Biochemical Engineering Journal 48 (2010) 323–331

Contents lists available at ScienceDirect

Biochemical Engineering Journal

journal homepage: www.elsevier.com/locate/bej

Review

Hair follicular cell/organ culture in tissue engineering and regenerative medicine

Bo-Young Yoo[a], Youn-Ho Shin[b], Hee-Hoon Yoon[c], Young-Kwon Seo[d], Jung-Keug Park[a,d,e,*]

[a] Department of Chemical & Biochemical Engineering, Dongguk University, 3-26 Pil dong, Seoul, 100-715, Republic of Korea
[b] Department of Pathology, Chung-Ang University College of Medicine, 221 Heukseok dong, Seoul, 156-756, Republic of Korea
[c] Biomedical Research Institute, Lifecord Inc., Suwon, 443-721, Republic of Korea
[d] Dongguk University Research Institute of Biotechnology (DURIB), 3-26 Pil dong, Seoul, 100-715, Republic of Korea
[e] Department of Medical Biotechnology, Dongguk University, 3-26 Pil dong, Seoul, 100-715, Republic of Korea

ARTICLE INFO

Article history:
Received 30 June 2009
Received in revised form 4 August 2009
Accepted 27 September 2009

Keywords:
Mesenchymal stem cell
Dermal papilla
Outer root sheath
Hair

ABSTRACT

Hair follicles are complex organs composed of the dermal papilla (DP), dermal sheath (DS), outer root sheath (ORS), inner root sheath (IRS) and hair shaft. Development of hair follicles begins towards the end of the first trimester of pregnancy and is controlled by epidermal–mesenchymal interaction (EMI), which is a signaling cascade between epidermal and mesenchymal cell populations. Hair grows in cycles of various phases. Specifically, anagen is the growth phase, catagen is the involuting or regressing phase and telogen is the resting or quiescent phase. Alopecia is not life threatening, but alopecia often causes severe mental stress. In addition, the number of individuals afflicted by alopecia patients has been increasing steadily. Currently there are two methods employed to treat alopecia, drug or natural substance therapy and human hair transplantation. Although drug or natural substance therapy may retard the progress of alopecia or prevent future hair loss, it may also accelerate hair loss when the medication is stopped after prolonged use. Conversely, the transplantation of human hair involves taking plugs of natural hair from areas in which occipital hair is growing and transplanting them to bald areas. However, the number of hairs that can be transplanted is limited in that only three such operations can generally be performed. To overcome such problems, many researchers have attempted to revive hair follicles by culturing hair follicle cells or mesenchymal cells *in vitro* and then implanting them in the treatment area.

Contents

1. Hair morphogenesis and cycle

Development of hair follicles begins towards the end of the first trimester of pregnancy. During this process, clusters of otherwise unremarkable basal cells begin to crowd together at intervals and

* Corresponding author. Tel.: +82 2 2260 3365; fax: +82 2 2271 3489.
E-mail address: jkpark@dongguk.edu (J.-K. Park).

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doi:10.1016/j.bej.2009.09.008

