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Research Highlights

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Hypoxia and metabolic adaptation drive self-organization in organoid morphogenesis and tissue regeneration

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The ultimate goal of regenerative medicine is to restore both the structure and function of damaged tissue. In adult skin, wound healing most often results in repair rather than regeneration. While the re-epithelialised tissue restores the basic epidermal and dermal layers, it lacks functional architecture like hairs and glands, suggesting that cells in the wound bed fail to enter a morphogenesis competent state to regenerate. This raises a fundamental question: what enables a healing tissue to transition from a reparative program to a regenerative one?

One way to approach this problem is to view regeneration as a sequence of morphogenetic states and consider that complex tissue architecture is achieved through multiple rounds of morphological transitions [1]. In embryonic development, cells undergo morphogenesis to achieve tissue patterns, and in the adult these patterns are re-established in some, but not all, conditions after wounding and in some organoids [2]. It is critical to learn what drives the successful tissue patterning process.

In a series of papers, Lei *et al*. have used newborn and adult mouse skin organoids to decipher what drives self-organization in the newborn skin organoids. At each stage, cells assemble into relatively stable configurations: aggregates, spheroids, coalescences of spheroids, and formation of a planar sheet ready for transplantation and hair regeneration [3]. In each step, cell collectives must acquire competence to drive the progression of self organization. The studies show that dissociated epidermal and dermal cells in the organoid form spheroids as intermediate structures as the first phase of morphogenesis.

These units establish epithelial–mesenchymal interactions and basement membrane organization, providing a structural basis for subsequent transitions [4]. As these spheroids evolve, the increasing surrounding dermal stiffness activates YAP signaling in basal epidermal cells, inducing Wnt and MMP pathways that remodel the extracellular matrix and enable spheroids to coalesce [5]. Yet, the coalescence process ends up with a huge flat sac. The question is, what drives the huge flat sac into a planar epidermal–dermal bilayered sheet?

Recent work by Jiang *et al.* identifies hypoxia-induced metabolic adaptation as a key driver for this last self-organizing process [6]. As these structures progress, an intrinsic hypoxic environment emerges due to increased cellular density and limited oxygen diffusion. This environmental constraint is sensed through HIF-1α, which initiates a shift toward glycolytic metabolism in epidermal cells. This metabolic change enables the system to reorganize, driving phase-separation and the transition from the huge flat sac to planarized tissue architecture. This planarized skin organoid can then be transplanted onto mouse skin to generate hair follicles.

At the molecular level, this transition is accompanied by transcriptional and epigenetic reprogramming downstream of HIF-1α. ChIP-seq and ATAC-seq analyses reveal that HIF-1α directly regulates key glycolytic enzymes such as *Eno1* and *Pgam1*, establishing a metabolic program required for morphogenesis. When these pathways are perturbed, planarization fails and hair regeneration is compromised, suggesting that metabolic reprogramming is functionally required for the system to move into the next morphogenetic state. From this perspective, HIF-1α may be viewed as a sensor that links environmental conditions to activate cellular state transitions.

Noteworthily, distinct cell populations within the organoid adopt different metabolic strategies according to their spatial context. Epidermal cells engage glycolysis and localize to hypoxic niches, facilitating epithelial layer formation. In contrast, dermal fibroblasts exhibit enhanced retinoid metabolism, which supports their positioning and interaction with the epidermis, contributing to basement membrane formation. Hypoxia-induced lysosomal activity enables the removal of keratin debris, allowing the system to remodel its internal structure. These compartment-specific responses suggest that metabolic heterogeneity is a key feature of self-organization, coordinating epidermal–dermal coupling, phase separation, and structural refinement as the organoid grows.

