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Viewpoint

The human hair follicle, a bistable organ?

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Abstract: The hair cycle and its control remain today an object of debate. A number of factors, which can modulate this process, have been identified but its choreography remains elusive. For years, the hunt for the conductor has been on, but nobody ever caught him. Intuitively, the process being considered as cyclic, an automaton controlling this cycle should be looked for, by analogy with a clock. However, the putative hair follicle oscillator that would control hair cycle failed to be identified and characterized. In fact, we have revealed that human hair follicle has an autonomous behaviour and that the transitions from one phase to the next occur independently for each follicle, after time intervals given stochastically by a lognormal distribution characterized by a mean and a variance. From this analysis, one can conclude that instead of a cyclical behaviour with an intrinsic automaton, a bistable steady state controls human hair follicle behaviour, which under a stochastic way jumps from the dormant to the active steady state and vice versa.

Key words: bistable steady state – hair cycle – hair follicle – neogen

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Introduction

For decades, the hair cycle and its control have been an object of debate. Although several systems, like endometrium, cycle in the mammalian body, the hair follicle is clearly one of the only organs in mammals, together with the mammary gland for example (1), which 'cyclically' degenerates and regenerates from stem cells (2). The understanding of such a unique behaviour would certainly give clues to tissue homoeostasis and regeneration. Interestingly, a number of factors that can modulate, trigger, stimulate or repress this process have been identified (3). Furthermore, the stem cells have been identified, localized and even molecularly characterized (4–6), although recent data suggest an impressive diversity in hair follicle stem cell populations (7). Although the list of actors keeps steadily increasing, the choreography remains elusive. For years, the hunt for the chief of orchestra has been on, but nobody ever caught him. Intuitively, the process being considered as cyclic, an oscillator controlling this cycle should be looked for, by analogy with a clock (8). Even though circadian clock genes were recently identified as possible contributors to the regulation of hair follicle cycling (9), a famous paper evidenced the failure in finding the regulators of the hair cycle (3) and the question, Why is it so difficult to identify and characterize this oscillator? remains. My answer is simple: it simply does not exist.

Neogen – a new phase taking into consideration the morphogenesis process

In fact, by carrying out monthly phototrichograms during 14 years on a group of ten male, alopecic and non-alopecic volunteers (10), we studied the behaviour of 930 individual follicles and recorded about 9000 hair cycles. We then discovered that the duration of each phase of the so-called hair cycle was highly variable, from a few weeks to several years, generating an apparently chaotic behaviour shared by all follicles, whatever the alopecia grade. We had indeed revealed that each follicle had an autonomous stochastic behaviour, the probability of duration of each phase fitting with a lognormal equation (11,12). Of note, even though a deterministic model would predict the average durations of anagen, telogen and kenogen phases around which fluctuations are observed, it would not be capable of accounting for these fluctuations of phase durations (12). Considering this peculiar dynamics, characterized by an absence of synchronized oscillations, one should reconsider the entire process of degeneration–regeneration of the hair follicle. Classically, the follicle undergoes successive steps of fibre production (anagen), regression (catagen) and rest (telogen), which in humans last for an average of 3 years, 3 weeks and a few months, respectively. A side phase, termed 'exogen', has been described, independent from the rest of the hair cycle, during which the club fibre is actively released (13) without direct consequence on anagen initiation (14). After hair loss, a latency period is observed in 80% of hair cycles (10), between elimination of a hair in exogen (14) and the appearance of the replacement hair in anagen. The duration of this period, called kenogen (15), varies from 2 to 5 months on average (10). Interestingly enough, if catagen designates the shift from anagen to telogen, no name characterizes the shift from telogen to anagen, only anagen stages being given (16). Indeed, to date, anagen phase includes a very quick and active morphogenetic process followed by a long-lasting steady fibre production state. It is nevertheless striking that the hair follicle undergoes steady periods (telogen and anagen) that are interrupted by short and intensively active periods of remodelling, regression and regeneration. If regression phase is termed catagen, I propose to call the regeneration phase 'neogen' in order to highlight, in a symmetric way to catagen, the dynamic and short-lasting character of this crucial process. The entire process of resting, regeneration, fibre production and regression would thus include four main successive phases, namely telogen, neogen, anagen and catagen. Two of those are very short, neogen and catagen, and two are quite long, telogen and anagen.

