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Review

Epithelial cell plasticity in metazoans: Evolutionary insights into roles and mechanisms

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ABSTRACT

Epithelial tissues function as multicellular communities that preserve tissue integrity while adapting to diverse environmental stresses by altering cell behaviors. A striking manifestation of such adaptability is cell plasticity, the ability of differentiated cells to revert to stem-like states or adopt alternative fates. Once considered rare and confined to highly regenerative species, cell plasticity is now recognized across the metazoan tree. In early-branching animals such as sponges and cnidarians, transdifferentiation and dedifferentiation are integral to life-cycle transitions and regeneration, whereas in more complex organisms, these processes typically emerge under stress, including stem cell loss or environmental perturbations. Here, we examine epithelial cell plasticity through evolutionary, cellular, and molecular perspectives. Focusing on the intestinal epithelium, we explore findings from mammalian and *Drosophila* models showing that progenitors and even terminally differentiated cells can dedifferentiate in response to external stimuli that disrupt homeostasis, such as pathogen infection and nutrient fluctuations. We further discuss conserved mechanisms involving intercellular signaling (e.g., Notch, EGFR, and JAK-STAT) and chromatin states primed for reprogramming, modulated by metabolic cues. Together, these insights position cell plasticity as an ancient environmental adaptation strategy, shaped by conserved molecular toolkits and refined by species- and cell lineage-specific innovations.

1. Introduction

The emergence of multicellular animals, or metazoans, from unicellular ancestors marked a major evolutionary transition in the history of life. The closest living relatives of animals, such as choanoflagellates, display simple epithelial-like organization in their colonial forms, with cells connected by adhesion molecules and polarized toward an apical flagellum [1]. These structural similarities suggest that key epithelial features such as cell polarity, cell adhesion, and coordinated cell behavior may have originated before the appearance of true multicellularity and were later elaborated in the first metazoans. Comparative genomic studies support this view, revealing that many molecular components of cell adhesion and polarity complexes were already present in these unicellular relatives [2–4], thus providing a pre-adapted molecular toolkit for the emergence of complex animal tissues. Notably, choanoflagellates such as *Salpingoeca rosetta* exhibit reversible transitions between unicellular and colonial forms, accompanied by changes in cellular morphology, in response to specific bacterial cues [5,

6]. This environmentally induced alternation between solitary and multicellular states represents a primitive form of cell fate modulation and plasticity—foreshadowing principles that later reappear in the context of animal development, regeneration, and environmental adaptation.

During animal development, a single-celled zygote undergoes embryogenesis to form an adult body, a process that extends into post-embryonic growth and tissue maintenance until the organismal death. At the foundation of body formation lies the organization of tissues, sometimes referred to as a “cellular society”, each composed of specialized cell types performing distinct functions. Among them, epithelial tissues stand out for their dynamic nature: they drive morphogenesis through folding and bending, serve as protective barriers, and mediate exchange with the external environment [7–9]. In most metazoans, epithelia arise from all germ layers during development and are maintained in adulthood through a finely tuned balance between cell loss and renewal. Within epithelia, defined cell-cell junctions connect neighboring cells, and cellular processes such as cell

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division, differentiation, and death are spatially and temporally coordinated to preserve polarized architecture [10–12]—conditions that, under homeostasis, may limit the expression of plasticity in the absence of mutations and/or environmental perturbations.

In the early era of developmental biology, cellular differentiation *in vivo*, particularly in mammals, was regarded as a unidirectional and irreversible process in which relatively unspecialized progenitors progressively restrict their potential to adopt mature cell fates. However, accumulating evidence from across metazoan phyla has overturned this paradigm, revealing that even fully differentiated epithelial cells retain latent plasticity [13,14]. One manifestation is the epithelial-to-mesenchymal transition (EMT), a program active in embryogenesis but also reactivated during wound healing and in pathological contexts such as cancer progression [15]. Beyond EMT, classical regeneration studies have provided striking examples of cell fate reversal (dedifferentiation) and conversion (transdifferentiation) [13] (Fig. 1). For example, in the green *Hydra*, the isolated gastrodermis devoid of stem cells can regenerate a complete polyp through dedifferentiation and transdifferentiation of differentiated epithelial lineages [16]. In the newt, pigmented epithelial cells of the iris can dedifferentiate, re-enter the cell cycle, and transdifferentiate into lens fibers to regenerate a fully functional lens [17,18]. In the fruit fly *Drosophila*, surgical dissection and transplantation of imaginal disc cells, larval epithelial progenitors normally committed to specific adult structures, can induce a fate switch from one disc type to another, a phenomenon known as *transdetermination* [19,20]. These cases underscore how environmental perturbations, particularly those involving tissue loss, can trigger dramatic shifts in cell identity.

Over the past two decades, advances in genetic lineage tracing, targeted cell ablation, and high-resolution imaging have greatly expanded our understanding of epithelial cell plasticity *in vivo*. Such plasticity is not limited to regeneration-specialist species, but is also evident in adult mammalian epithelia. In tissues such as the epidermis, intestine, trachea, and liver, somatic stem/progenitor cells maintain homeostasis under normal conditions. Yet, targeted ablation of these stem/progenitor populations frequently prompts differentiated cells or lineage-committed progenitors to dedifferentiate, reacquiring stem-like properties to support regeneration [14,21,22]. This regenerative flexibility,

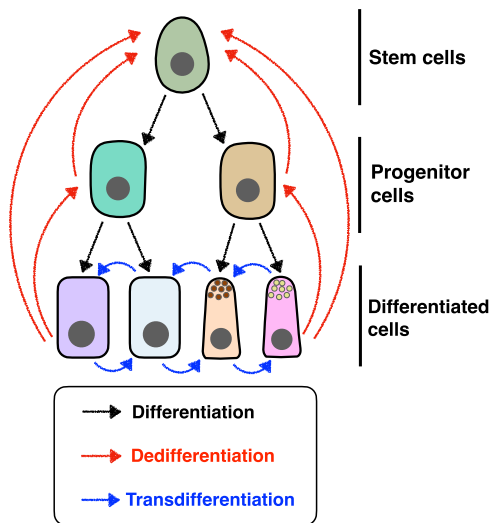


Fig. 1. Definition of differentiation, dedifferentiation, and transdifferentiation. In epithelial tissues, stem cells produce progenitors that subsequently mature into differentiated cells (differentiation). Under environmental perturbations, progenitors or differentiated cells can revert to a stem-like state (dedifferentiation), while mature differentiated cells can switch directly into other cell types (transdifferentiation). In this review, we collectively refer to dedifferentiation and transdifferentiation as cell plasticity.

documented in both vertebrates and invertebrates, challenges the long-held assumption that adult cell fates are permanently fixed. With the advent of single-cell transcriptomics and trajectory inference methods (e.g., RNA velocity [23–25]), the molecular and dynamic features of these fate transitions are now being characterized with unprecedented resolution [26].