From a systems perspective, these findings suggest that while different cells within organoids assume distinct roles, collectively, new biochemical or biophysical properties emerge that trigger the next morphological transition. Mechanical factors contribute to the physical dynamics, shaping how cells move, interact, and

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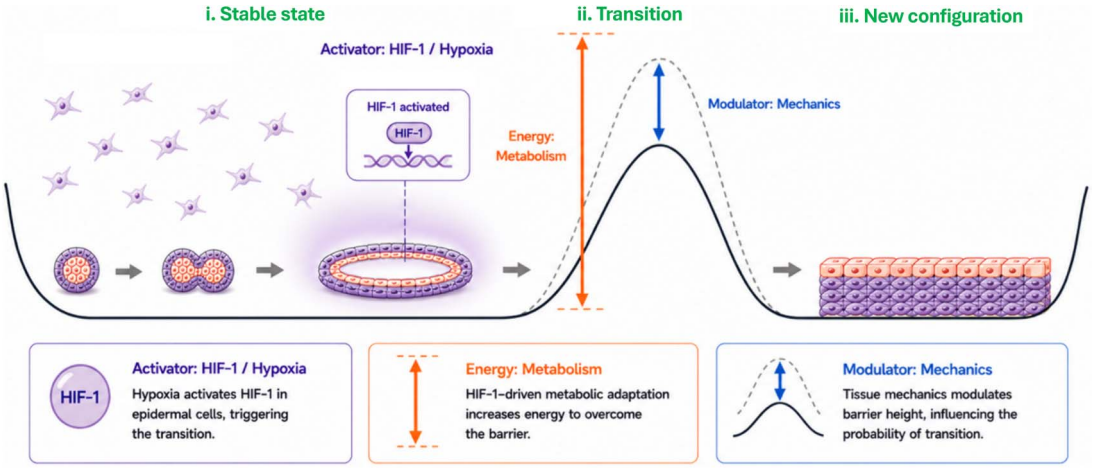


Figure 1 Hypoxia, metabolic adaptation, and mechanics drive self-organization in organoid morphogenesis

assemble. Chemical signaling senses, activates, and executes the necessary molecular programs. Hypoxia, emerging from system-level constraints, can also serve as a trigger that enables the system to transition to the next stable states, while metabolism provides the energy for cellular processes to occur (Figure 1).

A similar reasoning can be observed in endogenous regeneration. In the wound-induced hair follicle neogenesis model [7], the injured tissue initially enters a reparative phase characterized by re-epithelialization. As the wound matures, hypoxia develops within the tissue, activating HIF-1α signaling and promoting metabolic reprogramming, including enhanced glutamine metabolism [8]. This metabolic shift supports stem cell activation and regenerative competence, suggesting that hypoxia may again serve as a signal that enables the system to move beyond a stable reparative state.

In parallel, tissue mechanics also contribute to setting up the morphogenetic field for regeneration. The wound bed's spatial stiffness gradient sets up a permissive or restrictive state for regenerative pattern formation, with a stiffness range between 5–15 kPa as optimal for maximal probability of placode formation for hair follicle regeneration [9].

From this perspective, tissue mechanics serve as a modulator of regeneration by tuning the probability of self-assembly, and therefore, how patterns emerge. This is consistent with the concept of tensional homeostasis, in which cells continuously sense and respond to mechanical cues from their environment, integrating these signals with biochemical pathways to regulate behavior.

Taken together, these observations suggest a framework in which regeneration is governed by the interplay of three components (Figure 1): a sensing and activating signal (hypoxia and HIF-1α) acts as a potential initiating cue that enables symmetry breaking and transition between states; metabolic adaptation provides the energy required for cellular reorganization; and mechanical conditions set up the morphogenetic landscape, modulating where and how efficiently self-organization occurs.

From a conceptual standpoint, regeneration may be viewed as a system traversing an energy landscape of morphogenetic states, where each stable configuration represents a local minimum. In this model, hypoxia-induced HIF-1α signaling provides the perturbation that allows the system to exit from the stable state, metabolism supplies the energy required to cross the barrier, and mechanical constraints shape the trajectory toward the next stable configuration (Figure 1).

Different systems, organoids, wound beds, and developing tissues may utilize distinct molecular pathways yet converge on similar organizing principles [10].

Understanding how these principles operate across different contexts provides insight into how cells in morphogenesis self-organize and enter next phases. The keys to regeneration may lie in a sequence of coordinated transitions between morphogenetic states, where the ability to navigate these transitions determines regenerative outcomes. Targeting the mechanisms that activate these transitions may also offer promising therapeutic strategies.

Conflict of interest

None declared.

Author contributions

Hans I-Chen Harn (Conceptualization, Visualization, Writing—original draft, Writing—review & editing)

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