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Resting no more: re-defining telogen, the maintenance stage of the hair growth cycle

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Abstract

The hair follicle (HF) represents a prototypic ectodermal–mesodermal interaction system in which central questions of modern biology can be studied. A unique feature of these stem-cell-rich mini-organs is that they undergo life-long, cyclic transformations between stages of active regeneration (anagen), apoptotic involution (catagen), and relative proliferative quiescence (telogen). Due to the low proliferation rate and small size of the HF during telogen, this stage was conventionally thought of as a stage of dormancy. However, multiple lines of newly emerging evidence show that HFs during telogen are anything but dormant. Here, we emphasize that telogen is a highly energy-efficient default state of the mammalian coat, whose function centres around maintenance of the hair fibre and prompt responses to its loss. While actively retaining hair fibres with minimal energy expenditure, telogen HFs can launch a new regeneration cycle in response to a variety of stimuli originating in their autonomous micro-environment (including its stem cell niche) as well as in their external tissue macro-environment. Regenerative responses of telogen HFs change as a function of time and can be divided into two sub-stages: early ‘refractory’ and late ‘competent’ telogen. These changing activities are reflected in hundreds of dynamically regulated genes in telogen skin, possibly aimed at establishing a fast response-signalling environment to trauma and other disturbances of skin homeostasis. Furthermore, telogen is an interpreter of circadian output in the timing of anagen initiation and the key stage during which the subsequent organ regeneration (anagen) is actively prepared by suppressing molecular brakes on hair growth while

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activating pro-regenerative signals. Thus, telogen may serve as an excellent model system for dissecting signalling and cellular interactions that precede the active 'regenerative mode' of tissue remodeling. This revised understanding of telogen biology also points to intriguing new therapeutic avenues in the management of common human hair growth disorders.

Keywords

hair growth cycle; telogen; hair regeneration; energy; gene expression

I. INTRODUCTION: ORGAN REGENERATION BY CYCLING

> "The pilary system is a perfect microcosmic structure… [in which] … we can find birth, development, ageing and death, activity and rest …"
>
> Rothman [from W. Montagna & R.A. Ellis (eds) (1958)]

The hair follicle (HF) is a unique mini-organ of mammals and one of their most defining features. Its product, the hair shaft, is essential for thermal regulation, sensation, camouflage, dispersion of sebum and pheromones, visual communication and sexual dimorphism as well as for protection from solar radiation and physical trauma.

On the one hand, the HF is important in clinical medicine. Its dysfunction causes multiple forms of alopecia as well as undesired hair growth (Gilhar, Etzioni & Paus, 2012; Shimomura & Christiano, 2010; Breitkopf et al., 2013; Jackson & Price, 2013; Paus et al., 2013); it is targeted by a thriving personal care and beauty industry attempting to alter hair growth, structure, or pigmentation.

On the other hand, studying the biology of this 'microcosmic structure' (Rothman cited in Montagna & Ellis, 1958) allows one to investigate in this easily accessible and readily available model organ many fundamental biological problems pertinent to multiple disciplines, ranging from developmental, stem cell and pigment biology to neuro- and immunobiology, endocrinology, and chronobiology (Paus & Cotsarelis, 1999; Schneider, Schmidt-Ullrich & Paus, 2009). Moreover, analyzing hair phenotypes of mouse mutants has provided numerous novel insights into previously unknown gene functions well beyond skin and hair (Sundberg, Peters & Paus, 2005; Nakamura et al., 2013). It has, therefore, been argued that the HF provides an ideal systems biology research model (Al-Nuaimi et al., 2010).

The HF also serves as an excellent model for developmental biology and regenerative medicine due to its ability to undergo continuous, lifetime cyclic remodelling that recapitulates embryonic organ develo-pment as well as having features of a genuine regeneration phenomenon, a process referred to as the HF cycle (Dry, 1926; Chase, 1954; Schneider et al., 2009) (Fig. 1C). Immediately after the HF completes its morphogenesis, the HF cycle begins with a short stage of apoptosis-driven HF regression (catagen), followed by a state of relative 'rest' (telogen). Subsequently, the HF resumes its growth activity and production of a hair shaft (anagen), recapitulating many morphological and molecular events of the initial HF morphogenesis (Dry, 1926; Chase, 1954; Schneider et al., 2009). At least in

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mice, it is also during anagen that the old hair shaft from the preceding HF cycle ('club hair') is shed in a separately regulated process termed exogen (Milner et al., 2002a; Stenn, 2005; Higgins et al., 2009a; Sato-Miyaoka et al., 2012) (Fig. 1C).

These complex, autonomously controlled organ transformations permit the HF, which harbours multiple distinct adult stem cell pools (Tiede et al., 2007; Nishimura, 2011; Plikus, 2012), to regenerate itself cyclically. However, the 'clock' mechanism that drives the HF cycle remains incompletely understood (Paus & Foitzik, 2004; Geyfman & Andersen, 2010; Al-Nuaimi et al., 2012, 2014; Baker & Murray, 2012; Bernard, 2012; Murray et al., 2012; Plikus et al., 2013; Purba et al., 2014).

Until recently one period of the HF cycle, telogen, has attracted relatively little attention, since conventional wisdom viewed it as a stage of quiescence (Fig. 1). As new data emerge on the previously unappreciated complexity of the cellular and molecular processes during telogen, the semantics of which portion of the HF cycle truly constitutes telogen remains subject to debate. On may argue that any activities, even those preceding the onset of proliferation, should be considered as anagen or distinguished as a separate entity, i.e. a telogen–anagen transition stage.

Herein we consider telogen a stage of the HF cycle that follows the end of apoptotic activity during catagen and precedes the proliferation signifying anagen onset. Many of our statements regarding telogen are based on data from the mouse HF, the best-studied hair research model, but we make references to human hair as well as to other species where appropriate. We argue that despite their perceived quiescence, telogen HFs are biologically very active and highly important clinically. Regardless of the definition, in addition to its importance for understanding the HF cycle, dissecting the true nature of telogen may unveil general principles of how adult stem cells utilize intrinsic and macroevironmental signalling cues to halt cell cycle activity while maintaining robust metabolic life.

II. TELOGEN: CONVENTIONAL WISDOM

The term 'telogen' (from Greek telo meaning end and gen meaning produce) was coined to represent the minimal size, lack of proliferative activity and apparent quiescence of the HFs during this HF cycle stage (Dry, 1926). Indeed, compared to anagen, the telogen HF is small and histologically largely unchanged throughout the duration of the stage, exhibiting neither marked growth nor regression (Fig. 1A, 2A).

Towards the end of catagen and at the beginning of telogen, a completely keratinized hair shaft with a characteristic depigmented and club-like base, termed the club hair, is held firmly by a specialized junction complex at the base of the bulge (a group of slow-cycling keratinocytes located below the sebaceous gland) (Chase, 1954; Parakkal, 1970; Koch et al., 1998; Higgins et al., 2009a; Higgins, Westgate & Jahoda, 2009b; Hsu, Pasolli & Fuchs, 2011). Release of this club hair shaft has recently been proposed to be actively controlled by type 3 isoform of the inositol 1,4,5-trisphosphate/nuclear factor of activated T cells (IP(3)R3/NFAT)-dependent signalling (Sato-Miyaoka et al., 2012).

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A thin stretch of germinative epithelium, the secondary hair germ, separates the bulge and club from the mesenchymal control centre of the HF, the inductive fibroblasts of the dermal papilla (Jahoda & Reynolds, 1996; Ohyama et al., 2010). During the end of catagen and in telogen, the dermal papilla remodels to adopt a greatly condensed, ball-shaped morphology (Fig. 1C) (Muller-Rover et al., 2001). At the end of telogen, epithelial progenitor cells located in the secondary hair germ are activated to proliferate (Panteleyev, Jahoda & Christiano, 2001; Ito et al., 2004; Jaks et al., 2008; Greco et al., 2009; Schneider et al., 2009; Tornqvist et al., 2010; Mardaryev et al., 2011; Rabbani et al., 2011; Lin & Yang, 2013; Rompolas, Mesa & Greco, 2013; Takeda et al., 2013), marking the beginning of another anagen phase.

On the basis of these phenomena, telogen is conventionally thought of as an uneventful waiting period prior to proliferation, hair shaft differentiation and melanogenesis during anagen (Chase, 1954; Botchkarev & Kishimoto, 2003; Alonso & Fuchs, 2006; Cotsarelis, 2006). When HF epithelial stem cells were first identified in the bulge (Cotsarelis, Sun & Lavker, 1990), their discoverers simultaneously proposed a ‘bulge activation hypothesis’ that attempted to explain how anagen is initiated (Cotsarelis et al., 1990). Conversely, catagen, and even more so telogen, were viewed as mere states of epithelial proliferation exhaust, waiting for a dermal-papilla-derived signal to stimulate telogen stem cells to proliferate and produce a new matrix (i.e. anagen) (Blanpain & Fuchs, 2006). In this scenario highly proliferative matrix cells exhaust their proliferative capacity by the end of anagen, at which point hair growth stops and the destructive catagen ensues. Thus, the proliferative potential of the matrix also determines the length of the hair fibre.

Although the HF cycle scenario in which telogen is seen as an idle stage and a simple reference point for the active stage of anagen has long been questioned (Davis, 1962; Paus & Czarnetzki, 1994; Stenn & Paus, 2001; Paus & Foitzik, 2004), it still permeates the field of hair biology today. This has resulted in the tendency of many investigators to focus their attentions on the telogen-to-anagen and anagen–catagen transitions of the HF cycle. As a consequence, telogen remains the least-investigated and least-understood of all HF cycle stages.

