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Regenerative metamorphosis in hairs and feathers: follicle as a programmable biological printer

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Abstract

Present-day hairs and feathers are marvels of biological engineering perfected over 200 million years of convergent evolution. Prominently, both follicle types coevolved regenerative cycling, wherein active filament making (anagen) is intermitted by a phase of relative quiescence (telogen). Such regenerative cycling enables follicles to “reload” their morphogenetic program and make qualitatively different filaments in the consecutive cycles. Indeed, many species of mammals and birds undergo regenerative metamorphosis, prominently changing their integument between juvenile and adult forms. This phenomenon is inconspicuous in mice, which led to the conventional perception that hair type is hardwired during follicle morphogenesis and cannot switch. A series of recent works by Chi and Morgan change this perception, and show that many mouse follicles naturally switch hair morphologies, for instance from “wavy” zigzag to straight awl, in the second growth cycle. A series of observations and genetic experiments show that back and forth hair type switching depends on the number of cells in the follicle's dermal papilla, with the critical threshold being around 40-50 cells. Pigmentation is another parameter that hair and feather follicles can reload between cycles, and even midway through anagen. Recent works show that hair and feather pigmentation “printing” programs coevolved to rely on pulsed expression of Agouti, a melanocortin receptor-1 antagonist, in the follicular mesenchyme. Here, we discuss broader implications of hair and feather regenerative plasticity.

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Hairs and feathers are some of the most distinguishing characteristics of mammals and birds, respectively. The origin of these skin mini-organs is a fascinating, yet poorly understood topic in the Evolutionary Biology (1). The first definitive fossil evidence of hairs dates back to a mid-Jurassic period to *Castorocauda lutrasimilis*, a semiaquatic "beaver-tailed otter-like" mammaliaform from the now-extinct order *Docodonta* (2). Because *C. lutrasimilis* already featured prominent pelage, with long guard and short downy hairs, and since *Docodonta* diverged from the ancestor of all present-day mammals some 205 million years ago (3), hair follicles have already existed in late Triassic. Timing of feather evolution remains a fast moving target, as new paleontological evidence continues to emerge. Complex, bird-like feathers definitively existed in various *Coelurosauria* – the major clade of theropod dinosaurs that dominated during the Jurassic and which, among many others, included the formidable *Tyrannosaurus rex*. However, filamentous appendages were recently discovered in the fossil records of non-theropod dinosaurs, placing feather evolution alongside that of hair in the late Triassic, (this assumes that all filamentous skin appendages in dinosaurs have monophyletic origin) (4).

While hair and feather follicles clearly have distinct morphologies, many similarities coevolved. Perhaps, the most notable similarity relates to their regeneration. Both follicle types regenerate in cycles, wherein they repetitively transition between phases of active growth, involution, and relative quiescence. The period of active growth in hair follicles is called anagen, a term also used in feather studies (5). During anagen, hair and feather follicles work essentially as biological 3D printers – spatially and temporally orchestrated cellular activities occur at the base on the follicle, in the matrix and precortex of hairs, and in the collar and ramogenic zones of feathers (6). Eventually, a fully formed, keratinized filamentous structure emerges from the follicle's "printing center". The characteristics of bioprinted filaments in both follicle types are highly regulated and include length, overall shape, microstructure, and pigmentation.

Following up on the analogy with printers, the same follicle can reload morphogenetic programs between consecutive growth cycles, regenerating filaments with several distinct morphologies. Indeed, hair follicles in many mammalian species switch type, transitioning from often lightly pigmented and fuzzy juvenile hairs to darker and thicker adult morphologies. Examples of such *regenerative metamorphosis* exist across all mammals, prominently in Harp seal and Cougar (Order of Carnivora), Malayan tapir (Odd-toed ungulate), Wild boar (Even-toed ungulate), and Emperor tamarin (Primate) (Figure 1). For instance, Harp seals are born with long, fuzzy and distinctly white pelage that lasts for about two weeks. Following several molt cycles, adult Harp seals acquire a short, iridescent coat with complex pigmentation (Figure 1A). Pelage of newborn Malayan tapirs is brown-black with many distinct white stripes; however, at around seven months of age it changes to a shorter adult coat, featuring three black-white-black domains and no stripes (Figure 1C). Pelage in the House mouse does not noticeably change with age, which led to the conventional perception that hair type is hardwired during follicle morphogenesis and cannot switch. However, several recent works from Morgan's laboratory (7-10), including new work in the Experimental Dermatology (7), change this perception.

Dorsal mouse pelage features several distinct hair morphologies: guard, awl, auchene, and zigzag. Although guard hairs appear to remain guard, other hair follicles can switch between awl, auchene, and zigzag. The "history" of hair types can be studied by examining old hair filaments that follicles "collect" from consecutive growth cycles. By studying this hair history, Chi *et al.* (8) unambiguously demonstrated that in mice the majority of auchene hairs switch to awl, while up to 20% of zigzags switch to either awl or auchene between the first and second growth cycles. In their most recent work, Chi *et al.* (7) employed time-dependent hair dyeing to show that plastic zigzag hairs that switch type develop earlier compared to non-plastic zigzags. After the second cycle, hair type largely stabilizes, albeit switching can still occur, either naturally, or upon genetic manipulations (8). These findings underscore that some level of regenerative metamorphosis of hair follicles between juveniles and adults is common among mammals. In fact, prominent hair type switching also occurs in humans upon puberty in facial, axial, and pubic regions.