Despite these advances, the precise mechanisms governing cell plasticity *in vivo* remain elusive. Moreover, documented cases of cell fate reversion have largely come from specific experimental settings in model organisms, such as targeted ablation of stem/progenitor cells. Two key questions therefore remain:

1. To what extent is cell plasticity conserved across metazoans, and is the capacity for fate reversal or conversion more prevalent in early-branching animals?
2. What molecular mechanisms enable differentiated cells to regain stem-like potential *in vivo*, and are these mechanisms conserved across contexts or shaped by lineage-specific environments?

In this review, we explore recent advances that address these questions from evolutionary, cellular, and molecular perspectives. We begin by examining evidence for cell plasticity in early-branching, non-bilateria animals. We then focus on the intestinal epithelium as a tractable model system in which multiple cell types can undergo dedifferentiation, and highlight the *Drosophila* adult midgut as an experimental paradigm for studying physiological dedifferentiation. By comparing strategies across metazoans, we discuss conserved principles and lineage-specific adaptations that shape epithelial cell plasticity.

2. Evolutionary perspectives on cell plasticity in basal metazoans

In many metazoans, adult tissue homeostasis and regeneration rely on stem/progenitor cells with the capacity for self-renewal and differentiation into multiple or specific lineages. Resident tissue-specific, lineage-restricted stem cells are typically considered the primary source of these undifferentiated cells. In addition, some highly regenerative animals, such as planarians, coelms, annelids, and hydrozoans, possess body-wide pools of pluri-/multipotent stem cells that express conserved germline multipotency program (GMP) genes (e.g. *Piwi*, *vasa*, and *nanos*) with somatic and germ potential throughout adulthood [27–29]. However, such stem cell systems are distributed sporadically across the animal kingdom (Fig. 2), raising the question of whether they represent an ancestral trait or have emerged independently in various lineages. By contrast, early branching, or basal metazoans—including poriferans, placozoans, ctenophores, and cnidarians—all of which belong to non-bilateria phyla and exhibit extreme regenerative abilities [30], appear to rely more heavily on inherent cell plasticity (Fig. 2). These organisms often utilize transdifferentiation and/or dedifferentiation during ontogenesis, regeneration, and reverse development [31], suggesting a flexible mechanism for generating specific cell types or undifferentiated cells during life cycle transitions and in response to environmental perturbations. Given their phylogenetic positions and relatively simple body plans, basal metazoans provide valuable evolutionary insight into the origins and mechanisms of cell plasticity in multicellular animals.

2.1. Cell plasticity in poriferans, placozoans, and ctenophores

Poriferans, or sponges, represent one of the most basal metazoan groups and exhibit the simple form of multicellularity, lacking neurons, muscles, and organs such as a gut. Demosponges, the most abundant class in poriferans, possess several primary cell types, including epithelial pinacocytes, filter-feeding choanocytes, and mesenchymal pluripotent stem cells known as archeocytes [32]. Lineage tracing and transcriptomic profiling of the demosponge *Amphimedon* have shown

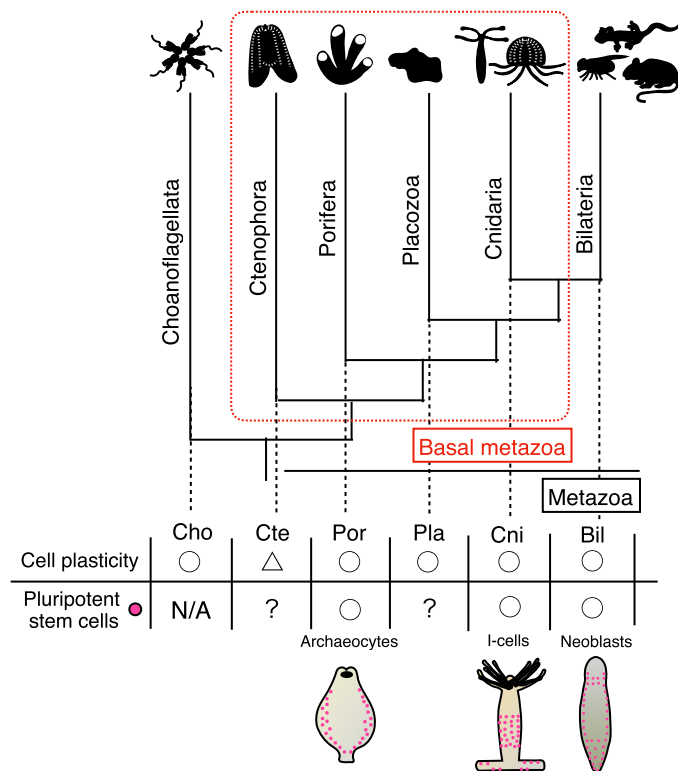


Fig. 2. Animal phylogeny and the distribution of cell plasticity and pluripotent stem cells. Current evidence indicates that cell plasticity is widespread across most animal phyla (see details in Section 2). In contrast, pluripotent stem cells (magenta in the scheme), such as poriferan archeocytes (e.g. *Amphimedon*), hydrozoan i-cells (e.g. *Hydractinia*), and planarian neoblasts, are distributed more sporadically across metazoans (ref. [31]). Given that unicellular relatives such as choanoflagellates exhibit reversible cell state changes and epithelial-like organization in their colonial forms, epithelial cell plasticity likely represents an ancestral trait of metazoans.

that choanocytes exhibit a metastable state and can convert into archeocytes [33,34], indicating a dynamic and reversible cell state underpinning sponge body plasticity. These observations suggest that, in poriferans, tissue maintenance and regeneration rely less on a rigid stem cell hierarchy and more on the ability of cells to reversibly transition between functional stem cell states.

Placozoans, the simplest free-living metazoans, which also lack organs and a nervous system [35], further exemplify this principle. Rather than discrete stem cell populations, placozoans harbor somatic cells with intermediate transcriptional states that exhibit potential for interconversion among distinct cell types [36]. This continuous spectrum of cell states supports the idea that extensive cell plasticity, rather than lineage-restricted stem cells, underlies tissue homeostasis and regeneration in these animals. These findings collectively reinforce the notion that broad cell plasticity may have been a foundational trait of early-branching metazoans.

Ctenophores (comb jellies), though morphologically more complex with distinct neurons and muscles, are considered as the sister group to all other animals based on the recent genomic and phylogenetic analyses [37]. While ctenophores harbor somatic stem cells in defined structures such as the tentacle bulb [38], these cells do not appear to contribute to regeneration. Instead, regeneration involves slowly-dividing cells dispersed throughout the body [39]. Notably, unlike many highly regenerative animals, ctenophores regenerate without forming a typical blastema, and tissue restoration proceeds through local cellular reorganization and fate changes rather than the accumulation of a proliferative progenitor mass [38]. The precise identity, lineage relationships,

and plastic nature of these slow-cycling cells remain elusive. Intriguingly, a recent report using the model ctenophore *Mnemiopsis leidyi* described a striking example of reverse development, in which lobate-stage animals revert to an earlier cydippid stage [40]. Together, these observations suggest that ctenophores employ a regeneration strategy fundamentally distinct from blastema-based regeneration, involving extensive tissue remodeling and somatic cell reprogramming, and might reflect an independently evolved mode of cell plasticity, analogous to hypotheses proposing an independent evolutionary origin of the ctenophore nervous system [41,42].