Below, we discuss findings that challenge this conventional view of telogen and argue that telogen is indeed an eventful and complex cycle stage, in fact, a stage of progressive molecular activity. Specifically, we develop a notion of why telogen is best viewed as the default state of the mammalian coat due to its energetic efficiency and maximum alertness due to club hair maintenance and heightened sensitivity to environmental stimuli, respectively.

III. TELOGEN AS THE DEFAULT STATE OF THE MAMMALIAN COAT: HAIR CLUB MAINTENANCE

Follicular organization and a cyclic mode of regeneration of epithelial appendages were novelties during vertebrate evolution that came into existence in the form of feather and hair follicles with a stem-cell-driven regeneration program, imbuing these organs with the ability to respond to stimuli in a highly coordinated and energy-efficient manner (Chuong et al.,

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2002). HF cycling is a highly energy-efficient regeneration strategy since this mini-organ can switch between short periods of maximal and long periods of minimal energy consumption (Fig. 2B).

By contrast, interfollicular epidermal homeostasis requires constant proliferation and thus continuous energy expenditure. In addition, compared to the scale-bearing skin of their reptilian ancestors, the cyclic nature of hair regeneration endowed mammals with a much more versatile and adaptable integument, arguably enabling them to survive the Cretaceous–Palaeogene mass extinction event some 66 million years ago.

Featuring a prominent stem-cell compartment, each HF can regenerate as a discrete unit independently of its neighbours. Alternatively, in response to a paracrine or systemic hormonal signal(s), each HF can regenerate in coordination or relative synchrony with tens of thousands of other HFs on the skin surface. These versatile regenerative scenarios in conjunction with the club hair maintenance mechanism and endothermy enable mammals to renew their integument dynamically and without exposing the underlying skin to heat loss. In an evolutionary context, this feature gave mammals a competitive advantage over reptiles, whose patchy epidermal moult leaves them vulnerable to environmental insults for extended periods of time, and restricts their thriving in temperate climate zones.

In seasonally moulting mammals, such as the mink Mustela vison and ferret Mustela putorius furo, the entire mature summer and winter coat is in telogen (Allain & Rougeot, 1980; Nixon et al., 1995).

It is often forgotten that, in contrast to human scalp HFs (Kligman, 1961; Paus & Cotsarelis, 1999), in most mammals the majority of the mature coat at any given time is in telogen. Despite their relative proliferative quiescence, telogen HFs actively hold on to their club hair (Chuong et al., 2002; Milner et al., 2002; Higgins et al., 2009a). Energetically, the formation of club fibres is a highly efficient strategy to maintain a stable fur coat at minimal energy expenditure (Fig. 2). In most mammals, HFs manufacture a fur coat through a short but massive proliferative and biosynthetic effort (anagen) and then retain it for a long period via the formation and anchorage of a club hair shaft.

In fact, hair club maintenance is the most important function of telogen. The hair club represents a fully completed product of the HF while anagen is considered as hair fibre synthesis. Seasonal fur changes thus represent adaptations not only for the generation of winter and summer coats but also for minimizing energy requirements via club hair formation. In seasonal animals, hair regeneration occurs at discreet times of the year during brief moulting periods; coat regeneration in non-seasonal animals occurs in stochastically regenerating domains in which only small regions of the coat undergo regeneration at any one time (Fig. 2B). Asynchronous hair regeneration (i.e. ‘mosaic’ HF cycling) is often linked to an exceptionally long anagen, such as in the human scalp. In nature, this energetically unfavourable state is the exception, not the rule.

The adult human scalp differs from the coats of rodents since human HFs tend to grow in an autonomous (‘mosaic’) fashion (Halloy et al., 2000), with the majority of scalp HFs at any given time being in anagen (80–90%); the remainder being either in catagen (1–2%) or

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telogen (10–15%) (Ebling, 1988; Paus & Cotsarelis, 1999). Given the high percentage of HFs remaining in anagen for years (Halloy et al., 2000; Stenn & Paus, 2001), human scalp skin is energetically expensive; only the balding scalp (with its characteristic HF miniaturisation process) becomes more economical. Perhaps the higher energy-efficiency of this hair phenotype is related to the purported trend of the human species towards progressive balding (Barman et al., 1967; Kushlan, 1985; Dawber, 1997).

Both human and mouse telogen skin has the lowest glycogen content possibly due to its relatively low energy consumption. By contrast, glucose utilization and glycolysis in anagen HFs reportedly increases by 200%, activity of the pentose phosphate cycle by 800%, metabolism by other pathways by 150%, and ATP production via the respiratory chain by 270% (Shipman, Chase & Montagna, 1955; Adachi, 1973). In fact, the dramatic increase in the proportion of follicles in telogen of human scalp skin under conditions of protein–calorie deficiency (e.g. in Kwashiorkor and marasmus) (Ebling, 1988; Dawber, 1997) underscores that telogen induction is an energy-conservation mechanism.

Interestingly, specialized hair regions in other mammals, such as manes, capes, and fringes, e.g. in lions or horses (Whittem et al., 1998; Jouvel et al., 2000), may be similar to human scalp hair with regard to desynchronization and a prolonged duration of anagen. This energetically inefficient HF cycle phenotype likely evolved to facilitate courtship and mating behaviour (Morris, 1967). Yet, the selective forces underlying the evolution of skin regions with spectacularly prolonged and increased anagen, and those that drive the apparent evolutionary trend of the human integument to gradually revert to a relatively bald and more energy-efficient state (Kushlan, 1980), lie outside the scope of this review.

An unusual feature of human skin is the near-absence of significant hair coverage of the human face and torso. Several proposed explanations exist for why Homo sapiens lack the fur coverage characteristic of the majority of mammals. The most likely is that modern man evolved in the African savannah, a hot and arid environment in which humans performed as hunter–gatherers; such energy-expensive exercise thus could have acted as a selective pressure for efficient cooling aided by sweating and naked skin (Morris, 1967). Other large African mammals such as the elephant Loxodonta africana and rhinoceros Diceros bicornis also have little hair coverage, possibly to facilitate body temperature regulation. Below we describe the hair regeneration cycle, and more specifically telogen, an aspect of hair follicle biology feature that may have evolved to maintain the hair coat in densely haired mammals with minimal energy expenditure.

IV. REFRACTORY *VERSUS* COMPETENT TELOGEN

As characterized in the mouse and rabbit, another approach to maximizing the energy efficiency of the maintenance of a hair coat via club hair retention is the regenerative wave mechanism of hair growth in which only small areas of the coat are renewed periodically, resulting in complex hair growth domains (Chase, 1954; Chase & Eaton, 1959; Plikus & Chuong, 2008; Plikus et al., 2008, 2009, 2011) (Fig. 2B). These domains are comprised of skin areas in which all hairs are either in telogen or anagen, forming visually distinct

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boundaries. The telogen zones in these domains can be either refractory or competent, based on the ability of their HFs to respond to activating signals by anagen induction.

The refractory telogen stage, which directly follows catagen and lasts for about 1 month in (6–7 week-old mice) mice, allows the HF to avoid excessive regeneration even in the presence of strong activation signal(s): refractory telogen HFs are unable to respond to endogenous anagen-inducing stimuli such as signals originating from neighbouring early-anagen HFs (Plikus et al., 2008, 2011). By contrast, competent telogen HFs can easily enter into a new anagen upon stimulation by neighbouring early-anagen follicles. In competent telogen, the HF inhibitory and pro-activation signalling environment (Fig. 3) reaches a balance, such that an incoming regenerative wave of propagating anagen stimulus can initiate its proliferative machinery into action (Plikus & Chuong, 2014).

The refractory versus competent functional state of telogen hair HFs is to a large extent underpinned by competing gradients of diffusible inhibitory signals [such as bone morphometric proteins (Bmps)] as well as stimulatory signals [such as wingless (Wnt) (Plikus & Chuong, 2008; Plikus et al., 2008, 2009)]; fibroblast growth factors (Fgfs) also play a important role in determining refractoriness versus competence of the telogen HF (Greco et al., 2009; Kimura-Ueki et al., 2012; Oshimori & Fuchs, 2012). In this scenario the inhibitory Bmps and Fgf18 compete with activating Wnts and Fgf7/10 in determining the readiness of telogen HFs to engage in active growth.

Thus the differential organization of telogen into two morphologically indistinguishable, but functionally very distinct sub-stages is not only energy-efficient, but also enables the HF to fine-tune its responses to both its intracutaneous microenvironment and to wider-scale environmental inputs.

V. TELOGEN: AN ALERT STATE OF THE HAIR FOLLICLE AND MAMMALIAN SKIN

Telogen HFs have an extraordinary ability to respond sensitively and promptly with anagen induction to a large array of stimuli (ranging from trauma via inflammation to hormones, growth factors, cytokines, neuropeptides and drugs (Chase, 1954; Paus, Stenn & Link, 1989; Paus, Müller-Röver & Botchkarev, 1999; Stenn & Paus, 2001; Paus, Nickoloff & Ito, 2005; Schneider et al., 2009). Telogen HFs rapidly 'sense' the removal of the club when a hair shaft is plucked and immediately enter into anagen (Chase & Montagna, 1951; Chase, 1954; Argyris & Argyris, 1962; Paus, Stenn & Link, 1990). Likewise, exposure to the immunosuppressive calcineurin inhibitor, cylosporine A, rapidly induces anagen in telogen HFs (Paus et al., 1989; Paus et al., 1996) presumably by releasing an NFATc1-activity-dependent molecular ‘brake’ on bulge stem cell activity (Horsley et al., 2008).

Animals with seasonal moults respond to short day lengths with increased circulating night time melatonin levels and consequently reduced pituitary prolactin release leading to the initiation of winter coat growth in the autumn (Rose et al., 1985; Rose, Oldfield & Stormshak, 1987; Dicks, Russel & Lincoln, 1994; Pearson et al., 1999).

