Published in final edited form as:

Curr Opin Genet Dev. 2016 October ; 40: 138–143. doi:10.1016/j.gde.2016.07.001.

Quorum sensing and other collective regenerative behavior in organ populations

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Abstract

Stem cell and microenvironment molecular interactions have been studied in detail but regenerative behavior at the organ population level has remained unexplored. Organ renewal can occur continuously or in cyclic episodes. Progenitors may be distributed as one entity or compartmentalized into multiple units. Multiple units offer advantages as each unit can be regulated differently in different body regions or physiological stages, adapting animals to their niche with flexible functional forms. Using the hair paradigm, we show how periodic patterning can convert one morphogenetic field into many hair germs, how follicles can be renewed with different cycle times and phenotypes in a region-specific manner, and how new properties, such as regenerative waves and quorum sensing, emerge to coordinate collective regenerative behavior.

In adult animals, organ cells need to be replaced in growth and homeostasis or replenished following injuries and regeneration [1]. Depending on the topological configuration of stem cells / progenitors in different organs, renewal can occur continuously or in cyclic episodes, and cells can come from resident stem cells, or through de-differentiation and reprogramming [2]. Resident progenitor cells such as those seen in hematopoiesis, villi, hairs, or feathers can be present as one entity or compartmentalized into multiple units [3]. A unique feature of the hair organ is that it is made of a population of small organ units, and stem cells are compartmentalized into each follicle. The advantage of this configuration is that groups of units can now be regulated differently in different body regions [3] or at different physiological stages, adapting animals to different conditions with flexible functional forms [4]. Here we briefly review new insights revealed by studying these newly emerged collective behaviors, with emphasis on conceptual advances.

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From one to many: Compartmenting one morphogenetic field into many units

During embryonic skin development, periodic patterning occurs and converts the morphogenetic field of the skin into many feather or hair germs (Fig. 1) [5]. This is a process that involves Turing activator / inhibitor interactions, and cell migration [6,7]. The different ways to achieve periodic patterns have been reviewed [8,9].

In wound regeneration, it has been difficult to re-initiate the periodic patterning, and thus many patients who receive treatment for severe burns will have healed skin which has no skin appendages. It was not until the discovery of wound induced follicle neogenesis (WIHN), that we learned this periodic patterning competent morphogenetic field could be re-established in adult mouse skin [10]. Later, the spiny mouse was found to have even more robust WIHN activity [11]. How to effectively re-activate this periodic patterning process in skin progenitors remains a challenge to tissue engineering and the effort to rebuild a fully functional skin for patients [12].

In average, there can be more than 30,000 hairs or feathers on one individual. Before we delve into the newly emerged properties of the organ population behavior, we should briefly review the characteristic of one single follicle. Each hair follicle begins to grow during embryogenesis through a series of epithelial – mesenchymal interactions leading to the formation of a follicle, with epithelial bulge stem cells and dermal papilla functioning as signaling centers [13–16]. Hair follicles are then renewed through episodic hair cycling. The hair cycle consists of phases of growth (anagen), degeneration (catagen), rest (telogen), and hair loss (exogen) [16,17] (Fig. 1). Transition between the phases are regulated by the activation and quiescence of hair stem cells, which will respond to the ratio of activator to inhibitor input [18]. Theoretically, follicles could be renewed again and again throughout the life of the animal, but there are many modulators that will affect this outcome.

Multiplicity allows variability

If skin progenitors were not compartmentalized, hair follicles might be renewed continuously like our epidermis or molted synchronously and periodically like snake skin. With hair stem cells residing in multiple follicles, they can now be regulated independently or coordinately. This allows units to be different in time and space, which can be appreciated on several hierarchical levels. At the level of a single follicle, the hair cycle time can vary, and the appendage phenotypes can also vary (this is more obvious in feathers). At the level of an organism, hairs can cycle fast or slow in young and aged skin (Fig. 1) [19–21], and different body regions can display different types of hairs (e.g., scalp, beard, facial hairs) [1]. At the animal population level, there are sexually dimorphic feathers in males and females. There is even social behavior-dependent formation of the facial flanges on Orangutans.

Skin from different body regions grow hair / feathers with different characteristic lengths and thicknesses. Hair follicles can also be distributed with different density in different areas. These characteristics can change at different life stages enabling individuals to adapt to their changing physiological needs. Newborn chicks grow radially symmetric downy

feathers all over the body to keep them warm. Adults chickens grow contour feathers on the trunk, remiges in wing to aid in flight and rectrices on the tail to attract a mate [22]. Humans also show region-specific differences in the number, size and thickness of hairs. For example, less dense and thinner hairs grow on our arms than on our scalp. The characteristics of these hair follicles also can change at different physiological stages (Fig. 1).

