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Review

Activation of fetal-like molecular programs during regeneration in the intestine and beyond

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SUMMARY

Tissue regeneration after damage is generally thought to involve the mobilization of adult stem cells that divide and differentiate into progressively specialized progeny. However, recent studies indicate that tissue regeneration can be accompanied by reversion to a fetal-like state. During this process, cells at the injury site reactivate programs that operate during fetal development but are typically absent in adult homeostasis. Here, we summarize our current understanding of the molecular signals and epigenetic mediators that orchestrate "fetal-like reversion" during intestinal regeneration. We also explore evidence for this phenomenon in other organs and species and highlight open questions that merit future examination.

INTESTINAL FUNCTION, STRUCTURE, AND HOMEOSTATIC MAINTENANCE

The mammalian intestine is a classic model of regeneration due to its high proliferative capacity and ability to recover from a wide array of injuries. This tissue represents the body's second-largest epithelium and carries out two essential functions: the uptake of nutrients from ingested food and protection against environmental insults.[1] To efficiently mediate nutrient uptake, the small intestine (SI) is organized into millions of crypt-villus units, which have been categorized into five distinct metabolic domains along the length of the organ.[2] Villi, finger-like protrusions covered by a post-mitotic epithelium, extend into the intestinal lumen, where they are exposed to various insults, including high acidity in the proximal part of the SI, ingested toxins, infectious agents, such as microbes, viruses, and parasites, and physical forces, such as friction caused by peristalsis.

Tissue integrity of the intestinal epithelium is maintained through continuous renewal, which occurs every 3 to 5 days in both mouse and human intestine. This turnover is thought to be driven by proliferative crypt-based columnar cells (CBCs), which express Wnt and Notch target genes, such as *Lgr5*[3] and *Olfm4*.[4] Recent studies also suggest that cells located above the crypt base, previously described as transit amplifying (TA) progenitors, may function as stem cells.[5,6] Intestinal stem cells (ISCs) differentiate into mature intestinal epithelial cells (IECs) belonging to the absorptive or secretory lineages.[7] Absorptive cells include enterocyte and microfold cells, which absorb nutrients and sample antigens, respectively. The secretory lineage is composed of several cell types: mucus-secreting goblet cells that lubricate and protect the intestinal surface against microbes, Paneth cells that produce antimicrobial compounds and niche factors for ISCs, chemosensory tuft cells that mediate immune responses, and enteroendocrine (EE) cells that produce hormones to regulate various physiological activities, including appetite.

The balance between self-renewal and differentiation of crypt-localized stem and progenitor cells is controlled by essential signals supplied by the surrounding niche (Figure 1A). The niche is composed of epithelial components, such as Paneth cells,[8] as well as non-epithelial cell types, including mesenchymal, immune, endothelial, and neuronal cells.[9–12] Together, these niche cells provide physical support and secrete growth factors, metabolites, and other signaling molecules, including WNT, R-spondin, Notch, epidermal growth factor (EGF), and BMP ligands.[12–16]

INTESTINAL RESPONSE TO STEM CELL LOSS

Many injuries to the intestine cause damage or loss of ISCs or progenitors, although the intestinal epithelium is surprisingly robust to these perturbations.[22] Initially, it was hypothesized that a rare and quiescent "reserve" stem cell population, located at the +4 position above the crypt base and proposed to be marked by the expression of *Bmi1*[22,23] and other markers, such as *Hopx*, *Lrig1*, *Mex3a*, or *mTert*,[24–27] was responsible for restoring ISCs after intestinal damage. The reserve stem cell model postulated that a quiescent stem cell would be less sensitive to insults than a rapidly proliferating stem/progenitor cell. However, several lines of evidence argue against the idea of a quiescent reserve stem cell. First, the frequency of such cells would be too small to explain the typical scale and speed of ISC restoration.[28,29] Next, multiple studies have shown that the expression of *Bmi1* and other putative reserve stem cell markers is less restricted than previously thought.[30–32] Finally, quiescent or label-retaining cells found at the +4 position have been shown to represent EE/tuft cell progenitors.[33,34] Together, the data indicate that additional cell types and mechanisms contribute to restoring ISCs after injury or loss.