2.2. Cell plasticity in cnidarians

Cnidarians, the sister group to bilaterians, are the best-studied early-branching metazoans [43,44]. Model species such as *Hydra*, *Nematostella*, *Hydractinia*, and *Clytia* have been investigated extensively at the molecular and cellular levels, providing mechanistic insights into development, regeneration, and stem cell biology. Despite their morphological and ecological diversity—encompassing two major clades, Anthozoa (sea anemones and corals) and Medusozoa (hydroids and jellyfish, including Hydrozoa, Scyphozoa, Cubozoa, and Staurozoa)—adult cnidarians, represented by polyp and/or medusa stages, share key features: radial symmetry, a diploblastic body plan, organized neurons and muscles, and specialized stinging cells (nematocytes) located on defined appendages (tentacles). In hydrozoans, interstitial stem cells (i-cells) have long been recognized as adult stem cells [45]. Although their potency varies among species, i-cells express conserved GMP genes and can give rise to both somatic and germline lineages [46]. Initially considered exclusive to Hydrozoa, similar multipotent stem/progenitor cells that express *Piwi1/Vasa2/Nanos2* have recently been identified in the anthozoan *Nematostella vectensis* [47,48], suggesting that such cell types may be conserved across cnidarians. Nevertheless, it remains unclear whether these stem cell populations alone account for the sole source of undifferentiated cells required for body plasticity and regenerative abilities. As detailed below, emerging evidence indicates that cell plasticity also plays a crucial role in regeneration and life cycle transitions in this phylum.

2.2.1. Cellular reprogramming in the polyp *Hydractinia*

The colonial hydrozoan polyp *Hydractinia* has provided *in vivo* evidence of stem cell-based regeneration and reprogramming [49,50]. During head regeneration as well as whole-body regeneration from aggregated cells after dissociation, resident migratory i-cells, which are normally located in the lower body column, become a source of newly regenerating cells, called blastema [51,52]. Through elegant grafting experiments involving single i-cell transplantation, *Hydractinia* i-cells have been shown to be pluripotent stem cells that can give rise to all somatic and germline lineages [53]. While upon decapitation, head regeneration from the body part occurs by recruiting i-cells [51], head itself can regenerate a functional polyp despite the absence of resident i-cells [54]. This process involves the *de novo* emergence of i-cell-like populations in the regenerating head, termed “secondary i-cells,” which express one of the GMP markers *Piwi1* [54]. The appearance of these *Piwi1*⁺ cells is significantly impaired by hydroxyurea treatment, indicating that cell cycle re-entry is prerequisite for the induction of secondary i-cells via somatic cell reprogramming. This finding highlights an alternative regenerative mechanism that does not rely solely on pre-existing stem cells.

2.2.2. Emerging evidence of cell plasticity in medusae

Compared to polyps, medusa-stage cnidarians possess more complex and well-defined organs, such as the manubrium, gonads, and tentacles, implying a potential need for both lineage-restricted stem/progenitor cells and a degree of cell plasticity to support regeneration and environmental adaptation [55]. Indeed, classic *in vitro* studies in *Podocaryne carnea* suggest a trans-/dedifferentiation potential of striated muscle

cells into multiple cell types after dissociation with collagenase treatment [56]. During reverse development in *Turritopsis sp.*, medusae undergo cyst formation before forming a tube-like structure (stolon) that connects polyps, which involves transdifferentiation-like events [57, 58]. However, direct *in vivo* evidence of cellular reprogramming meeting modern biological standards remains limited.

The hydrozoan jellyfish *Cladonema pacificum* has recently emerged as a model for studying regeneration in medusae [59]. In the *Cladonema* medusa, i-cells are localized in the tentacle bulb and act as resident homeostatic stem cells (RHSCs) [60–62], maintaining tissue integrity by producing all tentacle cell types, similarly observed in another hydrozoan jellyfish *Clytia* [63,64]. Upon tentacle amputation with the bulb left intact, a distinct population of repair-specific proliferating cells (RSPCs) appears near the injury site [62]. These cells are largely distinct from RHSCs and preferentially differentiate into epithelial cells during regeneration. This functional discrepancy in which RHSCs sustain homeostasis while RSPCs behave as blastema cells resembles blastema formation in vertebrates, such as during salamander limb regeneration wherein lineage-restricted stem/progenitors are induced upon amputation [65]. Although the precise origin of RSPCs remains unknown, they likely arise either from activation of reserved/slow-cycling stem cells or from dedifferentiation of epithelial cells. To conclusively determine the source and plasticity of these cells, cell-type-specific lineage tracing combined with single-cell transcriptomics is needed. These methods, already established in the model systems like mouse and *Drosophila*, are beginning to be applied to cnidarian models.

3. Intestinal epithelial plasticity

3.1. Cell plasticity in the mammalian intestine

As the primary digestive organ, the intestine, or gut, is among the most evolutionarily conserved organs across metazoans. Its epithelial lining constantly interfaces with external environmental factors, including dietary nutrients and microbial communities. In mammals, the intestinal epithelium is particularly notable for its high degree of cellular plasticity. Under homeostatic conditions, the dedicated Lgr5⁺ intestinal stem cells (ISCs), located at the crypt base, continuously give rise to absorptive enterocytes (ECs) and secretory lineages (enteroendocrine, Goblet, Paneth, and Tuft cells) via intermediate progenitor states. Following injury such as irradiation, which ablates Lgr5⁺ ISCs, both enterocyte and secretory progenitors are capable of dedifferentiating into multipotent ISCs that can replenish the entire crypt-villus mammalian intestinal epithelium [66–70]. This progenitor dedifferentiation has also been observed after targeted genetic ablation of Lgr5⁺ ISCs using diphtheria toxin receptor systems [71,72], suggesting that the cell fate reversion generally occurs in response to ISC loss. It should be noted that recently identified Fgfbp1⁺ upper crypt cells likely exhibit stemness and function as a source of Lgr5⁺ crypt base cells in the mammalian intestine [73,74]. It remains to be investigated if the progenitor population reverts into Fgfbp1⁺ cells during regeneration. Another possibility is that progenitors defined by marker genes may be just a part of Fgfbp1⁺ stem cells.

Cell plasticity in the mammalian intestinal epithelium is not limited to progenitor populations. Differentiated Paneth cells can also dedifferentiate into ISCs upon depletion of Lgr5⁺ ISCs [69,75]. The capacity of cell fate reversion in differentiated cells further supported by the restoration of ISCs from enteroendocrine and tuft cell lineages after treatment of 5-fluorouracil, an agent that disrupts DNA replication in ISCs and proliferating progenitors [72]. Notably, the enteroendocrine and tuft cell lineages occasionally revert into ISCs without experimental injury, suggesting the possibility of natural cellular reprogramming even under physiological conditions [70,72].

