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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