Regenerative metamorphosis of feathers is widespread among birds (Figure 2). Famously, Hans Christian Andersen used this phenomenon as a metaphor for personal transformation in his 1843 "The Ugly Duckling". Indian peafowl is another illustrative example, whose chicks have brown feathers (Figure 2A) that change into opulently iridescent blue-green plumage in adult males (peacocks; Figure 2B). Peacock saddle feathers also vividly illustrate that follicles can "reload" their morphogenetic programs not only between anagens, but also midway during anagen. Indeed, each peacock "eye"-type feather has several drastically different morphologies along its length (and thus along the temporal axis of anagen). It starts with a distinct "eye" pattern, followed by a fan of loosely arranged barbs, and ends with barb-free calamus, the hollow shaft.

What mechanism controls the follicular "print" program and how can it reload between cycles? Classic tissue recombination studies suggested that many hair follicle characteristics are regulated by the dermal papilla, its principle mesenchymal niche (11). Recent works ascertain the leading role of dermal papilla and yield further insights (7-10, 12). A study by Chi *et al.* (8) showed that the morphology of some pelage hairs is specified by the number of cells in their dermal papillae, so that follicles making zigzags have fewer dermal papilla cells (∼23 cells in the first anagen) than those making awls (∼45 cells). In their new study, Chi *et al.* (7) show that earlier-born plastic zigzag follicles have more dermal papilla cells (∼26 cells) than later-born non-plastic zigzags (21 cells), and this difference appears to predispose earlier-born zigzags to hair type switching. Furthermore, genetically induced depletion of dermal papilla cells can switch hair types in reverse order –follicles that originally made awls or auchenes start making diminutive zigzags (8). Taken together, back and forth zigzag-to-awl/auchene hair type switching presents itself as a threshold phenomenon – hairs switch type at around 40-50 dermal papilla cells (8). It remains to be understood how changes in the dermal papilla cell number convert to qualitative differences in the hair "printing" program. Schlake (13) implicated insulin-like growth factor binding protein 5 (Igfbp5) in the formation of zigzag hairs – periodic *Igfbp5* expression is observed in hair medulla at the sites of zigzag bending, and Igfbp5 overexpression leads to dramatically curved hairs, including guards and awls. The connection between dermal

papilla size and the switch in Igfbp5-dependent zigzag “printing” program remains to be elucidated.

Similar to hair, many filament “printing” control functions in feather follicle seem to be delegated to its mesenchyme, consisting of dermal papilla and the overlaying pulp. Simplistically, feather bioprinting starts at its base from a ring of epithelial stem cells (14). Stem cell progeny move upward, forming an epithelial cylinder. During feather differentiation, additional cellular activities reshape the initial cylinder into a bilaterally symmetric (or asymmetric) sheet, with the shaft (*aka* rachis) in the middle and two vanes, one on each side. Classic studies (15) showed that the dermal papilla holds information about the feather rachis position – surgical rotation of dermal papilla, such as by 90 degrees, results in the corresponding axial rotation of the rachis in the newly regenerated feather. Recent study by Lin *et al.* (16) also shows how feathers “print” their pigmentation patterns. Similar to epithelial stem cells, melanocyte progenitors form a ring at the follicle's base, and send their progenies upward along the perimeter of the feather cylinder to color keratinocytes. Differentially pigmented feathers appear to arise via several complimentary mechanisms: deletion of melanocyte progenitors from their ring-shaped niche, enforced progenitor quiescence, or suppression of progeny differentiation. The latter mechanism, in particular, appears to depend on the differential expression of Agouti signaling protein in the pulp –Agouti from the pulp suppresses melanocyte differentiation in the neighboring segment of the feather cylinder, leading to its whitening. Hypothetically, an all-black follicle can print a white “eye” pattern by temporarily modulating the size of the Agouti domain in the pulp – over time, the pulp Agouti domain would appear, enlarge, then shrink and disappear. Interestingly, Agouti-dependent pigmentation “printing” also coevolved in hairs. In mouse pelage, dermal papillae transiently express Agouti, a melanocortin receptor-1 antagonist, at the beginning of anagen. This temporarily switches melanogenesis program from eumelanin to pheomelanin, leading to a sharp yellow band at one end of otherwise black hairs. Recent dermal papilla-specific genetic studies place this pigmentation switch mechanism downstream of canonical WNT signaling, whereas *Agouti* is sensitively inhibited by WNT both directly, at the transcription level, and indirectly through upregulation of *Corin*, a negative regulator of Agouti activity (10).