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The potency of prolactin as a hair growth modulator in mice and man (Craven et al., 2001; Foitzik et al., 2003, 2006; Langan et al., 2010; Paus et al., 2014) and the fact that the HF, like many other organs, contains a functioning peripheral circadian clock mechanism responsive to the endocrine output of the brain clock (Zanello, Jackson & Holick, 2000; Geyfman & Andersen, 2009; Lin et al., 2009; Tanioka et al., 2009; Geyfman et al., 2012; Plikus et al., 2013; Al-Nuaimi et al., 2014) underscores the capacity of HFs to respond to environmental cues that are translated into neuroendocrine cues. Other sensory inputs can also prolong the duration of telogen. For example, sonic and pain stress can prolong telogen by limiting proliferation and thus delaying anagen initiation (Arck et al., 2001; Aoki, Shibasaki & Kawana, 2003; Katayama et al., 2007). Likewise, topical application of glucocorticoids, prototypic stress hormones, or estrogen can 'freeze' murine HFs in the telogen state (Stenn et al., 1993; Oh & Smart, 1996; Ohnemus et al., 2005, 2006).

The ability of telogen skin to respond to a great variety of stimuli implies that telogen HFs must exhibit relatively high expression levels of receptors and other response systems; paired with their low level of 'activity', this loosely resembles what neuroscientists would consider an alert state (Posner, 2008; Tang, Rothbart & Posner, 2012).

VI. ACTIVE BIOLOGICAL PROCESSES IN TELOGEN

Microarray gene expression studies aimed at identifying gene expression over the hair cycle have provided insights into the telogen gene expression program and, by inference, into the biological processes characteristic of telogen (Lin et al., 2004, 2009; Schlake et al., 2004; Ishimatsu-Tsuji, Moro & Kishimoto, 2005; Umeda-Ikawa, Shimokawa & Doi, 2009; Geyfman et al., 2011). One of these studies identified a 425-gene 'telogen signature' defined as the set of transcripts expressed 1.5-fold higher or lower in each of three telogen timepoints corresponding to early, mid and late telogen compared to all other stages of the first synchronized hair cycle (Geyfman et al., 2012). Multiple other studies have identified genes expressed most highly or at their lowest levels during telogen (Table 1). Additionally many transcripts change dynamically in early, mid and late telogen whole skin (Geyfman et al., 2012) and in isolated secondary germ and bulge cells (Greco et al., 2009).

The sheer number of differentially expressed and dynamic transcripts suggests highly robust and regulated biological activities during telogen. Interestingly, amongst the most prominent biological functional categories upregulated in telogen are cholesterol metabolic process, innate immunity, and the circadian clock mechanism (Geyfman et al., 2011) (Fig. 4).

(1) Circadian clock regulation

The circadian clock is a transcriptional oscillatory network that modulates daily cellular activity in response to the earth's rotation with a periodicity of approximately 24 h. A central clock located in the suprachiasmatic nucleus of the hypothalamus is thought to synchronize the activity of clocks found in all cells of peripheral tissues, including the skin (Geyfman & Andersen, 2009; Tanioka et al., 2009). While circadian clock activity in skin is observed throughout the hair cycle, there is evidence for more robust clock output throughout telogen (Lin et al., 2009; Geyfman et al., 2012); indeed, the secondary hair germ is the site of the most striking expression of clock target genes in telogen follicles (Lin et al., 2009). Mice

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constitutionally mutated for Bmal1, a core clock gene, exhibit a week-long delay in anagen activation due to cell cycle arrest in the secondary hair germ.

The circadian clock, therefore, contributes to regulation of the HF cycle, specifically at the telogen–anagen transition, with the telogen HF serving as an important interpreter of circadian output in the timing of HF cycling. However, recent work with microdissected, organ-cultured human scalp HF demonstrates that the peripheral clock is also involved in regulating the anagen–catagen transformation of the HF cycle (Al-Nuaimi et al., 2014).

Mice with intraepithelial deletion of Bmal1 in the skin have a normal HF cycle, implying that murine HF cycle control is accomplished by the central brain clock, the HF's dermal papilla, or other extrafollicular clocks within the skin (Geyfman et al., 2012). Interestingly, work on organ-cultured human HFs demonstrates that a BMAL1- and PERIOD1-dependent intrafollicular clock mechanism is operative in human HFs in the absence of central clock inputs (Al-Nuaimi et al., 2014) and also regulates human HF pigmentation (Hardman et al., 2014).

Seasonal hair growth is also regulated during the telogen–anagen transition (Rogers, 2006), raising the possibility that the secondary hair germ of telogen HFs could serve as an interpreter of photic timing cues for seasonal hair growth (Geyfman & Andersen, 2010).

Additionally, the telogen bulge is known to contain a heterogeneous population of cells with high and low expression of circadian clock target genes, including transforming growth factor-β (Tgfβ) and Wnts. Thus in the telogen bulge, the clock may help to establish cells in a ‘ready-to-go’ state characterized by a low level of Tgfβ and high Wnt activity, determining which of the bulge progenitors are destined to divide and contribute to HF renewal and which cells will await future cycles (Janich et al., 2011).

A recent report demonstrates that another circadian target gene, a cell cycle arrest mediator p21, is enriched in bulge keratinocytes in telogen and its expression is antagonized transcriptionally by runt-related transcription factor 1 (RUNX1) (Lee et al., 2013). Whether p21 is part of the heterogeneity model of stem cell activation in the HFs is yet unknown. In addition to circadian clock mechanisms, expression of Myc-induced SUN-domain-containing protein (MISU), an RNA methyltransferase, marks murine bulge cells as destined for cell cycle entry at the telogen–anagen transition (Blanco et al., 2011). Thus, stem cells of the mouse telogen bulge may exist in a state of heterogeneity where some cells marked by expression of clock or other genes, such as Misu, are more likely to enter the cell cycle upon activation.

The explanation for enhanced circadian clock activity in murine telogen is purely speculative at present. One possibility is that recruitment of circadian clock machinery in cell-cycle-regulation stem cell compartments is required to minimize DNA damage arising from reactive oxygen species (ROS) generated as a result of time-of-day-dependent changes in oxidative metabolism (Geyfman et al., 2012). In nocturnal mouse telogen skin, peaks of proliferation and ROS accumulation occur at different times (night and day, respectively), while in diurnal organisms, such as humans, these rhythms are antiphasic to those of mice (Geyfman et al., 2012). Interestingly, the outer root sheath, including its progenitor-cell-rich

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segments, displays major mitochondrial activity in human HFs (Vidali et al., 2014). Thus, HF progenitor cells may well reside in an environment that is inherently prone to damage by ROS, rendering the establishment of local stem-cell-protective mechanisms very important. In anagen, when proliferation is at extremely high levels circadian clock involvement is suspended thus leaving HFs at a higher risk of DNA damage. This may be another reason why anagen is relatively short in most species.

Additionally, higher concentrations of circadian clock components in the telogen secondary hair germ may be due to this region's particular ability to perceive circadian cues signalling the beginning of biannual moult cycles and to respond by initiating cell division (anagen). Therefore the function of the circadian clock in the telogen upper follicle may be prevention of ROS DNA damage resulting from the oxidative phosphorylation chain, and in the secondary hair germ may be part of the response to perennial light–dark photoperiod variations.

(2) Immune function

The immune status of murine skin changes significantly during HF cycling, both phenomenologically and functionally, with heightened immune responses generally associated with telogen skin, while anagen skin is relatively immunoinhibited (Paus et al., 1998, 2005). The latter is most notable with respect to type IV immune responses: contact hypersensitivity responses are lowest in anagen and highest in telogen skin (Hofmann et al., 1996, 1998; Paus et al., 2005). Interestingly, in telogen, but not in anagen, rat skin appears to be completely resistant to dermatophyte (ringworm) infection (Kligman, 1956). In a murine candidiasis model, telogen and anagen HFs developed infectious foci at an equivalent rate, yet in telogen skin foci of Candida albicans infection were never found below the skin (Sohnle, Collinslech & Hahn, 1986).

These phenomena suggest that both acquired innate immune mechanisms may be up-regulated and that cellular immune responses operate at maximal capacity in telogen skin (Paus et al., 2005). Indeed, expression of a member of the β-defensin family, β-defensin 8 (Defb8), is 300-fold higher in telogen skin compared to other stages of the HF cycle (Geyfman et al., 2012). Also, mRNA levels for the hair-growth-inhibitory cytokines interleukin-1α (IL-1α) and IL-1β peak during synchronized, spontaneous telogen in murine skin (Hoffmann, Happle & Paus, 1998). Recently it was shown that isthmus and infundibulum regions of both telogen and anagen HFs produce chemokines required for Langerhans cell entry into the epidermis (Nagao et al., 2012). However, whether telogen skin is a more proficient recruiter of Langerhans cells remains to be determined.

While the function of increased innate immunity in telogen skin remains unclear, some innate-immunity-associated genes play an additional role in hair growth suppression during telogen.

VII. TELOGEN: A RESULT OF ACTIVE HAIR GROWTH INHIBITION

One important telogen-associated biological activity is the intracutaneous accumulation of as yet incompletely defined growth-inhibitory activities in telogen skin (Chase, 1954; Paus

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et al., 1990; Paus, Stenn & Elgjo, 1991; Paus & Foitzik, 2004; Plikus et al., 2008). In the early days of philosophizing over the enigmatic mechanisms that may drive the HF cycle, Chase (1954) pioneered the idea that the HF cycle is essentially controlled by an inhibition–disinhibition system. During anagen, he speculated, a hair-growth-inhibitory activity such as ‘chalones’, which had attained both popularity and notoriety in the epithelial growth control community (Bullough & Laurence, 1968; Marks & Richter, 1984), switches off anagen once a certain threshold has been exceeded; anagen is switched on again after this has fallen below a critical threshold, releasing a molecular brake on HF cycling (Chase, 1954).