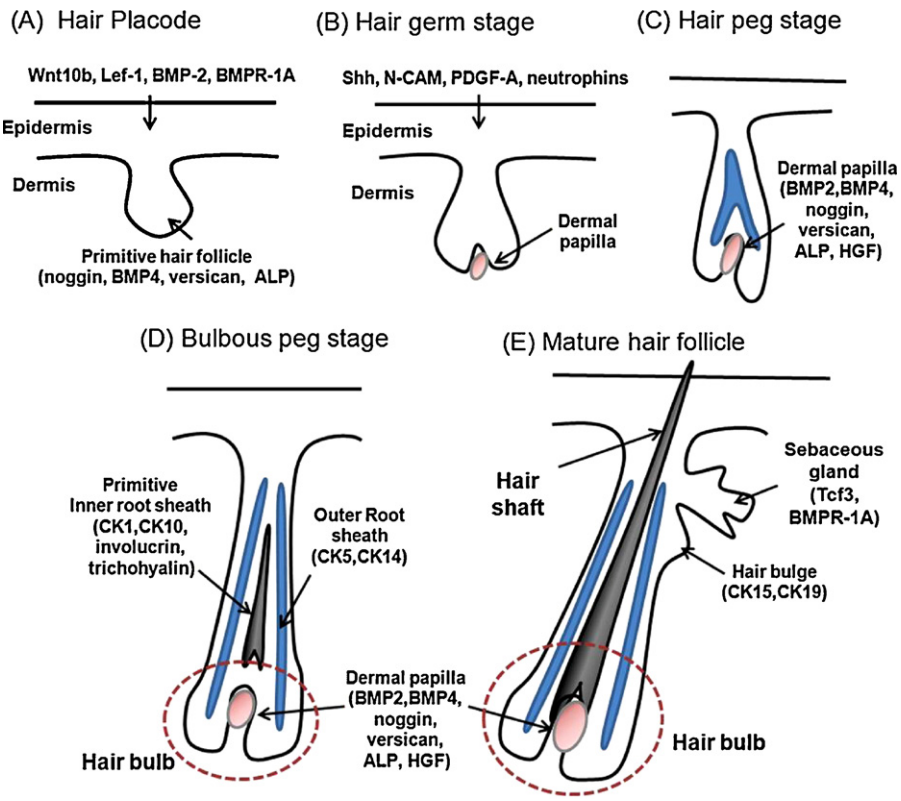

Fig. 1. Schematics of hair morphogenesis and molecules secreted in each of cells during hair morphogenesis. The dotted circle indicate hair bulb region which made hair morphogenesis.

then project into the dermis overlaying fibroblasts that eventually become the dermal papilla (DP) (Fig. 1). Each follicle produces hair twice *in utero* [1,2]. The first batch of fine long hair (lanugo hair) develops during the third trimester and is shed at about 8 months of gestation. The second batch of hair is shed at about 3–4 months post partum. Growth of these first two batches of hair occurs synchronously, as opposed to later hair development, which occurs asynchronously. Lanugo hair is longer and darker than body hair formed post partum. It has been suggested that no new hair follicles develop after birth, and there is no increase in the number of hair follicles after birth [2].

A hair follicle is part of the skin that grows hair by packing old cells together. Sebaceous glands, which are tiny sebum-producing glands found everywhere except on the palms, lips and soles of the feet, are attached to each hair follicle. The thicker the density of hair, the more sebaceous glands are found. Stem cells are located at the junction of the sebaceous gland and the follicle and are primarily responsible for ongoing hair production via a process known as the anagen stage.

Hair grows in cycles of various phases [1] known as anagen, catagen and telogen, which are the growth phase, involuting or regressing phase, and quiescent phase, respectively. Each phase has several morphologically and histologically distinguishable sub-phases. Prior to the start of cycling a phase of follicular morphogenesis occurs. There is also a shedding phase, or exogen, which occurs independently of anagen and telogen and can result in several hairs arising from single follicle exits. Normally, up to 90% of the hair follicles are in the anagen, phase while 10–14% of the hair follicles are in telogen and 1–2% of the hair follicles are in catagen. Additionally, the length of the cycle varies in different parts of the body. For example, the cycle is completed in about 4 months in the eyebrows, while it takes 3–4 years in the scalp. These differences in cycles explain why eyebrow hairs have a fixed length, while hairs on the head seem to have no limit. Growth cycles are controlled by a chemical signal like epidermal growth factor.

All of these transformations are controlled by the epidermal–mesenchymal interaction (EMI), which is a signaling cascade between epidermal and mesenchymal cell populations. The mesenchymal cells in the hair follicles are dermal sheath cells (DSCs) and dermal papilla cells (DPCs). DPCs play a direct crucial role in EMI, while DSCs are known as stems/progenitors of DPCs [3]. EMI is known to mediate important functions in various biological processes in hair follicles such as the development and maintenance of hair follicles, growth of the hair shaft and activation of the hair cycle; however, its precise mechanism has not yet been elucidated [4,5]. Microanatomically, various and complex EMIs are generated continuously in hair follicles between the germinative epithelium (GE) of the matrix bordered by the glassy membrane and DP in the bulb [6,7].

Hair follicles are divided into two major classes that occur in epidermal tissues and dermal tissues [8]. Hair follicles that occur in the epidermal tissues are composed of the ORS and the matrix, and it has been reported that epidermal stem cells are present in the ORS layer [9]. Such stem cells impact both the hair follicles and the formation of the interfollicular epidermis and are primarily located in the ORS in the bulge [10]. In addition, progenitor cells that maintain the formation of interfollicular epidermis and the growth of the hair shaft of the hair follicle are generated via self-renewal and terminal differentiation of the stem cells [11,12]. DPCs and DSCs are present in the dermal tissue of the hair follicle that originates from the mesenchyme, and their cell pattern is similar to that of dermal fibroblasts [13]. DP are located in the lower center of hair follicles and maintain hair shaft growth through the complex and continuous interaction that occurs with hair matrix cells, while the DS surrounds the entire hair follicle [14,15]. It was recently reported that progenitor cells are present in the DSCs and that these cells terminally differentiate to DPCs [16]. Among these