The hair follicle, a bistable organ

Instead of a cycle, the human hair follicle behaviour would rather be described as a stochastic process operating on a bistability. The hair follicle would exist in two steady states, active and dormant. From time to time, under a stochastic way, the follicle would

jump from one state to another one. Thus, the follicle would not have a cyclic behaviour, but would undergo a succession of steady states (Fig. 1). Considering that many of the individual cell-fate decisions which control organism and organ development are binary in nature (life or death, proliferation or quiescence), that stochasticity of gene expression could lead to bimodal output (17) and bistable gene expression (18) and that binary choices are typically made by bistable switches (19,20), one might define the hair follicle – at a higher order – as a bistable organ.

Under this model, the bistable steady state is controlled by a combination of numerous factors with stochastic incremental variations, and the jump from one steady state to the other one would be triggered when given thresholds are reached. To capture this behaviour, an integrative multiparametric equation remains to be elaborated, which would include as variables all the factors so far identified in hair growth control, like growth factors, hormones, nuclear receptors, transcription factors and circadian molecular clock genes (21). Owing to the existence of thresholds, one prediction of this model is that both steady states would be endowed with refractory and competent phases, as recently shown for telogen (22–24). Indeed, refractory telogen is characterized by high bone morphogenetic proteins (BMPs) while competent telogen is characterized by low BMPs (22), a condition required for neogen to take place. Depending on the follicle considered, neogen would thus start after a variable time in the competent telogen phase (22) and last until full anagen development. Similarly, one could predict that anagen would be characterized by competent and refractory phases; the former involving IGF-1, HGF, GDNF and VEGF signalling, and the latter involving FGF5, TGFβ and BDNF in the onset of catagen (3). By analogy with the bistable calcium-/calmodulin-dependent protein kinase II switch that could control long-term memory upon stable persistent activation (25), a second prediction is that follicle could be blocked on either steady states that is an active state or a dormant state. In fact, several examples of unlimited hair growth have been recently reported in China, with anagen duration over 25 years (26). On the contrary, eyelashes are an example of follicles mainly blocked in dormant state, since 70–90% of them are in telogen (27). Chronic telogen efflu-vium and androgenetic alopecia would in fact translate subtle changes in the general multiparametric equation controlling the stochasticity of hair follicle behaviour (28) and more specifically the transition thresholds of the bistable steady states.

The dermal papilla, a key controller

Finally, if it is conceivable that catagen translates the jump from active to dormant state and stops when the follicle regression is completed, how can we explain that the neogen phase also stops, when it reaches the active steady state? Probably, this is partially controlled by the balance between extracellular matrix (ECM) and morphogens production by the dermal papilla (DP), linked to its dynamics. Indeed, DP is voluminous with the cells far apart in anagen, and flattened with the cells compacted in telogen (29). In anagen phase, the DP can be considered as a ball of ECM, surrounding specialized fibroblasts. The cross-talk of DP with neighbour matrix cells results in the maintenance of hair fibre production. An alteration in this cross-talk, induced by modifications of some variables of the multiparametric equation controlling the steady states, such as the transient FGF5 expression (30), would result in the onset of catagen and initiate the jump to the dormant steady state. During this phase, DP is left behind the regressing follicle, while its ECM starts degrading. When the DP ultimately reaches the telogen follicle, it is a simple cell aggregate, with no ECM. A new cross-talk can take place, and morphogenetic signals can be exchanged which, after having reached a given threshold, trigger the neogen phase, that is the jump from dormant to active steady state. Simultaneously, the synthesis of DP ECM is reinitiated. This ECM is rich in components like GAGs