Subsequently, it was shown that telogen mouse skin indeed contains an (unidentified) tissue-specific, but not species-specific hair-growth-inhibitory activity with chalone-like properties that significantly retards plucking-induced anagen (Paus et al., 1990). The best-defined chalone, a synthetic pentapeptide, exerted the same effect (Paus et al., 1991). While the contrasting arguments regarding Chase's elegantly simple inhibition–disinhibition HF cycle theory do not concern us here (for discussion, see Paus & Foitzik, 2004; Al-Nuaimi et al., 2012), it is worth observing that this theory further cemented the prevailing view of telogen as a state of passive hair growth inhibition.

Only a few years after the first experimental evidence in partial support of Chase's theory became available, a series of studies was published which documented that anagen can also be switched off actively by increased transcription, translation and/or secretion of potent hair-growth-inhibitory growth factors such as FGF5, TGFβ1 and TGFβ2 (Hebert et al., 1994; Philpott & Kealey, 1994; Petho-Schramm, Muller & Paus, 1996; Suzuki et al., 2000; Hibino & Nishiyama, 2004). It was not clear whether such active regulation of the anagen–catagen transition of the HF cycle by growth factors (and by the withdrawal of anagen-maintaining growth factors, such as insulin-like growth factor 1 (IGF-1) (Rudman et al., 1997; Weger & Schlake, 2005) and hetatocyte growth factor (HFG) (Lindner et al., 2000) also extended to the catagen–telogen transition. However, these findings made it increasingly unlikely that the telogen HF is simply a surviving rump structure after ‘epithelial exhaust’, but rather represents an actively regulated state.

Although early- and mid-telogen follicles (i.e. refractory telogen HFs) (Plikus & Chuong, 2008) are often regarded as dormant, their epithelial progenitor cells, including bulge stem cells and secondary hair germ cells, are kept quiescent and maintained in an undifferentiated state through an active signalling process; in mice, this involves BMP4 release from the dermal papilla, BMP6 and FGF18 from keratin-6- (K6)-positive niche cells and BMP6 from subcutaneous fat cells (Woo & Oro, 2011). Clearly, proliferative inactivity must not be confused with biochemical and signalling inactivity.

At the genome level, the expression of hair lineage differentiation genes is suppressed in quiescent bulge stem cells through repressive polycomb group (PcG)-mediated histone H3K27 trimethylation, while genes involved in stem cell quiescence itself are expressed and lack this repressive histone modification. Upon activation, bulge cells gain H3K79me2 marks at nonPcG-regulated cell-cycle regulatory genes (Lien et al., 2011). Therefore in telogen, quiescence is also established epigenetically, in addition to the repressive cellular-signalling milieu.

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In addition to non-hormonal auto- and/or paracrine inhibitors, cyclic hair regeneration is modulated by multiple circulating hormones, including androgens, thyroid hormones, glucocorticoids, estrogens, and prolactin (Johnson, 1958; Foitzik et al., 2003; Plikus et al., 2008; Langan et al., 2010). During pregnancy and lactation the entire coat is maintained in telogen (Plikus et al., 2008; Paus et al., 2014), underscoring that telogen is an energy-efficient mode of coat maintenance during times of duress (Fig. 2A).

In conclusion, active mechanisms suppressing proliferation maintain the bulge and secondary hair germ of telogen HFs in proliferative quiescence, demonstrating that the apparent 'silence' of telogen HFs represents, in reality, a state of prolific activity.

VIII. CELL PROLIFERATION AND EPITHELIAL STEM CELLS IN THE TELOGEN FOLLICLE

Cells of the lower telogen HF, namely the secondary hair germ and the bulge, do not appear to proliferate, although it has not yet been established whether keratinocytes in these regions of the telogen HF epithelium undergo active DNA synthesis ('endoreplication') (Zanet et al., 2010). This has fostered the oft-repeated notion that the defining feature of telogen HFs is a lack of cell proliferation. However, this is a misconception: the distal (upper) regions of the telogen HF epithelium immediately above the bulge, i.e. the infundibulum and the isthmus (Schneider & Paus, 2014), actually contain numerous proliferating cells throughout telogen, including during the extended second telogen in the mouse (Geyfman et al., 2012) (Fig. 1B).

The infundibulum, from the Latin word for funnel, is above the entry of the sebaceous duct and merges with the interfollicular epithelium (Schneider & Paus, 2014). The isthmus of the HF is the short region between the point of attachment of the arrector pili muscle and the entry of the sebaceous gland duct (Fig. 2). Several distinct multipotent stem/progenitor cell populations in these regions of the HF contribute to the continuous renewal of the so-called 'permanent' part of murine HFs (Fig. 5, which in fact also undergoes hair cycle-dependent remodeling (Lindner et al., 1997)).

Leucine-rich repeats and immunoglobulin-like domains (LRIG1)- (Jensen et al., 2009) and malignant transformation suppression 24 (MTS24)-positive (Nijhof et al., 2006; Jensen et al., 2009) stem cells are found in the upper isthmus. The support that MTS24 and LRIG1-positive cells proliferate during telogen comes from data demonstrating that these cells are only weakly label retaining, in contrast to more quiescent CD34-positive bulge progenitors (Nijhof et al., 2006). Lgr6-positive stem cells (Snippert et al., 2010) are located in the lower isthmus directly above the bulge.

Below the Lgr6-positive cells are recently identified glioma-associated oncogene 1 (GLI1)-positive cells that respond to sonic hedgehog (Shh) paracrine signalling from the sensory nerves of the upper bulge with another subpoplation of these cells located in the secondary germ (Brownell et al., 2011). Interestingly Gli-1 originating from secondary germ and bulge can activate a chromatin remodeling factor brahma-related gene 1 (Brg1) that, in turn, can repress P27 in late telogen causing secondary germ and bulge activation, and can later signal matrix proliferation via nuclear factor kappa B (NF-κB) during anagen, thus providing an

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elegant explanation for the existence of sensory nerve–HF signalling (Xiong et al., 2013). Finally, PR domain-containing protein 1 (Blimp1)-positive progenitor cells are located at the opening of the sebaceous gland duct, and may contribute exclusively to the renewal of the sebaceous gland (Horsley et al., 2006).

Below the isthmus lie HF structures that proliferate exclusively in anagen, namely the bulge and the secondary hair germ. The bulge, lying immediately below the isthmus at the site of the insertion of the arrector pili muscle, first described by Franz van Leydig in 1859 as a thickening of the outer root sheath (Schneider, 2011), and was later shown to contain label-retaining progenitor cell populations (Cotsarelis et al., 1990; Cotsarelis, 2006). Below the bulge and in intimate contact with the dermal papilla is an epithelial cluster of cells referred to as secondary hair germ. It is this region that responds first to the dermal-papilla-derived pro-anagen signal (Greco et al., 2009; Sennett & Rendl, 2012).

Both lower bulge and secondary hair germ in mice contain Lgr5-positive cells, a non-slow-cycling yet multipotent cell population. Lower bulge cells positive for Lgr5 and expressing the homeobox gene homeodomain-only protein homeobox (Hopx) eventually give rise to K6-positive non-stem-cell bulge residents important for maintaining bulge quiescence (Takeda et al., 2013)

In summary, while telogen HFs are relatively ‘quiescent’ compared to highly proliferative anagen HF, they are far from devoid of proliferating cells (indeed, keratinocytes of the upper HF proliferate during telogen). Only the bulge and the secondary hair germ, i.e., hair-lineage-committed progenitors responsible for the construction of the prominently cycling proximal part of the HF, demonstrate proliferative quiescence during telogen.

It should be noted that in late second telogen, prior to mitosis, a few DNA-synthesizing cells are already present in the ‘dormant’ secondary hair germ (Silver & Chase, 1970), marking cell cycle entry. Once this is systematically investigated, the secondary hair germ may well turn out to be a site of significant ‘endoreplication’ (i.e. DNA synthesis without mitotic activity) (Gandarillas, Davies & Blanchard, 2000; Zanet et al., 2005, 2010). Other processes outlined below highlight how stem and progenitor cells in these regions are activated already late in telogen in preparation for cell proliferation that will ensue upon anagen transition. Again this is not consistent with the telogen HF being ‘quiescent’.

IX. PRE-ANAGEN ACTIVITY IN LATE TELOGEN

It has long been known that rodent skin with all HFs in telogen is exquisitely sensitive to a diverse range of anagen-inducing stimuli. These include trauma (e.g. by hair shaft depilation) (Chase, Montagna & Malone, 1953; Chase, 1954; Argyris & Trimble, 1964; Paus et al., 1990), immunosuppressive immunophilin ligands (Paus et al., 1989, 1996; Horsley et al., 2008), signals such as selected prostaglandins and cytokines (Paus et al., 1994, 1995; Stenn & Paus, 2001; Blume-Peytavi et al., 2012; Garza et al., 2012; Nieves & Garza, 2014), and neuropeptides such as substance P and adrenocorticotropin hormone (ACTH) (Paus et al., 2005; Schneider et al., 2009; Paus et al., 2014). The discovery of ‘competent telogen’ (Plikus et al., 2008) (Fig. 3), and the stepwise elucidation of molecular changes in the telogen HF's signalling milieu that prepare it for entry into anagen, have

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provided a rational basis for explaining why it is so easy to induce anagen in defined subpopulations of telogen HFs, and by such divergent stimuli.

