebaceous gland lineage and the later described hair germ, both of which promote cyclic phases of postnatal follicles

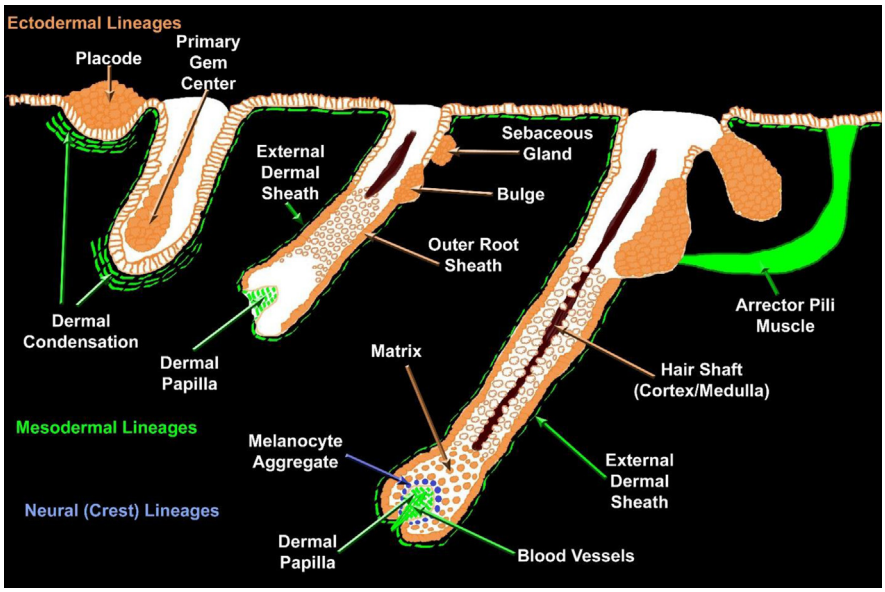

FIG. 1 Schematic representation of hair follicle morphogenesis during nascent development by germ stem cells and their niches from Stage 0 to Stage 8.