In conclusion, both hairs and feathers evolved several convergent features of the regenerative cycle. First, the filament “printing” program is not always hardwired within the follicle, but can switch between two or more alternative morphologies between cycles. This behavior results in the regenerative metamorphosis of pelage and plumage in mammals and birds respectively. Secondly, both hairs and feathers can alter their printing programs along the temporal axis of anagen, leading to spatially complex filaments, both in terms of shape and coloration. Further studies on related mechanisms can yield new insights into the long-range biological clocks, an inherently challenging property in the biological systems (17). Hair and feather follicles evidently can time multiple filament printing parameters with a clock-like precision. Deciphering their clock mechanisms is likely to have a profound effect on the larger field of chronobiology.

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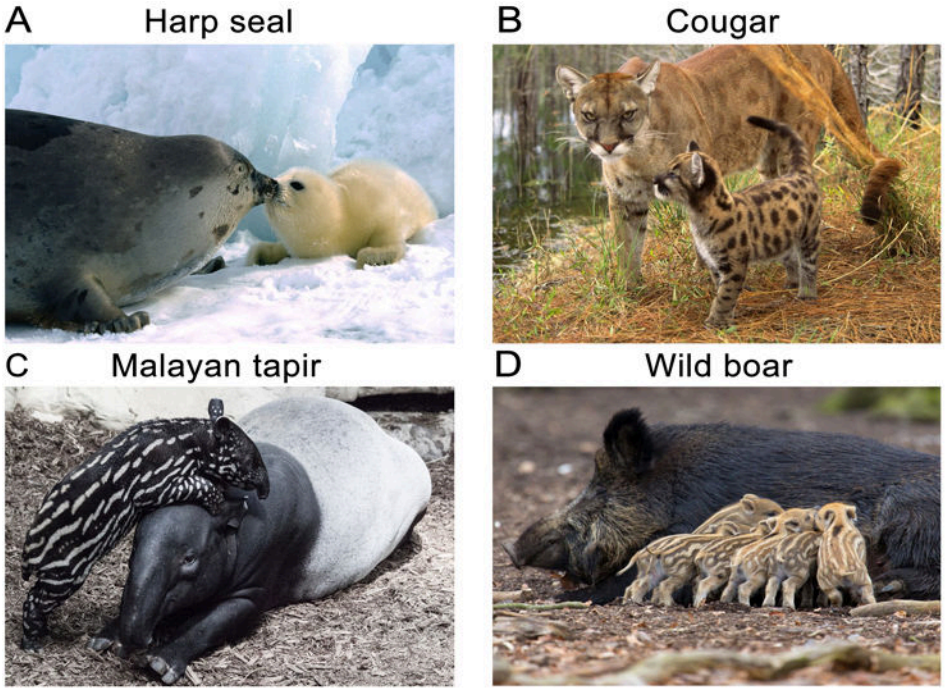

Figure 1. Examples of regenerative metamorphosis of mammalian pelage

(A) Harp seal, **(B)** Cougar, **(C)** Malayan tapir, **(D)** Wild boar. (Photographs credit: A, B, D - Creative Commons; C: Tim Cooper).

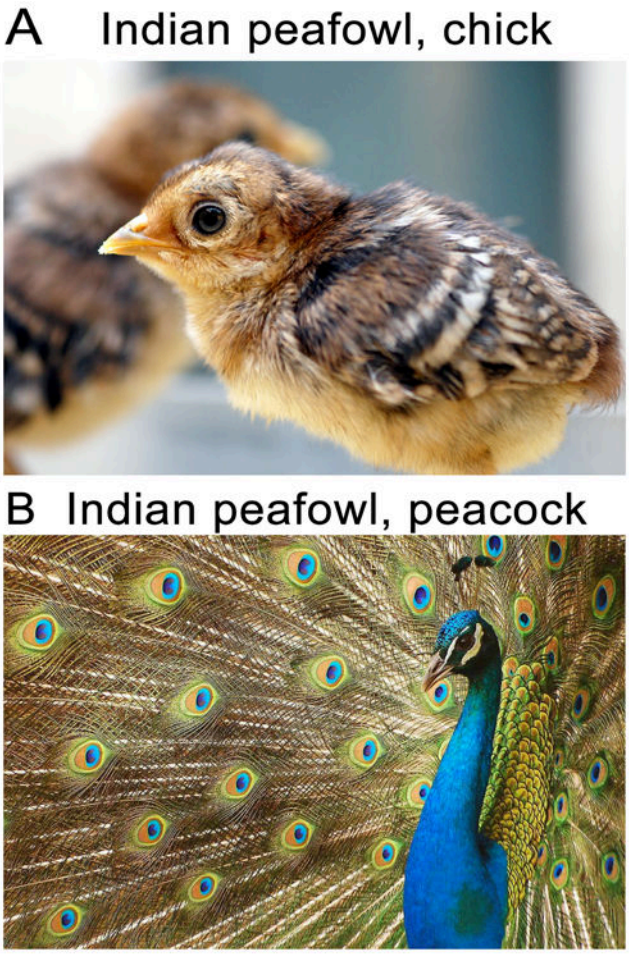

Figure 2. Regenerative metamorphosis in Indian peafowl

(A) Chicks have brown feathers; **(B)** peacocks have iridescent blue-green plumage with prominent “eye”-type tail feathers. (Photographs credit: Creative Commons).