Moreover, aberrant induction of cell plasticity can have pathological consequences in mammals. Dual activation of WNT signaling and NF- κ B signaling can initiate tumorigenesis in the villus compartment, which is

primarily composed of differentiated cells [76]. The secretory lineage appears particularly susceptible to tumorigenic dedifferentiation, as oncogenic mutations in both secretory and EC lineages causes tumor formation while EC lineage-specific oncogenic mutations alone do not [71]. These findings suggest while the remarkable plasticity of intestinal epithelial cells underlies efficient regeneration following injury, it also poses an inherent risk of dysplasia and malignant transformation.

3.2. Cell plasticity in the *Drosophila* adult midgut

The *Drosophila* adult midgut has long served as a genetically tractable model for studying cell fate determination and differentiation since the identification of ISCs [77,78]. The lineage hierarchy of *Drosophila* ISCs is similar but simpler than that of mammalian ISCs: ISCs give rise to two types of progenitor cells, enteroblasts (EBs) and enteroendocrine progenitors (EEPs), which subsequently differentiate into absorptive ECs and secretory enteroendocrine cells (EEs), respectively [79–81] (Fig. 3A). While ISC proliferation and differentiation are indispensable for both homeostatic turnover and regenerative regrowth of the epithelium, recent studies have revealed that *Drosophila* ISC lineages, like their mammalian counterparts, exert cellular plasticity during environmental adaptation.

3.2.1. EB-to-ISC dedifferentiation following intestinal challenges

Pathogenic bacterial infection causes extensive EC loss and shrinking of the adult midgut [82–86]. Upon infection with *Pseudomonas entomophila* or *Erwinia carotovora carotovora* 15, damaged ECs secrete mitogenic signals that promote ISC division to restore the lost tissue. In addition to increased ISC division, EBs, normally post-mitotic progenitors that undergo endoreplication to become polyploid ECs, can re-enter the mitotic cycle and dedifferentiate back into ISCs under infectious conditions [82] (Fig. 3B). Intriguingly, these mitotic EBs lack ISC markers, yet their daughter cells reacquire ISC identity and multipotency, suggesting that EB dedifferentiation occurs after a single round of mitotic division [82]. As an alternative mechanism of dedifferentiation within the EC-lineage, amitotic cell division was also reported in the *Drosophila* midgut during recovery from severe starvation, a condition that ablates approximately 80% of ISCs [87]. In normal differentiation, diploid EBs undergo endoreplication to mature into polyploid ECs [88]. During amitosis, tetraploid intermediates become binucleated (2 \times 2 n) in the absence of a mitotic spindle and subsequently divide into two ISCs without forming a mitotic contractile ring [87]. These observations indicate that reactivation of cell division—whether mitotic or amitotic—is a prerequisite for EB-to-ISC fate reversion, highlighting restoration of proliferative capacity as a key step in cellular reprogramming.

The molecular basis of these EB-to-ISC dedifferentiation events is not fully understood, but recent work sheds light on possible mechanisms [89]. Puig-Barbe et al. identified the bHLH transcription factor *extra macrochaetae* (*emc*), which is highly expressed in EBs and ECs, as a key regulator of EB commitment toward EC fate, and showed that the loss of *emc* leads to cell fate reversion of EB lineages into ISCs [89]. Mechanistically, *Emc* forms a heterodimer with another bHLH factor Daughterless (*Da*) [90,91] to repress ISC identity, which is normally maintained by Da:Da homodimers. Supporting this, EB-specific overexpression of Da:Da homodimers similarly induces dedifferentiation, suggesting that bHLH transcription factor dynamics regulate EB plasticity (Fig. 3B). Furthermore, EB-specific overexpression of Scute, which forms Da:Sc heterodimers to induce EE fate in ISCs [91–93], results in formation of EE-enriched EB-derived cellular masses [89]. Depletion of *tramtrack* (*ttk*), a transcription factor that represses EE-related genes [94], also triggers transdifferentiation of EB-lineage cells into EEs [95]. Together, these findings highlight the high plasticity of EB cell fates, capable of reprogramming toward either ISCs or EEs depending on transcriptional inputs.

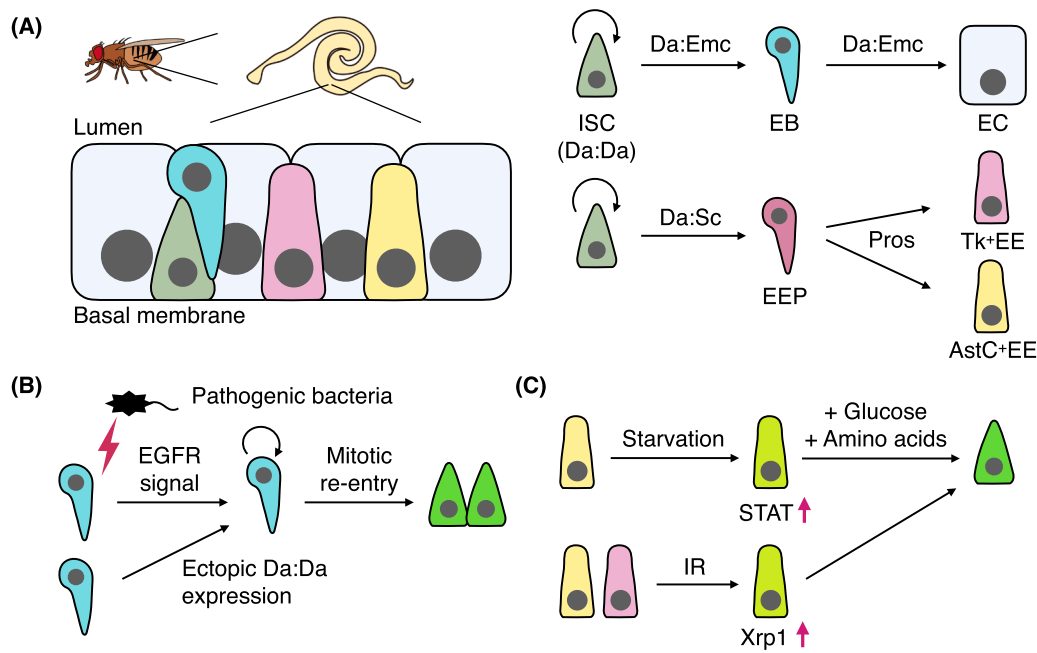


Fig. 3. Cell plasticity in the *Drosophila* adult midgut. (A) The adult midgut forms a pseudostratified monolayer composed of five cell types: Intestinal stem cells (ISCs), enteroblasts (EBs), enteroendocrine progenitors (EEPs), enterocytes (ECs), and enteroendocrine cells (EEs). EEs are divided into two subpopulations, $AstC^+$ EEs and Tk^+ EEs, based on their neuronal peptide expression profiles. Differentiation in the ISC lineage is regulated by the bHLH transcription factors, Daughterless (Da), Extra macrochaetae (Emc), and Scute (Sc). Da:Da homodimers maintain ISC stemness, whereas Da:Emc and Da:Sc heterodimers drive EB-to-EC and EEP-to-EE differentiation, respectively. (B) Cell plasticity of EBs. Upon pathogenic infection, EBs undergo dedifferentiation via EGFR-dependent mitotic re-entry. Ectopic expression of Da:Da homodimers similarly promotes EB-to-ISC reversion. (C) Cell plasticity of EEs. Starvation activates STAT signaling in $AstC^+$ EEs, enabling dedifferentiation upon refeeding with glucose and amino acids. In addition, ionizing radiation (IR)-induced damage promotes EE-to-ISC reversion through upregulation of the transcription factor Xrp1.