This recent progress also helps to explain why the HF is extremely susceptible to both growth-inhibitory and growth-stimulatory signals in late telogen. In essence, competent telogen HFs appear to exist in a delicate state of equilibrium between growth arrest and proliferation, easily pushed towards growth induction and anagen entry. However, rather than being a passive state, this is a highly actively regulated HF cycle condition (Plikus, 2012; Kandyba et al., 2013).

Several recent studies have supported the original concept of Davis (1962) that late (competent) telogen follicles display pre-anagen activity. In late telogen, prior to the actual telogen-to-anagen transition, dermal papilla cells activate canonical Wnt signalling and start producing Fgf7/10 ligands (Greco et al., 2009; Enshell-Seijffers et al., 2010). The so-called ‘point of no return’ in HF cycle initiation occurs when secondary hair germ cells themselves turn on canonical Wnt signalling and start to proliferate (Panteleyev et al., 2001; Greco et al., 2009; Plikus et al., 2011; Myung et al., 2013). Multiple additional signalling events occur between Wnt activation in the dermal papilla and secondary hair germ, and the complexity of the signalling interplay at this crucial time point of the hair cycle is only now starting to become unraveled.

This complexity also includes the as yet incompletely understood bidirectional signalling exchanges that occur between adipocytes and the HF during its development (Hausman et al., 1981; Kandyba et al., 2013; Wojciechowicz et al., 2013) and cyclic transformation (Festa et al., 2011; Schmidt & Horsley, 2012; Donati et al., 2014; Driskell et al., 2014) as well as during hair-wave pattern formation (Plikus et al., 2008, 2009). For example events leading to suppression of Bmp activity required for stem cell activation occur extrafollicularly, when the expression of inhibitory dermal Bmp2 shuts down in late or competent telogen, thus removing a molecular brake on HF cycling (Plikus et al., 2008). Also, adipocyte precursor cells whose generation starts in catagen and telogen, release platelet derived growth factor (PDGF) to act on the HF's dermal papilla; this event is also required for anagen onset (Festa et al., 2011).

Therefore it is conceivable that the telogen HF is purposely retracted into a fibroblast-dominated signalling environment, the dermis, so as to distance it from signalling interactions with adipocytes during this HF cycle stage.

Fgf18 and Bmps are important factors for telogen maintenance, and their downregulation is a key event in anagen initiation (Fig. 3).

In mice, Fgf18 is expressed by K6-positive bulge keratinocytes that form during late catagen (Hsu et al., 2011) as well as by the dermal papillae (Greco et al., 2009), CD34-positive bulge cells, and weakly in the secondary hair germ (Kimura-Ueki et al., 2012) during refractory telogen. Its expression in the bulge is regulated by transcription factor forkhead box protein P1 (Foxp1) whose expression is highest during early telogen (Leishman et al., 2013). Expression of Fgf18 in these compartments is dramatically reduced at the telogen–anagen

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transition (Greco et al., 2009; Kimura-Ueki et al., 2012). What causes a drop in Fgf18 expression is currently unknown although it appears that Foxp1 is critical in this event.

Another provocative hypothesis is that Fgf18 may be a component of the elusive 'epidermal chalone' activity that was hypothesized to switch-off anagen and whose loss of activity may be needed for anagen re-onset (Chase, 1954; Ebling & Johnson, 1961; Paus et al., 1990; Paus & Foitzik, 2004). However, to qualify as a 'chalone' in the original definition of this term (e.g. Bullough, Laurence & Hewett, 1964; Bullough, 1973) Fgf18 would have to exert tissue-specific effects even across species.

Additional intrafollicular actors play a role in late telogen, prior to the start of the new HF cycle. For example, TGFβ2 synthesized in the dermal papilla activates transmembrane protein with EGF-like and two follistatin-like domains 1(Tmeff1) via similar to mothers against decapentaplegic (Smad2/3) signalling, leading to the reduced expression of BMPs in late telogen (Oshimori & Fuchs, 2012). Suppression of BMP signalling in the late telogen HF, in turn, activates Wnt7a promoting anagen entry (Kandyba et al., 2013). Interestingly, such suppression could, at least in part, be accomplished by a voltage-gated calcium channel (VGCC) Cav1.2 that is expressed in the bulge and can activate transcription of follistatin-like1 (Fstl1), a potent BMP inhibitor in late telogen (Yucel et al., 2013).

Interestingly, although the majority of the secondary hair germ is derived from select outer root sheath cells that survive catagen (Hsu et al., 2011), a few bulge cells depart from the niche to populate the secondary hair germ in late telogen where they contribute to the expansion of this compartment prior to initiation of cell division (Zhang et al., 2009). These departed bulge cells lose the expression of the majority of bulge markers and begin expressing several previously identified hair matrix signature genes and HF differentiation-related genes prior to anagen initiation (Zhang et al., 2009). Thus, the cell biology of telogen HFs, despite the deceptive quiescence of bulge stem cells, becomes functionally very distinct towards the end of telogen.

Taken together, telogen is not just a passive period of waiting for activation signals, but rather a period in which active growth-inhibitory signals operate during early and mid telogen, followed by active repression of quiescence mediators, mainly Fgf18 and Bmps, during late/competent telogen. In this repressive activity, estrogen, prolactin and leptin receptor mediated signaling are implicated as well (Table 1) (Paus et al., 2014).

Well beyond the confines of hair research, the telogen HF may therefore serve as an instructive general model system for dissecting the molecular controls that underlie tissue interaction systems that are about to enter into a regenerative state, but have not yet done so morphologically.

X. CLINICAL IMPORTANCE OF TELOGEN

Besides the importance of model aspects of telogen biology for investigating fundamental biological questions, a deeper understanding of telogen is also clinically important. From a clinical perspective, the crucial HF cycle switch occurs between anagen and catagen, since premature catagen entry will increase the percentage of telogen HFs. This shortens hair

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length and promotes diffuse shedding of club hairs ('telogen effluvium'), while retarded catagen entry of the anagen HF may result in unwanted hair growth (hirsutism, hypertrichosis) (Paus & Cotsarelis, 1999; Stenn & Paus, 2001; Paus, Theoharides & Arck, 2006; Breitkopf et al., 2013; Guarrera, Fiorucci & Rebora, 2013).

Thus, gaining control of telogen is a central challenge in clinical hair medicine (Dawber, 1997; Paus & Cotsarelis, 1999; Miteva & Tosti, 2012). Moreover, whether a HF is in refractory or competent telogen will greatly impact on the efficacy of anagen-inducing agents, such as minoxidil or finasteride and selected prostaglandin receptor antagonists (Miteva & Tosti, 2012). Thus, widely available, but as yet poorly effective hair-growth-promoting agents may be administered more effectively if we can learn how to switch a human telogen HF from its refractory state into competence before these agents are applied.

The percentage of telogen HFs in a given skin area (e.g. the scalp) dictates the number of HFs that will subsequently release their club hair during exogen, an actively regulated process of hair shaft extrusion and shedding that only occurs in early anagen (Milner et al., 2002b; Van Neste, Leroy & Conil, 2007; Higgins et al., 2009a, 2009b; Sato-Miyaoka et al., 2012). 'Telogen effluvium' (Headington, 1993; Dawber, 1997; Guarrera et al., 2013) is probably a misnomer as this phenomenon reflects excessive exogen, either due to the presence of a higher-than-normal percentage of telogen HFs in a given skin area or due to telogen-independent (as yet unclear) controls of exogen itself (Milner et al., 2002a; Stenn, 2005; Van Neste et al., 2007; Higgins et al., 2009a; Sato-Miyaoka et al., 2012).

While the pathobiology of 'telogen effluvium' remains unknown (in fact, it would be more appropriate to term this 'exogen effluvium'), several mouse models show features resembling this phenomenon. For example, a mutation in desmoglein 3 leads to wave-like hair loss in telogen due to lack of proper anchorage of club hairs (Koch et al., 1998), while mice deficient in cathepsin L, a lysosomal endopeptidase, display premature anagen entry and hair shedding in telogen (Roth et al., 2000; Tobin et al., 2002). Msh homeobox 2 (Msx2)-deficient mice also show premature and likely excessive exogen (Ma et al., 2003), and IP(3)/NFAT signalling has been implicated in the control of club hair shedding (Sato-Miyaoka et al., 2012).

In any case, so-called 'telogen effluvium' can only occur if the HF has run through catagen and telogen and has thus generated a club hair (Fig. 1). This makes it clinically important to decipher the controls of both telogen and exogen, and to compare the club-hair-loss phenotype in selected mouse models (e.g. Chen et al., 2002; Sato-Miyaoka et al., 2012; Nakamura et al., 2013) with club-hair-dominated effluvium in humans (Kligman, 1961; Headington, 1993; Dawber, 1997; Guarrera et al., 2013).

If one views the telogen HF as an interpreter of chronobiological cues that regulate HF cycling, possibly as a means of coat adaptation to seasonal changes in the environment, even this is clinically relevant. Vestiges of seasonal fluctuations in hair growth are still present in humans (Randall & Ebling, 1991; Randall, 2007; Kunz, Seifert & Trueb, 2009), and seasonal fluctuations in the degree of effluvium associated with female-pattern balding (androgenetic alopecia in women) are well appreciated (Dawber, 1997; Kunz et al., 2009).

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Therefore, it may be most efficient to counteract undesired seasonal variations of human hair growth by impacting hair during telogen.

Additional clinical considerations make it compelling to invest more effort into defining the controls of telogen in human HFs. For example, one of the most common autoimmune diseases of man, the CD8+ T-cell-mediated hair loss disorder, alopecia areata, primarily attacks anagen and spares telogen HFs (Messenger, Slater & Bleehen, 1986; Gilhar et al., 2012; McElwee et al., 2013). Thus, if one were able effectively to induce refractory telogen in the periphery of an alopecia areata scalp skin lesion and could then 'freeze' the HFs in this state, this may provide an effective means of halting disease progression (McElwee et al., 2013).