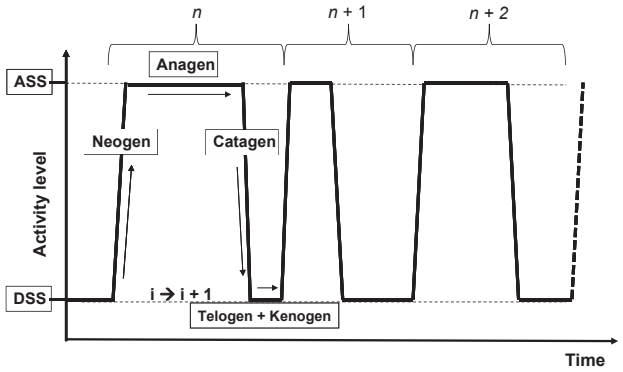

Figure 1. A new representation of the hair follicle behaviour, with an active steady state (ASS) of fibre production (anagen) and a dormant steady state (DSS) (telogen/kenogen), interspaced by short-lasting phases of neomorphogenesis (neogen) and regression (catagen). Three successive periods (n, $n + 1$, $n + 2$) are represented.

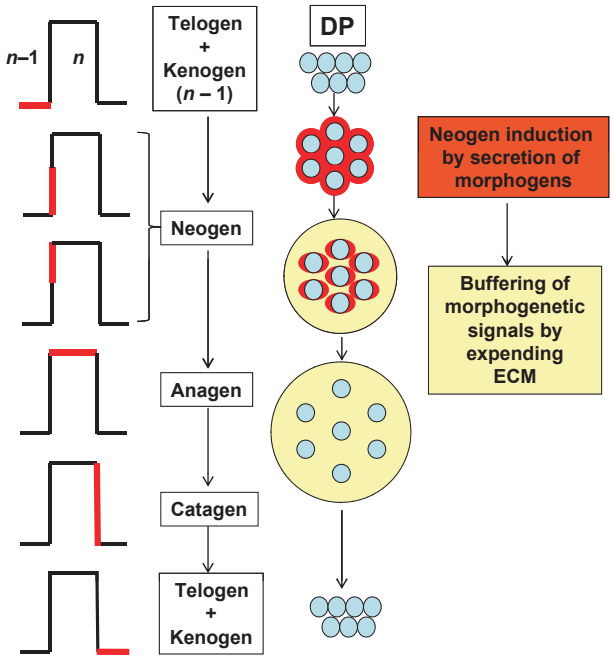

Figure 2. Dynamics of dermal papilla (DP) and consequences. On the left column are represented the successive phases of human hair follicle behaviour (see Fig 1). (n – 1) and (n) correspond to two successive periods. The red fragment denotes the phase corresponding to associated DP drawings (on the right column). In this model, the competition between morphogens and extracellular matrix (ECM) secretion is postulated to regulate the duration and extent of neogen phase. Morphogens secretion corresponds to the red area surrounding DP cells (depicted in blue) while DP ECM is depicted in pale yellow.

(31), which can progressively trap morphogenetic factors and buffer matrix cells activating factors (Fig. 2). A new steady state is established, the neogen phase is finished, and the anagen phase starts.

Conclusion

Although seasonal changes and periodicity in the growth and shedding of human hair have been reported (32,33), large-amplitude oscillations resulting from follicular synchronization are not observed in human scalp, likely because each follicle behaves independently of each other and hair regeneration/degeneration only depends on intrinsic activation/inhibition mechanisms. Of note, desynchronized hair follicle behaviour looks specific for human being, as a different type of dynamic behaviour with periodic moulting is observed in a number of mammalian species (34–37). We have previously demonstrated that moultings would correspond to oscillations of follicular cycles resulting from synchronization by periodic external and/or hormonal signal(s) (34–37), which would trigger the transition from anagen to telogen phase (12). Moreover, regenerative wave patterns in adult mouse hair follicle populations have been linked to macroenvironmental regulation of stem cell activity instead of – or superimposed to – hair follicle intrinsic microenvironment (22,23).

To summarize, the human hair follicle appears as a prototypic systems biology model (38) and as such, the first example of an organ under the control of bistable steady state, which under a stochastic way jumps from dormant to active state and vice versa. This implies that minute variations of some key variables might trigger these jumps to neomorphogenesis or degeneration. If this concept holds true, it might be of value to consider tissue homoeostasis as the result of a bistable steady state and to identify key variables involved in the control of normal and pathological epithelial–mesenchymal interactions, the hair follicle being a true paradigm of this type of interactions.

Conflict of interests

Bruno A. Bernard is an employee of L'Oréal Company.

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