3.2.2. EE-to-ISC dedifferentiation during nutrient adaptation

In addition to EBs, EE-lineage cells also exhibit cell fate plasticity under environmental challenges such as nutrient fluctuations and irradiation [96,97] (Fig. 3C). Starvation reduces intestinal size, but rapid recovery occurs upon refeeding (adaptive growth), driven in part by ISC expansion [86,98–100]. While this has traditionally been attributed to a switch in ISC division mode from asymmetric to symmetric, recent work by Nagai et al. revealed that a subset of mature EEs dedifferentiate into ISCs during refeeding after starvation [96]. Unlike terminally differentiated polyploid ECs (>4n), diploid (2n) EEs can revert to multipotent ISCs by downregulating *prospero* (*pros*), a master regulator of EE identity [95,96]. This EE-to-ISC dedifferentiation during nutrient adaptation exhibits three notable features:

1) Subtype specificity: Among two major EE classes [101–103], Class I EEs, marked by Allatostatin C (AstC, the *Drosophila* homolog of mammalian somatostatin), preferentially dedifferentiate [96]. $AstC^-$ somatostatin are secreted during starvation in both flies and mammals [104,105]. The loss of $AstC^+$ granules is consistent with the concept of ‘paligenosis’, wherein differentiated cells lose lineage-specific cellular machineries via autophagy prior to mitotic re-entry [14,106].

2) Regional differences: Although $AstC^+$ EEs distribute across the adult midgut [102], dedifferentiation primarily occurs in the anterior midgut, where symmetric ISC divisions are less frequent and mitotic activity is lower compared to the posterior region [96]. Notably, in this region, EE-to-ISC conversion is relatively frequent at the population level, with approximately 80–120 EEs undergoing fate reversion during starvation–refeeding, accounting for 40–60% of newly generated ISCs [95]. This spatial bias suggests that regional strategies for ISC pool expansion may differ along the gut axis: ISC symmetric division

dominates in the posterior midgut, while EE dedifferentiation represents a major source of stem cell expansion in the anterior region.

3) Differentiation bias: EE-derived ISCs tend to produce ECs preferentially, with some forming EC-only clones through symmetric differentiation into two daughter ECs [96]. The JAK-STAT pathway, which promotes EB-to-EC differentiation (see Section 4–1 for details) may be involved in this bias during dedifferentiation. The preferential generation of EC may facilitate rapid adaptation to nutrient availability, as ECs function as main digestive and absorptive cells. Given that ECs serve as a physical barrier by forming septate junction (tight junction in mammals) that is crucial for intestinal regeneration [107–109], it is tempting to speculate that the injury-dependent dedifferentiation also accompanies the differentiation bias toward ECs [97].

Altogether, these findings in the *Drosophila* midgut suggest that EE-to-ISC dedifferentiation serves as a context- and region-specific mechanism to expand stem cell pools under environmental stress. This plasticity primes differentiated cells for lineage-biased adaptive responses, offering a versatile strategy for maintaining epithelial homeostasis and digestive function during nutrient fluctuations.

4. Mechanisms of cell fate conversion

4.1. Intercellular communications that control cell plasticity

How do differentiated cells sense the demand to replenish their parental stem cells? Two major modes of intercellular communications, direct cell-cell contact mediated by transmembrane proteins and paracrine signaling via secreted cytokines, play central roles in regulating cell plasticity, particularly in epithelial tissues such as the intestine. In

addition, cell fate conversion can be influenced by systemic endocrine cues that reflect organismal physiological states.

4.1.1. Direct cell-cell contact in cell plasticity

Adjacent epithelial cells can control stemness in one cell and differentiation of the other through lateral inhibition mediated by Notch signaling, in which Notch-activating cells inhibit the signal induction in surrounding cells [110,111]. In the mammalian intestinal crypt, Paneth cells stay beside Lgr5⁺ ISCs, unlike the other differentiated cells that move into the villus, and express transmembrane Notch ligands Delta 1 and Delta 4 that activate Notch receptors in ISCs to support their stemness [66,69,112,113]. While Paneth cells exhibit minimal Notch activity under homeostatic conditions, following irradiation that ablates resident ISCs, Notch signaling is activated in Paneth cells, leading to their dedifferentiation into stem-like states [69]. This suggests that the loss of the lateral inhibition enables cell fate reversion. Prior to Notch activation, irradiated Paneth cells rapidly activate Yap [69], a mechanosensitive transcription factor that can target Notch [114]. Both Yap and its *Drosophila* homolog Yorkie have been implicated in cellular reprogramming in various cell types [115,116]. Given the evolutionary conserved mechanical regulation of Yap [117], ISC loss may cause remodeling of cytoskeleton, cell polarity, and/or junctional integrity in neighboring cells, resulting in cell fate plasticity.

4.1.2. Paracrine signaling control of cell plasticity

Studies in the *Drosophila* midgut have identified paracrine signaling pathways that induce cell fate reversion. For example, EGFR signaling is both necessary and sufficient for the EB-to-ISC reversion in response to pathogenic infection [82] (Fig. 3B). EGF ligands such as *vein* (Neuregulin-1 in mammals), *Keren* (structurally similar to mammalian TGF- α), but not *spitz* (canonical EGF in mammals), are up-regulated during the mitotic re-entry of EBs [82,84,118]. These *Drosophila* EGF ligands are produced not by EBs but by visceral muscle cells in response to intestinal damage [118], akin to stromal fibroblast-derived Neuregulin-1 in the regenerating mammalian intestine [119]. Furthermore, the expression of EGFRs is induced by EC-derived Upd3, an IL-6 like cytokine, during midgut regeneration in *Drosophila* [83,118,120–124]. These studies suggest a possibility that EC-muscle-EB signaling relay underlies cell plasticity in EBs. Considering the fact that ECs are the most abundant epithelial cell type in the adult *Drosophila* midgut and directly interface with luminal contents, they likely sense pathogenic infection and initiate regenerative responses including dedifferentiation. Similar inter-cellular communication is not limited to the intestine and is also observed in the mouse brain: EGFR signaling activation drives dedifferentiation of astrocytes following *p53* loss and brain injury [125], during which EGF ligands are likely secreted from the injured brain microenvironment [126].