Over the past decade, compelling evidence has accumulated for a model of intestinal repair based on the concepts of cell

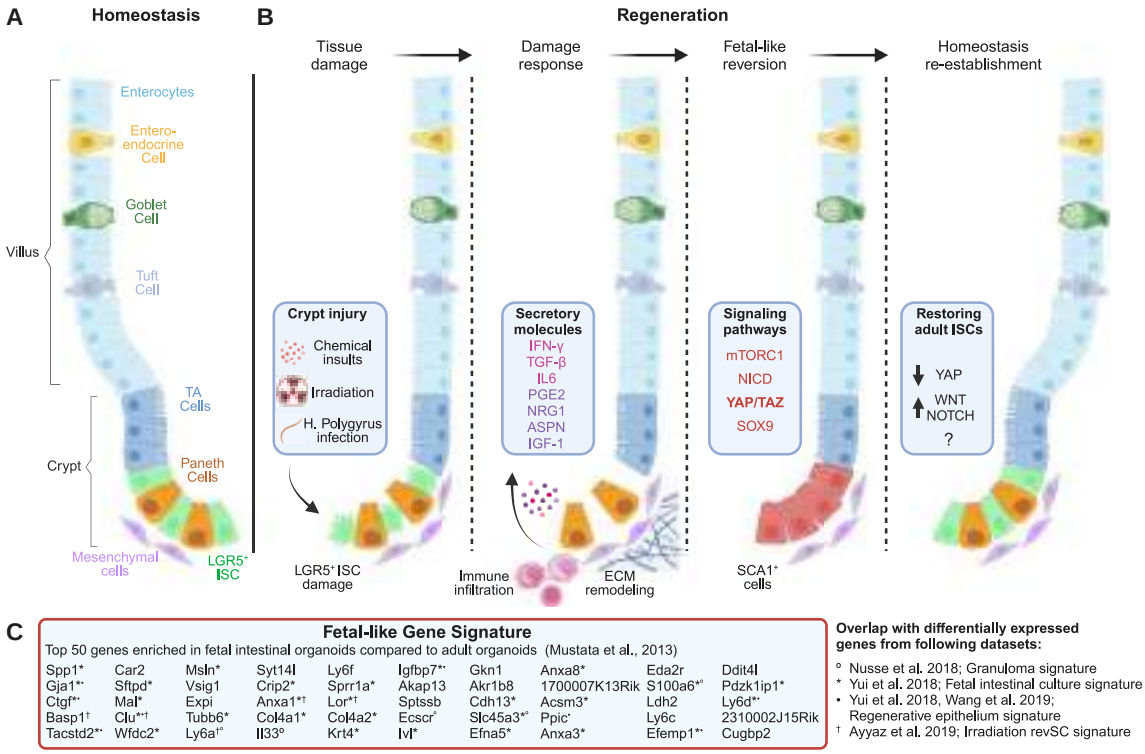

Figure 1. Overview of fetal-like reversion during intestinal regeneration

(A) The homeostatic small intestine epithelium is composed of crypt-villus units. Crypts contain LGR5$^+$ ISCs, Paneth cells, and transit-amplifying (TA) cell progenitors. The villi contain IECs belonging to the secretory (goblet, enteroendocrine, and tuft) and absorptive (enterocytes) cell lineages.

(B) Many injuries of the small intestine involve the loss of crypt-based proliferative cells. Signals from infiltrating immune cells, surrounding mesenchyme, restructured extracellular matrix (ECM), or surviving epithelial cells activate a distinct transcriptional response marked by expression of *Ly6a* (SCA1) and other genes expressed by fetal epithelial intestinal organoid cultures. This gene expression program is regulated by mTORC1 and Notch signaling (NICD, Notch-intracellular-cleaved domain) and driven by YAP/TAZ and SOX9 transcription factors. It is currently unknown how fetal-like reprogramming is resolved to re-establish tissue homeostasis, but this process likely involves downregulation of YAP signaling and restoration of canonical ISC signals (e.g., Wnt/Notch signaling).

(C) Fetal-like signature genes; the top 50 differentially expressed genes enriched in the initial report comparing fetal intestinal spheroids to adult enteroids by Mustata et al.[17] Symbols denote genes that were also found to be differentially expressed in several regenerative signatures (°Nusse et al.,[18] ●Wang et al.[19] /Yui et al.,[20] and †Ayyaz et al.[21]) or in a second dataset comparing fetal and adult intestinal cultures (*Yui et al.[20]).

plasticity and dedifferentiation.[35] Lineage-tracing studies employing inducible Cre-drivers marking the two main intestinal lineages have demonstrated that both secretory[33,36,37] and absorptive[38,39] progenitors can restore ISCs and contribute to regeneration following their loss. Subsequent studies showed that differentiated IECs, such as EE [30] and Paneth cells,[40,41] also contribute to restoring crypt-based ISCs during regeneration. While these studies revealed that ISCs can arise from various lineages following damage, the molecular mechanisms and cellular intermediates underlying this process have remained unclear.