Circulating hormones regulate the hair cycle in a regional-specific manner. Androgens induce terminal hairs on the face (beards, eyebrows, nose, ears) yet can lead to alopecia on the scalp with advancing age. During pregnancy in mice, hairs accumulate in telogen and cannot initiate a new hair cycle until after lactation [23]. While the hormone responsible for this activity has not been identified, the murine dermal papillae expresses the estrogen receptor during telogen and exogenous estrogen can block hair cycle renewal [24,25], suggesting its involvement [26]. Since hormones circulate, there must be intrinsic differences in hormone metabolism or receptor mediated signaling that regulate these region-specific responses.

Multiple units, can be regulated separately via different interfaces to produce high modulability. Some of the regulatory factors may be intrinsic (Wnts) to the hair follicles, others can come from extrinsic sources, such as the adipose tissue (BMPS, PDGFs) and circulating hormones [27]. Each follicle then integrates local levels of the activators, inhibitors hormones and other influencing factors to decide whether or not it is time to activate stem cells to start a new cycle [26]

From many to one: Collective decision making through quorum sensing

Though stem cells are compartmentalized, they can communicate with one another to regulate when to initiate a new hair cycle. A traveling pigmentation wave marking early anagen phase of the hair cycle was seen to traverse the back of mutant nude mice suggesting mouse hair follicles cycle in waves (Fig. 2) [28]. In normal mice, this was found in part to be regulated by extrinsic BMP signaling in the underlying adipose tissue which inhibits hair cycle initiation [23] (Fig. 2, middle panel). PDGFs which stimulate hair growth were also found within the adipose tissue [29]. Rabbit hair follicles propagate very fast in fractal-like waves. They form compound follicles whose components activate simultaneously [30]. Rabbit skin is approximately 30 times larger than mouse skin but they demonstrate similar principles regulate the initiation and spread of the traveling wave. In contrast to mouse and rabbit hair follicles, adult human hair follicles cycle independently of one another [31] (Fig. 2, left panel). In aging scalp skin, the percent of time spent in anagen is decreased producing vellus hairs. The duration of anagen is further decreased in cases of alopecia (Fig. 2, left panel) due to decreasing levels of extra-follicular Wnt and BMP inhibitors (Dkk1, Sfrp4 and Follistatin) [20].

Hair follicles can also be induced to regenerate in response to injury. Interestingly, using the extra-follicular environment as the media, one can trigger the regenerative response in the whole populations. By plucking 200 hair follicles at different densities and in different configurations we found that below a threshold, neither plucked nor unplucked hairs were

replaced. Above the threshold, all plucked and unplucked hair follicles within the tested region responded as a single unit to synchronously renew their hairs. Optimal configurations can induce the replacement of 5 times the number that were originally plucked. These data suggest that the regenerative response to injury is based upon a collective decision making process based on quorum sensing [32] (Fig. 2, right panel). Further testing demonstrated that quorum sensing in the skin was mediated by an immune cascade in which plucking injury induced the release of CCL2 which then recruited TNF- α -secreting macrophages to hone toward plucked hair follicles and their unplucked neighbors. TNF- α then stimulates the NF- κ B pathway to increase Wnt signaling activating stem cells to induce hair regeneration [32] (Fig. 2, right panel). In this way hair follicle populations can ignore a subthreshold injury and give a full-scale cooperative response when the threshold is surpassed. This finding places the immune system as another source of extrinsic signaling that contributes to hair cycle regulation which helps to maintain stem cell homeostasis for the hair follicle population [26,32].

Collective decision making in regeneration beyond hair follicles

The above examples demonstrate that multiple systems within the body (ie., endocrine glands, adipose tissues, etc) influence the growth and structural reorganization of hair follicles by multiple means (growth factors, circulating hormone levels, immune response). Do other organs also interact to coordinate regeneration and growth control in the skin or in other model systems? Here we review a few examples of this phenomenon.

In mice, sensory neurons surrounding the follicle bulge release Shh to the upper bulge of telogen follicles while lower follicle bulge cells express K15. In response to skin injury, progenitor cell populations in both the upper and lower bulge contribute to early wound healing of interfollicular skin but the upper bulge progenitor cell population became permanent interfollicular epidermal progenitor cells while the K15+ lower bulge stem cells returned to the bulge after their wound healing response [33]. This study clearly demonstrates that the release of Shh from sensory neurons induced plasticity in hair follicle stem cells allowing them to assume a new regenerative program.