In addition to activating EGFR signaling, the JAK-STAT pathway promote cell fate reversion in diverse contexts, including EE-to-ISC dedifferentiation during nutrient adaptation [96,127,128]. In the *Drosophila* midgut, dedifferentiating AstC⁺ EEs upregulates the Upd receptor *Domeless*, *Stat92E* (the sole *Drosophila* orthologue of the mammalian STAT family), and its downstream target *Socs36E* [96,129]. Similar to the intercellular signaling relay during EB-to-ISC reversion [82,118,120], the cytokine Upd3 is secreted by ECs, not in EEs, in response to starvation [96,130]. Such paracrine activation and the role of STAT family proteins in cellular reprogramming are evolutionarily conserved and are likely shared across different organs and tissues: during mammalian liver regeneration, the liver resident macrophages (Kupffer cells) secrete IL-6 to induce dedifferentiation of mature hepatocytes via STAT3 activation [127]. Moreover, microglia-derived IL-6 converts mature oligodendrocytes into bipotent progenitor cells upon brain injury [128]. These lines of evidence imply that the niche-mediated activation of STAT signaling broadly underlies cell

plasticity in animals.

Notably, JAK-STAT signaling appears to prime cells for reprogramming rather than directly triggering dedifferentiation. In the *Drosophila* midgut, Stat92E activation occurs during starvation, not in response to refeeding that triggers the EE dedifferentiation [96] (Fig. 3C), as does Upd3 production in ECs [96,130]. Similarly, in the mammalian brain, IL-6 upregulation occurs well before the onset of oligodendrocyte fate reversal after injury [128]. These findings collectively support the notion that JAK-STAT signaling serves as a molecular permissive cue, alleviating the reprogramming barrier in differentiated cells rather than directly inducing fate change.

4.1.3. Systemic regulation of cell plasticity

Beyond local cell–cell interactions and niche-derived paracrine signals, cell plasticity may also be regulated by systemic physiological cues that reflect organismal states. Endocrine hormones can coordinate cell fate conversion with changes in nutrition, reproduction, and developmental timing, thereby linking tissue plasticity to whole-body homeostasis. Systemic hormones such as juvenile hormone (JH) and 20-hydroxy-ecdysone (20HE) have been implicated as potential regulators of cell plasticity in *Drosophila*. Both JH and 20HE are up-regulated upon mating and promote midgut growth in adult females, thereby enhancing reproductive success [131–135]. The mating-induced midgut growth is accompanied by increased food intake, expansion of ISCs, and enhanced generation of ECs [131,133–136], resembling the adaptive intestinal growth observed during starvation-refeeding cycles [96,98,99]. Given that EEs undergo dedifferentiation in response to nutrient fluctuations and that EE-derived ISCs preferentially generate ECs [96], cell plasticity may also contribute to midgut growth during reproduction. Following mating, corpus allatum-derived JH induces metabolic reprogramming in ECs and increases ISC proliferation, while ovary-derived 20HE promotes ISC differentiation toward the EC lineage [131–135]. Although it remains unclear whether systemic hormones directly influence EEs and their fate plasticity during midgut growth, one intriguing possibility is that EEs integrate either or both JH and 20HE to trigger cell fate reversion and subsequent EC generation.

4.2. Epigenetic regulation of cell plasticity

Epigenetic changes are fundamental for cellular differentiation, cancer progression, and *in vitro* reprogramming into induced pluripotent stem cells (iPSCs) [137,138]. Recent studies have highlighted the pivotal roles of epigenetic remodeling in regulating cell plasticity *in vivo*.

4.2.1. Chromatin landscapes of cell plasticity in the intestinal epithelium

In the intestinal epithelium, progenitor and differentiated lineages exhibit unique chromatin states associated with their reversion potential [139]. In mice, enhancer regions that are accessible in ISCs remain open in their progeny, even though ISC-related genes are transcriptionally repressed [67] (Fig. 4). Although secretory lineages additionally open enhancers of cell type-specific genes, this chromatin remodeling does not accompany gain of active histone marks such as H3K4me2 and H3K27ac [67,140,141], both of which strongly associate with differentiation of other cell types, including mammalian skin keratinocytes, neurons, and myocytes [142–145]. Likewise, mammalian EC lineages also exhibit similar patterns of H3K4me2 and H3K27ac to those of ISCs [67,140]. In *Drosophila*, differentiated EEs retain ISC-like chromatin accessibility around most ISC-enriched genes [95,146], similar to mammalian secretory lineage cells [67]. However, *Drosophila* ECs likely decrease chromatin accessibility, reduce H3K27ac deposition, and increase repressive histone mark H3K27me3 on ISC-enriched genes [146,147]. These permissive chromatin landscapes may allow mammalian EC lineages and mammalian/*Drosophila* secretory cells to rapidly remodel chromatin accessibility and activate stemness-associated genes upon ISC