A similar concept may be applicable to chemotherapy-induced hair loss, which primarily affects rapidly proliferating anagen HFs, while chemotherapeutic agents typically leave telogen HFs and their non-proliferating bulge epithelial stem cells relatively undisturbed ((Paus et al., 2013). Thus, it is to be expected that iatrogenic telogen induction (e.g. of scalp hair) would still eventually result in increased hair loss (exogen effluvium), but may circumvent occurrence of the dramatic, much-feared anagen effluvium that is seen with many chemotherapeutic agents ((Paus et al., 2013).

Finally, the management of unwanted hair growth, i.e. hirsutism and hypertrichosis, would also profit from a renaissance in telogen research. The underlying, cosmetically undesirable and biologically striking, organ conversion of tiny, unpigmented (vellus) HFs into large, pigmented and medullated terminal HFs (Dawber, 1997) requires that vellus HFs enter into competent telogen followed by anagen. Thus, hirsutism and hypertrichosis may best be tackled if, after depilation of unwanted hair shafts by conventional means (e.g. depilatory creams and devices, laser epilation), induction and/or maintenance of refractory telogen could be achieved by the administration of topically applicable hair-growth-inhibitory agents.

XI. CONCLUSIONS

1. Telogen is characterized by complex, functionally relevant biological activities centred around the active maintenance of the hair fibre and the prompt, well-orchestrated response to its loss. Therefore, it is no longer justifiable to portray telogen as the 'resting' stage of the HF cycle. Telogen deserves to be appreciated as one the biologically fascinating and clinically important components of HF biology.
2. Telogen represents the default state of the mammalian coat, which may have evolved in order to retain the hair fibre to avoid the energy expenditure of massive proliferation and macromolecular synthesis that is the hallmark of anagen.
3. Beyond club hair maintenance for energy-efficient coat preservation, telogen HFs engage in a multitude of important biological activities that impact the cutaneous environment. Some of these are aimed at establishing a fast-response signalling environment to trauma and other disturbances of skin homeostasis. This maintains

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the stem cell niche, in addition to several stem and progenitor cell populations, in the upper (distal) HF epithelium undergoing active proliferation during telogen and actively prepares (in competent telogen) the HF for regeneration during the subsequent anagen stage. Possibly as a reflection of the enhanced vulnerability of telogen skin to injury and its reduced repair capacity, this 'alert' state is accompanied by a heightened immune response in telogen skin, particularly by enhanced innate immunity signalling.

4. The crucial period of HF activity during telogen occurs during its state of competence (late telogen), when the HF begins to prepare actively for the subsequent organ regeneration event (anagen development) by releasing defined molecular brakes on hair growth such as FGF18 and BMPs, and by up-regulating pro-regenerative signals such as Wnts.

5. Besides their relevance to hair biology, these insights into the true nature of telogen suggest that this HF cycle stage may serve as an excellent model system for investigating other, less accessible tissue interaction systems that prepare themselves for switching to a 'regenerative' mode.

6. This redefined notion of telogen biology also advocates the development of a novel classification of HF cycling, which relies on a distinct, functionally defined molecular signature for each HF cycle stage (Lin et al., 2004, 2009; Ishimatsu-Tsuji et al., 2005; Umeda-Ikawa et al., 2009; Mardaryev et al., 2010; Geyfman et al., 2012), rather than primarily on morphological criteria (Muller-Rover et al., 2001; Dry, 1926).

7. Recognizing telogen as a master-switch stage in the control of HF cycling opens intriguing new therapeutic avenues in the management of common human hair growth disorders.

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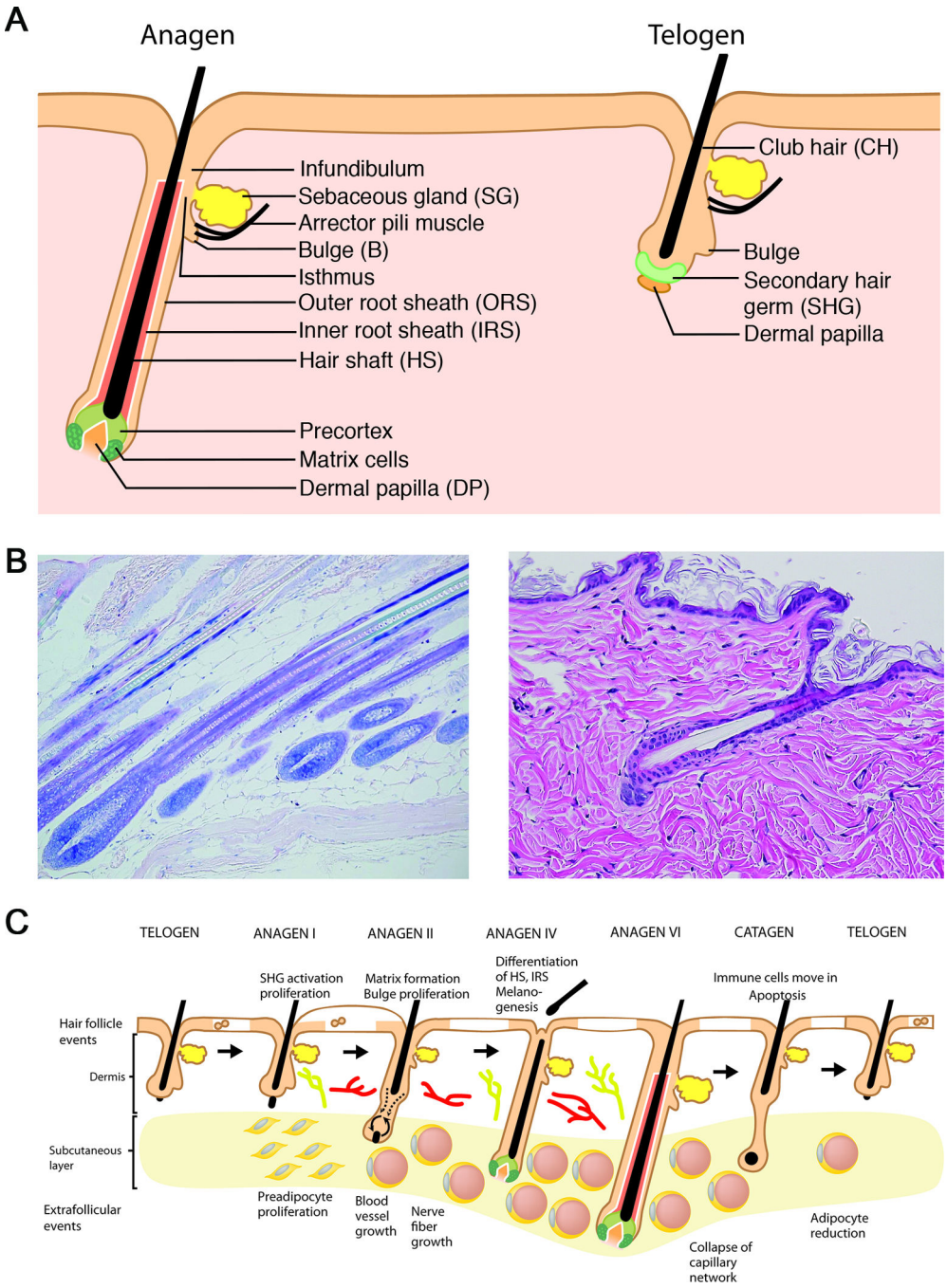

Fig. 1.

Hair cycle-associated dynamic changes in morphology of the skin and striking contrast in size and anatomy of anagen and telogen hair follicles. (A) Located deep in the subcutis, the terminal anagen follicle bulb contains a compartment of transiently amplifying keratinocytes referred to as the matrix, surrounding a spindle-shaped dermal papilla (DP). Above the matrix is the differentiation and melanin synthesis centre, the precortex. The hair shaft (HS) in the centre is surrounded by the inner (IRS) and outer (ORS) root sheaths. The bulge, isthmus and infundibulum, found both in anagen and telogen follicles, represent the

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permanent portion of the hair follicle containing multiple stem cell populations. The telogen follicle contains the secondary hair germ (SHG), which responds to the initial regeneration signals generated by the dermal papilla sitting directly below it. Club hair, a fully differentiated depigmented club-like hair shaft, is anchored to the hair follicle by specialized junction proteins. (B) Micrographs of longitudinal histological sections of mouse skin demonstrating stark morphological differences between anagen and telogen hair follicles. (C) In addition to obvious hair follicle remodelling associated with the hair follicle growth cycle, the entire skin undergoes dramatic morphological remodelling including interfollicular epidermal and adipocyte progenitor proliferation at the onset of anagen and nerve and blood vessel neogenesis in anagen leading to a dramatic increase in both dermal and subcutaneous fat volume (Chase et al., 1953; Donati et al., 2014; Driskell et al., 2014). Loss of the hair shaft during either telogen or anagen (shown), termed exogen, constitutes a separate, actively regulated event (Milner et al., 2002, Higgins et al., 2009b).