Another example of tissue interactions that regulate regeneration exists between the nail and digit tip. Unlike hair follicles which grow episodically through the hair cycle, nails grow continuously. Yet a quiescent stem cell population was identified which could form the nail and peri-nail epidermis [34]. Because of their proximity, nail stem cells were found to be involved in regulating the regeneration of the mammalian digit tip. Wnt signaling for nail regeneration also promotes innervation leading to mesenchymal blastema formation required for digit tip regeneration [35] while BMP signaling favors nail formation [34]. These studies demonstrate that nail stem cells can be recruited to regenerate a digit when the digit stem cells are excised. This function may to a large part be mediated through Wnt signaling.

In axolotls, amputated limbs regenerate and closely resemble the original amputated structures. Tail amputation in axolotls with CRISPR-Cas9 mediated deletion of Sox2 failed to regenerate properly because neural stem cells lacking Sox2 showed inhibited proliferation causing spinal-cord-specific defects during unsuccessful regeneration [36]. Another study

demonstrated the importance of Meis expressed from connective tissue rather than myogenic cells in coordinating appropriate proximal-distal limb regeneration following amputation [37]. These studies show that Sox2 and Meis regulate proper limb regeneration in the axolotl.

In wound regeneration, different tissues comprising the wounded area must coordinate with each other so the regenerated tissue architecture will be proportioned properly. This appears to function through a process of cooperative communication involving different interacting and finely tuned molecular signaling pathways.

Perspectives

Here we provide a perspective on how a multi-stem-cell unit configuration helps feathers and hairs function more successfully. In fact, this new stem cell configuration helped animals evolve feathers and hairs as cardinal integument features for birds and mammals, respectively. The renewability of feathers and the possibility to grow different feather phenotypes in different body regions greatly enhanced the evolutionary success of feathered dinosaurs [38]. In birds today, downy feathers help to keep chicks warm, while adult flight feathers help birds fly and tail feathers are used for display. Similarly, in mammals, hair coat can change in winter vs summer to provide crypsis through protective coloring (ie., snow hare). Seasonal changes, regional-specificity and adaptation to different phases are all made possible based on the multiplicity of the hair / feather organ population.

The integument is the first line defense toward injuries. To deal with the daily wear of appendages or wounding, the multi-unit configuration also provides an effective answer. With compartmentalization of hair follicles, animals can “cut their losses”, and the remaining follicles can serve as the repertoire to replenish cells for the damaged region. Furthermore, we observed propagative regenerative waves and quorum sensing as new behaviors only observed in an organ population. What is the functional significance of organ level quorum sensing? We think it is involved in establishing the threshold of tissue homeostasis. In the skin quorum sensing involves coupling between the immune system and regeneration. Co-option of immune signaling helps to set up the threshold for an overall tissue response, or collective cell behavior in response to an injury. For the hair plucking induced collective response, the CCL2-macrophage pathway was used, but other signaling may be used in other situations. We speculate similar behavior also exist in other organs. We also predict, when the balance of this homeostasis-setting threshold mechanism is tilted, auto-immune or defense weakening may occur, leading to the pathogenesis of diseases.

Acknowledgments

C.-M.C. and RBW are supported by NIH grants AR47364. C.-M.C. is supported by NIH grant AR60306.

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Figure 1.

Periodic patterning converts one morphogenetic field into multiple hair germs. Each hair germ undergoes regenerative cycling. This gives the follicle an opportunity to generate variability by generating hairs with different growth periods or different morphological phenotypes in different skin regions (Phenotype modulation). The phenotype can change in response to key biological events (Life stage modulation) to produce diverse hair forms. This effects the response to intrinsic and extrinsic factors (growth factors, hormones, etc) on aging facial skin (right panel). On the right is Darumo, a Zen master painted by 16th century Japanese artist, Sh kei, demonstrating regional differences in the head: the growth of eyebrow, ear and nose hairs is enhanced while that of the scalp hair is greatly reduced.

Figure 2.

The hair cycle in different regions and at different life stages and in different organisms can be controlled at the level of individual follicles (left panel) or coupled to produce coordinated regenerative hair waves regulated by communication between hair follicles (middle panel) or their environments. Upon injury, they can be activated via quorum sensing, coupled by an immune mechanism (CCL2 and macrophages), where all follicles make an all or none decision to simultaneously re-enter the hair cycle.