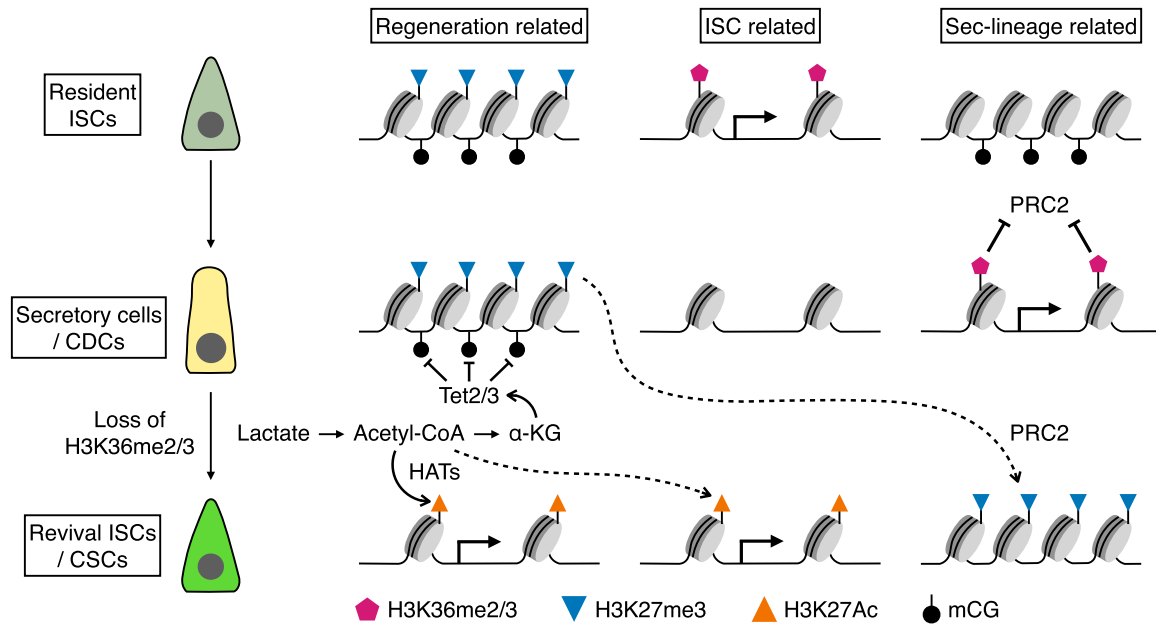


Fig. 4. Epigenetic remodeling during differentiation and dedifferentiation in the intestinal epithelium. (1) Most ISC-related loci remain accessible in differentiated cells, lowering the reprogramming barrier in secretory lineages and cancer differentiated cells (CDCs). (2) H3K36me2/3 marks cell type-specific loci to prevent H3K27me3 repressive modification by Polycomb Repressive Complex 2 (PRC2). Loss of H3K36me2/3 leads to H3K27me3 dilution from regeneration-related loci into cell type-specific (e.g., secretory-lineage) loci, thereby contributing to cell fate reversion. (3) Acetyl-CoA cooperates with histone acetyltransferases (HATs) to establish H3K27ac modification at regeneration-related loci and potentially at ISC-related loci, enhancing transcriptional activation and promoting reversion of CDCs into cancer stem cells (CSCs). (4) α -KG promotes dedifferentiation of secretory cells by inducing DNA demethylation through Tet2/3 activity.

loss, thereby enabling dedifferentiation [67].

Despite these similarities in chromatin accessibility, ISCs and differentiated cells display largely distinct transcriptional profiles under homeostatic conditions [67,148,149], indicating the presence of active mechanisms that repress cell plasticity. Notably, H3K36 methylation (H3K36me2 and H3K36me3) has been identified as a key mark on cell type-specific gene loci in mammalian intestine [150] (Fig. 4). Loss of H3K36 methylation leads to ectopic deposition of the repressive mark H3K27me3, which antagonizes H3K36 methylation [151,152], resulting in the accumulation of immature EC-like cells and secretory precursors co-expressing features of Paneth and goblet cells. Furthermore, H3K36 demethylation upregulates regenerative genes including *Clusterin* (*Clu*), a marker of revival ISCs [115], by decreasing H3K27me3 at these loci [150]. This reduction of H3K27me3 on regenerative loci may be due to its dilution into H3K36me2/me3-depleted domains. These observations together suggest that H3K36 methylation negatively regulates cell plasticity in the mammalian intestinal epithelium. Consistent with this notion, irradiation reduces H3K36me3 levels through repression of its methyltransferase, Setd2. Importantly, modulation of H3K36 methylation also affects other cellular reprogramming contexts, such as the induction of iPSCs and EMT, further indicating its broad contribution in cell fate conversion [153,154].

Studies in the *Drosophila* midgut have shed light on how differentiated cell identity is maintained by regulation of nuclear lamins, which control high-order genome organization around nuclear periphery [155]. In differentiated ECs, a transcription factor Hey binds to two nuclear lamin genes, Lamin C (LamC, mammalian type-B Lamin) and LaminDm0 (LamDm0, mammalian type-A Lamin) [147]. While EBs and ECs highly express LamC to repress ISC-related genes, ISCs and EEs express LamDm0 to repress EC-specific genes. Hey maintains EC identity by transcriptionally up-regulating LamC while down-regulating LamDm0. Moreover, Non-stop identity complex (NIC), composed of E(y)2, Sgf11, Cp190, mdg4, Nup98, and deubiquitinase Non-stop, stabilizes LamC protein levels in ECs, likely by inhibiting proteasomal degradation [156]. Age-related loss of Hey and NIC components induces EC-like

polyploid cells that aberrantly express the ISC marker Delta, leading to disruption of septate junction and intestinal barrier dysfunction [147, 156]. Notably, ectopic expression of Hey and Non-stop prevents EC identity loss and improves gut barrier function in aged midguts [147, 156]. The contribution of nuclear Lamin regulation to dedifferentiation remains to be investigated.

4.2.2. Metabolic regulation of chromatin states and cell plasticity

Nutrient availability and composition profoundly influence chromatin states, as many metabolites serve not only as building blocks for cellular processes but also as cofactors for epigenetic regulators [157]. While metabolic control of epigenetic modifications is relatively well characterized in normal development and *in vitro* reprogramming to iPSCs [157–159], its role in cell plasticity *in vivo* still remains poorly understood. Nevertheless, recent studies have begun to uncover how metabolic pathways epigenetically regulate intestinal cell plasticity via histone/DNA modifications in both physiological and pathological contexts [160–162].

Mechanistic insights into how glycolytic metabolites influence chromatin states have been obtained from cancer models. Nguyen et al. found that glycolytic metabolite lactate drives dedifferentiation of cancer differentiated cells (CDCs) by regulating histone acetylation [160]. In this process, CDCs activity convert lactate into acetyl-CoA, an acetyl donor used by histone acetyltransferase such as p300, to induce H3K27ac at *MYC* locus. Pharmacological inhibition of p300, even in the presence of exogenous lactate, effectively prevents the lactate-induced CDC dedifferentiation. Moreover, inhibition of BRD4, an H3K27ac reader that up-regulates nearby target genes including *MYC*, also suppresses the CDC dedifferentiation. These results indicate that lactate functions not just as an energy source but as a metabolic substrate that directly supports histone acetylation-dependent cell fate conversion.

Evidence from *in vivo* models also suggests a close association between glycolytic metabolism and H3K27ac in intestinal cell fate plasticity. In the adult *Drosophila* midgut, nutrient-dependent EE-to-ISC conversion during refeeding requires glucose availability [96]. This

plasticity correlates with the expression level of the glycolytic enzyme Phosphoglucose isomerase (Pgi), implicating glycolytic flux in fate reversion [96]. Moreover, chromatin regulators that antagonize histone acetylation constrain plasticity in differentiated cells: the NuRD complex, which possesses H3K27ac deacetylase activity, limits plasticity in differentiating ECs [95]. Similarly, H3K27 methylation maintains lineage fidelity in EEs [163]. Together, these findings support a model in which metabolic state and chromatin accessibility jointly regulate intestinal cell plasticity *in vivo*, although additional functional studies will be required to define their causal relationship.