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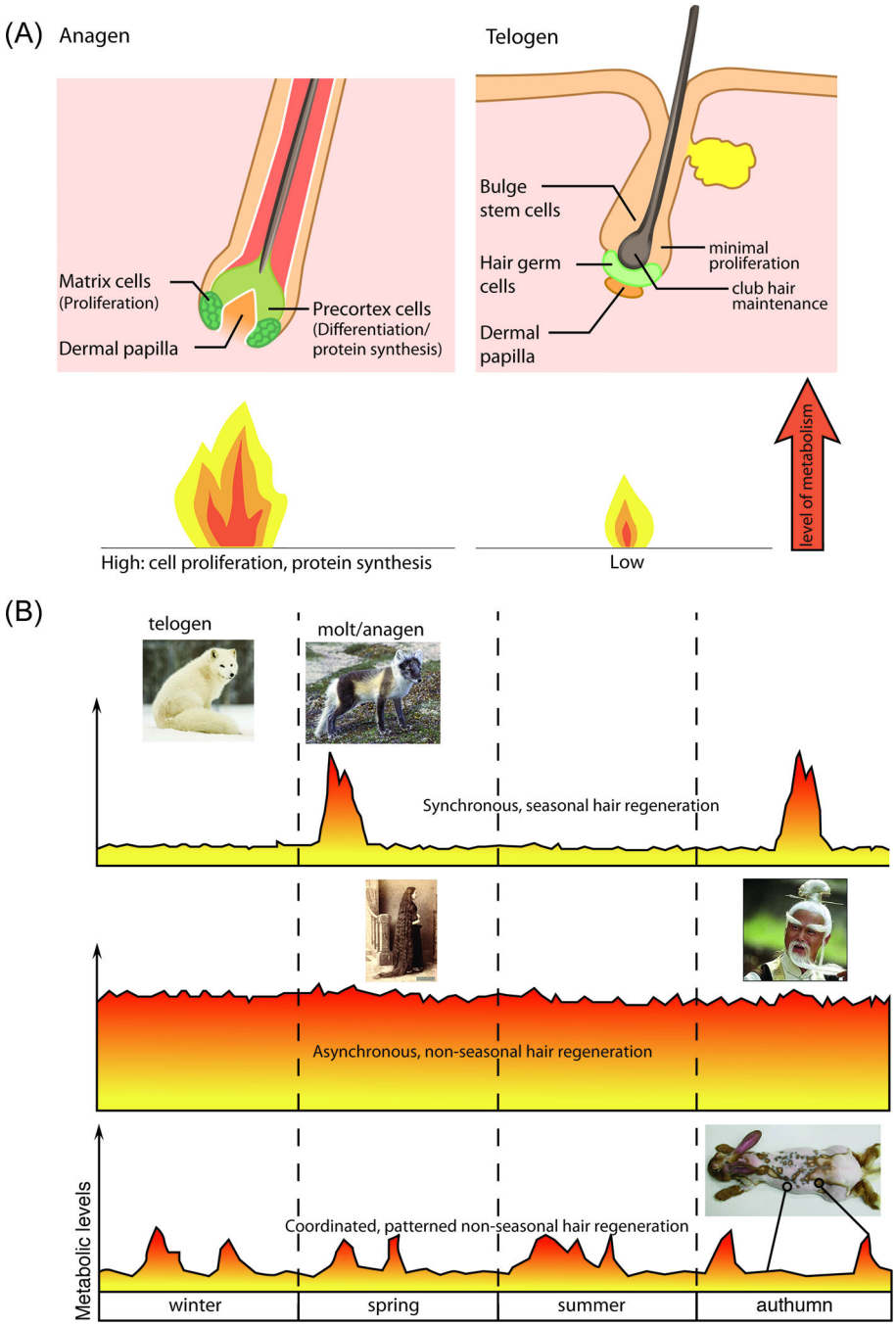

Fig. 2.

Hair coat regeneration and energy consumption models. (A) Sustaining the anagen follicle's intense proliferation and protein synthesis efforts requires significant ATP hydrolysis, whereas the telogen follicle's relative proliferation and translational quiescence is much less energetically expensive. (B) Seasonal regeneration where the hair follicle spends most of its time in telogen with intermittent bouts of anagen during late autumn to generate the winter coat and spring to generate the summer coat is energetically favourable compared with long and asynchronous anagen such as in the human scalp with its mosaic HF cycling pattern

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(Paus & Cotsarelis, 1999). Regeneration using hair regeneration domains where only small parts of the coat undergo anagen at any given time (Plikus & Chuong, 2008) is another efficient mode of coat regeneration.

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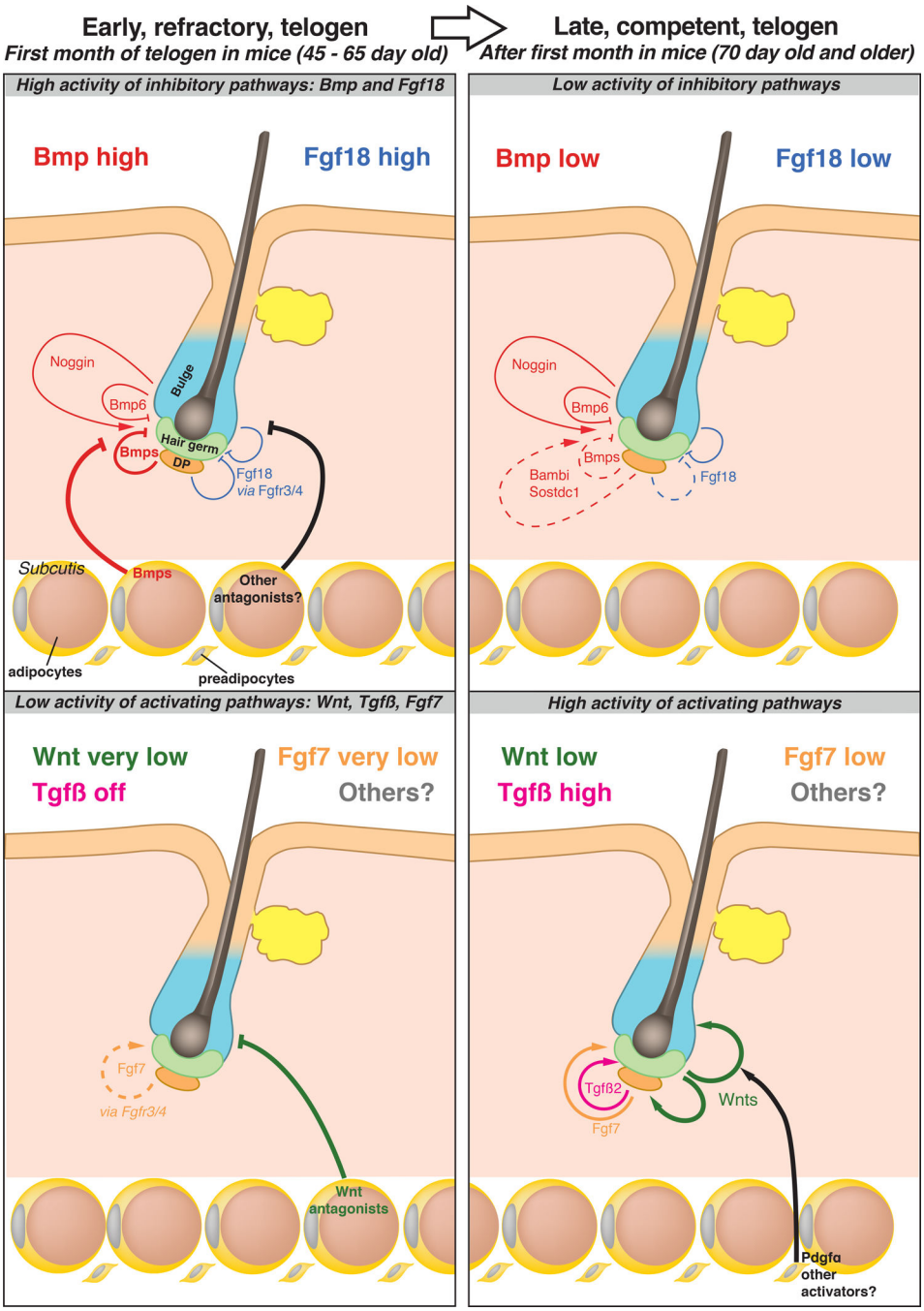

Fig. 3.

Competent and refractory telogen. In refractory telogen BMP signals emanating from the subcutis as well as high levels of Fgf18 maintain quiescence of secondary hair germ and bulge keratinocytes. In the competent telogen, macroenvironmental Bmp concentrations drop, Fgf18 levels and macroenvironmental WNT antagonist concentrations are low. Additionally Tgfβ signalling in the dermal papilla stimulates production of the Bmp inhibitors Sostdc1 and Bmbi. Fgf7 is secreted by dermal papilla fibroblasts as well. Together

Fgf7 and Bmp inhibition stimulate Wnt activity in the secondary hair germ thus tipping the scale towards regeneration. DP, dermal papilla.