Beyond serving as an acetyl donor for H3K27ac, acetyl-CoA can further influence other epigenetic processes through its integration into the tricarboxylic acid (TCA) cycle [164]. In particular, acetyl-CoA promotes generation of alpha-ketoglutarate (α -KG), which is a co-factor of Jumonji domain histone demethylases and DNA demethylases Tet family proteins [164,165]. In the mammalian intestine, α -KG accumulates in secretory lineages due to downregulation of its metabolic enzyme 2-oxoglutarate dehydrogenase [162]. Notably, α -KG levels decline during regeneration, and exogenous α -KG supplementation enhances dedifferentiation of secretory cells during recovery phase [162], implicating α -KG as a positive regulator of plasticity. Although the precise mechanisms remain unknown, α -KG-dependent DNA demethylation by Tet enzymes facilitates iPSC reprogramming *in vitro* [153]. Moreover, intestinal regeneration is accompanied by DNA demethylation at fetal enhancers [150,153]. These observations raise the possibility that metabolic regulation of α -KG levels contributes to dedifferentiation via DNA demethylation and reactivation of fetal developmental programs (Fig. 4). Alternative mechanisms, such as indirect effects of nutrient availability on cell-cycle re-entry, may also contribute to fate conversion and warrant further investigation.

5. Future perspective

A growing body of work across metazoans has reshaped our view of differentiated cells from fixed terminal states to dynamic participants in life-cycle transitions, regeneration and environmental adaptation. Yet, several key questions remain unresolved. Much of our current understanding comes from experimental models in which resident stem/progenitor pools are ablated or severely impaired. While these “extreme” settings have yielded invaluable mechanistic insights, they may not fully reflect the naturally-occurring forms of dedifferentiation in intact organisms. It is therefore essential to explore how cell plasticity operates under physiological or ecologically relevant conditions. Recent studies in the *Drosophila* midgut highlight dedifferentiation as a rapid, flexible strategy for adapting to environmental changes, triggered by cues such as nutrient fluctuations and pathogen exposure [82,96,97]. Extending such investigations to diverse organisms, from basal metazoans to mammals, may uncover both conserved and lineage-specific principles of adaptive plasticity.

Among the environmental cues, nutrient availability stands out as a particularly compelling trigger for cell plasticity. In the *Drosophila* midgut, EEs dedifferentiate into ISCs in response to refeeding after starvation, as well as in the newly eclosed adults that naturally resume feeding after the pupal stage [96]. Notably, this nutrient-dependent dedifferentiation occurs irrespective of stem cell loss, indicating that the starvation-refeeding cycle does not merely recapitulate the damage-induced regeneration. Instead, availability of specific nutrients and/or altered dietary regimens likely modulate chromatin environments, thereby inducing cell fate conversion. Similarly, glucose supplementation promotes dedifferentiation of CDCs in human intestinal tumor organoids [160], suggesting that nutrient cues can influence stemness even in pathological contexts. Strikingly, in ctenophores—one of the earliest-branching metazoan lineages—reverse development, potentially involving fate conversion, is observed only after starvation-refeeding cycles [40]. Together, these findings position nutrient fluctuation as a potent, broadly relevant regulator of cellular plasticity

that warrants systematic, cross-species investigation.

A central question is whether a unifying principle governs cell plasticity. As highlighted in this review, diverse environmental cues, such as stem cell loss, injury, infection, and nutritional changes, can trigger local cell-cell communication, which in turn activates downstream transcriptional and epigenetic programs that drive plasticity. The broad involvement of conserved signaling pathways, particularly IL-6 and JAK-STAT, in cellular reprogramming across species underscores the importance of mapping transcription factor binding sites (e.g., STAT) and assessing chromatin accessibility before and after such environmental challenges. Notably, niche-mediated interactions may gradually shift with age. Under chronic stress associated with aging, cellular senescence emerges, characterized by stable cell cycle arrest and a senescence-associated secretory phenotype (SASP) enriched in cytokines such as IL-6 [166]. Paradoxically, senescent cells can promote tissue regeneration by inducing cellular reprogramming *in vivo* [167], as observed in regenerating newt limbs [168], *Hydractinia* whole-body regeneration [54], and reprogrammable mouse models expressing the Yamanaka factors [169,170]. This raises the possibility that age-related alterations in niche interactions—likely driven by senescent cells and their SASP factors—can modulate the extent and quality of cell plasticity.

While the exact molecular machinery likely varies across species, the cellular states that permit fate conversion may be evolutionarily conserved. In the cnidarian *Hydractinia*, cell cycle re-entry is required for acquiring stemness and regenerating a functional polyp [54]. This parallels EB-to-ISC dedifferentiation in the *Drosophila* midgut during pathogenic infection, where EB mitotic re-entry precedes the reappearance of ISC characteristics [82]. Beyond cell cycle reactivation, altering DNA replication dynamics, such as reducing the level or activity of DNA replication component (DNA Polymerase α) can promote dedifferentiation in the *Drosophila* male germline and enhance human iPSC induction [171]. These observations suggest that chromatin remodeling events coupled to cell cycle transitions may provide a conserved mechanistic link between replication/division machinery and reprogramming capacity.

Another open question is whether *de novo* stem cells generated via dedifferentiation are functionally equivalent to resident stem cells. In the regenerating mammalian intestine, dedifferentiation-derived ISCs initially adopt a transcriptional state distinct from that of resident ISCs, yet functionally resemble them, supporting effective regeneration and subsequent tissue maintenance [72,115]. During mouse skin wound healing, differentiated Gata6-lineage-positive cells dedifferentiate into epidermal stem cells that are transcriptionally indistinguishable from resident populations [172,173]. These findings suggest that, in the context of stem cell loss, dedifferentiation-derived stem cells can assume functions comparable to those of resident stem cells. By contrast, when *de novo* stem cells emerge alongside intact resident stem cell pools, their role may differ. Although phylogenetically distant, both *Drosophila* EE-derived ISCs and jellyfish RSPCs, while retaining multipotent capacity, act as transient, lineage-biased stem cells [62,96]. Such specialized stem-like states may represent an adaptive strategy to meet immediate functional demands without permanently altering the resident stem cell pool. Future work comparing the transcriptional and epigenetic landscapes of these transient stem cells with those of resident stem cells will be crucial for defining their unique roles. It will also be important to determine whether similar transient populations exist across a broader range of systems, including mammals.

Finally, translating insights on cell plasticity into medical applications will require a deeper understanding of the balance between its regenerative benefits and oncogenic risks of plasticity. In mammalian epithelia, inappropriate activation of plasticity programs can drive dysplasia and tumorigenesis [76,139]. Dissecting how environmental cues, niche-mediated interactions, and chromatin remodeling tip this balance could enable targeted interventions that harness beneficial plasticity while minimizing malignant potential. Recent advances in

single-cell multi-omics, spatial transcriptomics, and long-term lineage tracing now allow *in vivo* mapping of fate transitions [26]. Integrating such approaches across species with diverse regenerative capacities offers an opportunity to determine whether a universal “plasticity signature” exists and to construct an evolutionary framework that unites the biology of regenerative specialists with that of regeneration-limited species. Such a framework could, in turn, enable synthetic biology approaches, including the exogenous expression of genes unique to highly regenerative animals [174,175] and the transfer of regeneration-specific enhancers [176], ultimately paving the way for developing novel strategies to modulate cell plasticity with potential applications in regenerative medicine and synthetic food production.

Declaration of Competing Interest

The authors declare no competing interests.

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