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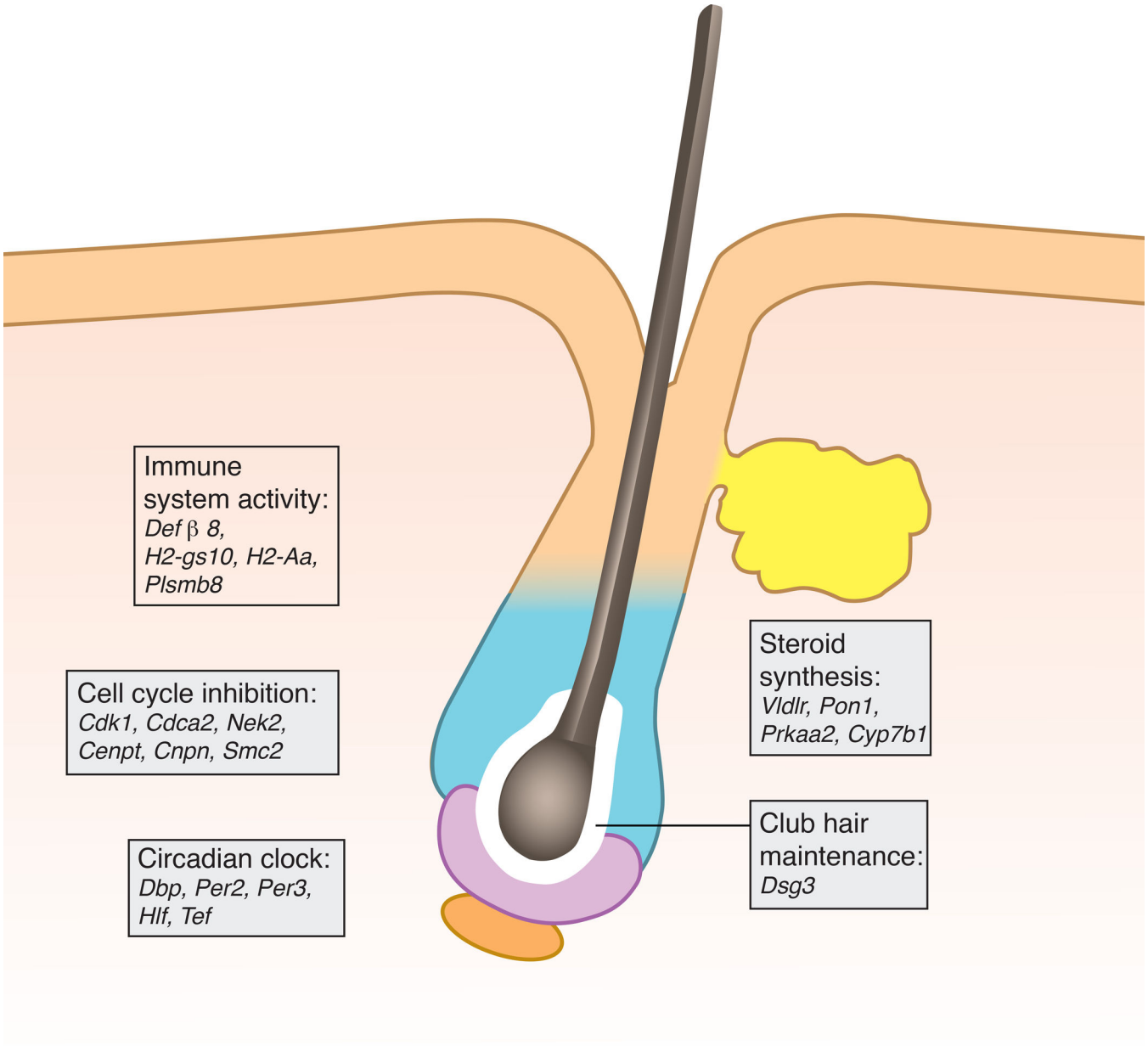

Fig. 4.

Telogen-specific biological activity. Recent whole-genome profiling studies aimed at defining gene expression signatures of various hair follicle growth cycle stages have identified numerous transcriptional programs with highest activity in telogen. Among these programs are innate immunity, the circadian clock and steroid synthesis. Additionally, cell-cycle inhibition and club hair maintenance are active processes (Geyfman et al., 2011).

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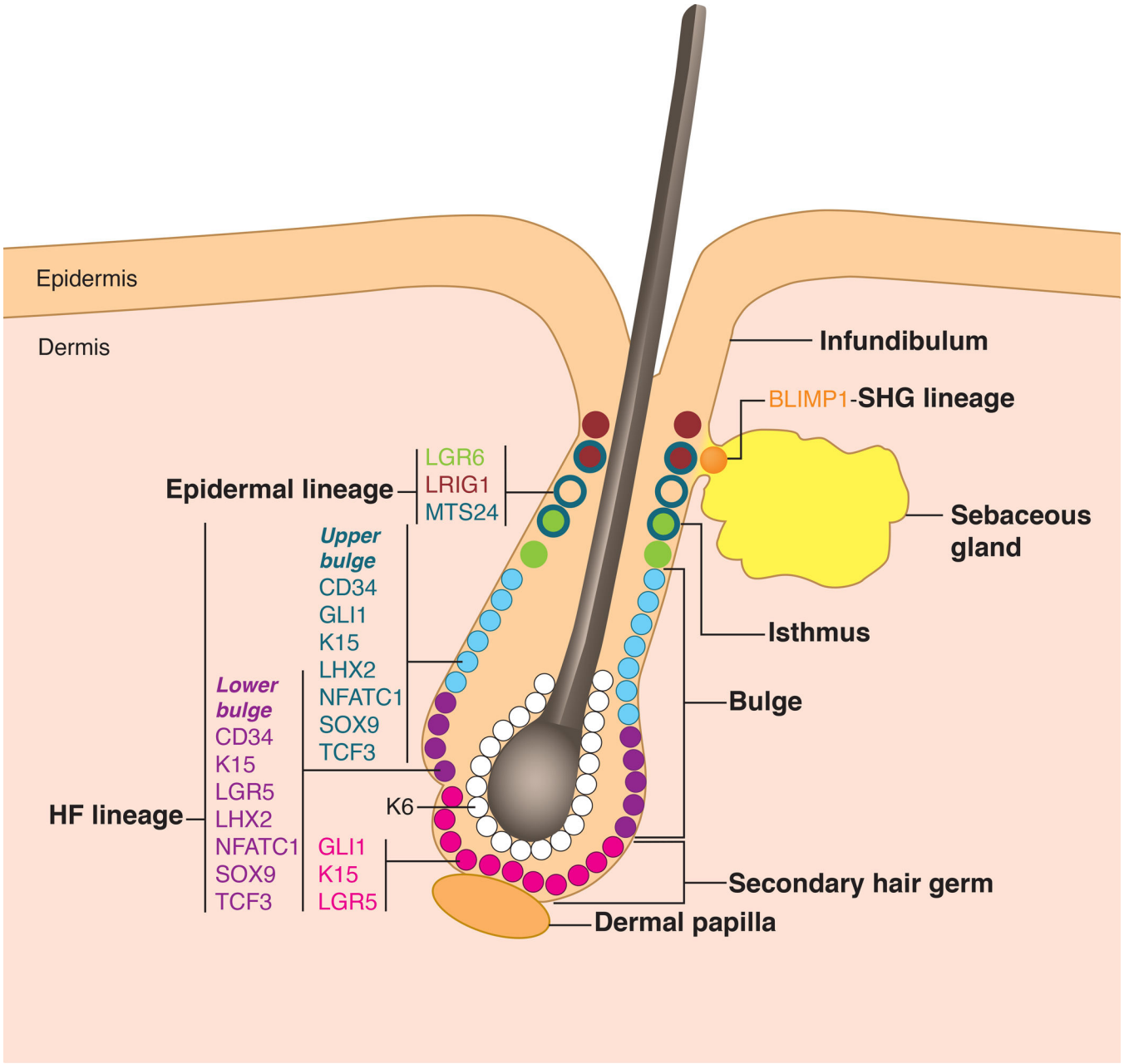

Fig. 5.

Hair follicle stem cells in murine telogen hair follicles. The telogen hair follicle contains multiple stem cell compartments identified by various cell surface markers and nuclear factors, located not only in the bulge but also in the secondary hair germ and in the upper follicle (isthmus and infundibulum). Stem cell populations above the bulge are responsible primarily for the renewal and repair of the upper follicle, sebaceous gland and interfollicular epidermis (Woo & Oro, 2011). SHG, secondary hair germ; HF, hair follicle.

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Table 1

Selected genes/proteins with highest or lowest expression in telogen

Highest expression	
Estrogen receptor alpha	(Oh & Smart, 1996; Chanda et al., 2000; Ohnemus et al.,2005)
Polycystic kidney disease 1 homologue	(Lowry et al., 2005)
Latent transforming growth factor beta binding protein	(Lowry et al., 2005)
Cadherin 13	(Lowry et al., 2005)
Synuclein, gamma	(Lowry et al., 2005)
Desmogein 3	(Koch et al., 1998)
p75neurotrophin receptor	(Adly, Assaf& Hussein, 2009)
Circadian clock regulated genes (Rev-erbs, Dbp, Hlf, Per 1, 2, 3, Crys 1,2)	(Lin et al., 2009)
β-Defensin 8	(Geyfman et al., 2011)
AE binding protein 1	(Geyfman et al., 2011)
Keratin 24	(Geyfman et al., 2011)
Leptin	(Yang et al., 2014)
Lowest expression	
Heparansulphate proteoglycan	(Couchman, 1993)
Basement membrane specific chondroitin sulfate proteoglycan	(Couchman, 1993)
Chondroitin sulfate proteoglycan	(Couchman, 1993)
Chondroitin-6-sulfate	(Gibson, Westgate &Craggs, 1991)
Collagen, type II and III	(Messenger et al., 1991)
Connexin alpha	(Risek, Klier&Gilula, 1992)
Prolactin receptor	(Foitzik et al., 2003)
Ras homolog family member B	(Adly, Assaf& Hussein, 2010)
Heat shock proteins 27, 60, 72	(Hashizume et al., 1997)
MiR-31	(Mardaryev et al., 2010)
Cyclin dependent kinase 1	(Geyfman et al., 2011)
Cell division cycle associated 2	(Geyfman et al., 2011)
NIMA-related kinase 2	(Geyfman et al., 2011)
Centromere protein F	(Geyfman et al., 2011)
Centromere protein N	(Geyfman et al., 2011)
Structural maintenance of chromosomes protein 2	(Geyfman et al., 2011)
Peptidylprolylisomerease (cyclophilin)-like 1	(Geyfman et al., 2011)
Serin/arginine-rich splicing factor 1	(Geyfman et al., 2011)
Exoribonuclease 1	(Geyfman et al., 2011)
Hepatocyte growth factor	(Lindner et al., 2000)