FETAL-LIKE REVERSION AS A PARADIGM FOR REPAIR AFTER INJURY

The concept of fetal-like reversion was initially proposed as a regenerative mechanism in the SI of mice infected with the helminth *Heligmosomoides polygyrus* (*Hp*).[18] As part of their life cycle, *Hp* larvae disrupt the intestinal barrier by invading the subserosal layer and generating inflammatory granulomas below SI crypts.[42] Surprisingly, epithelial cells in granuloma-associated crypts (GACs) downregulated the transcriptional signature of *Lgr5*$^+$ ISCs and mature IEC lineages. Despite the absence of expression of canonical ISC markers (*Lgr5*, *Olfm4*), GACs were hyperproliferative, and epithelial integrity was maintained, indicating retention of self-renewal capacity. RNA sequencing (RNA-seq) analysis of GACs and non-granuloma crypts showed that cells in GACs upregulated expression of *Ly6a* (also referred to as Stem Cell Antigen-1, or SCA1) along with a suite of genes that had previously been characterized as enriched in fetal intestinal epithelial cultures, compared with enteroids generated from adult intestinal cells.[17,43] In addition to this fetal organoid gene signature, cells isolated from GACs and cultured in standard organoid conditions generated smooth spheroids, similar to those formed by fetal epithelial cells, in contrast to the budding enteroids typically formed by adult ISCs.[44] These spheroid cultures could be stably passaged and expressed high levels of fetal organoid markers (e.g., *Ly6a*, *Il33*, *Gja1*, *Spp1*, *Tacstd2*, and *Sprr1a*). Similar to *in vitro* cultures derived from fetal intestine, which do not require canonical Wnt signaling to maintain stem cells,[17,43] spheroids generated from GACs were insensitive to R-spondin1 withdrawal, indicating that SCA1$^+$ GAC cells had adopted and retained a distinct stem cell state from homeostatic adult ISCs. This study also showed that re-entering into a

Table 1. Comparison of *in vivo* injury models in which a fetal-like regenerative response has been observed

Injury type	Tissue	Domain/cell type	Implicated pathway	Reference
H. polygyrus infection (granuloma stage)	small intestine	crypt	IFN-γ	Nusse et al.[18]
DSS damage	colon	crypt	ECM/mechanotransduction, FAK/Src, YAP/TAZ, gp130/IL6, and NRG1	Yui et al.,[20] Ayyaz et al.,[21] Taniguchi et al.,[46] and Lemmetyinen et al.[47]
Radiation damage	small intestine	crypt (proliferating cells)	YAP, IFN-γ, Tgf-β, prostaglandin E2, and NRG1	Gregorieff et al.,[48] Nusse et al.,[18] Ayyaz et al.,[21] Roulis et al.,[49] Malagola et al.,[6] Chen et al.,[50] and Lemmetyinen et al.[47]
Lgr5 ISC ablation	small intestine	crypt (Lgr5 + ISCs)	YAP and IFN-γ	Nusse et al.,[18] Ayyaz et al.,[21] and Singh et al.[29]
Chemotherapy (5-FU)	small intestine	crypt (proliferating cells)	asporin, Tgf-β, Wnt/Rspo, and NRG1	Iqbal et al.,[45] Palikuqi et al.,[9] and Jardé et al.[51]
Poly I:C	small intestine	villus (enterocytes)	YAP, prostaglandin E2, and gp130/IL11/IL6	Ohara et al.[52]
H. polygyrus infection (luminal stage)	small intestine	crypt and villus	YAP and oxidative stress	Karo-Atar et al.[53]
Biopsy wound	colon/rectum	crypt	prostaglandin E2 and YAP	Miyoshi et al.[54] and Ohara et al.[52]

"fetal-like" stage represented a generalized mechanism by which intestinal crypts remodel to sustain function following multiple kinds of injury. A concurrent publication described a similar mechanism in the repair of colon epithelial damage induced by dextran sulfate sodium (DSS),[20] reporting that regenerating colon epithelial cells displayed a striking enrichment in the expression of fetal-like markers, including *Ly6a*, *Anxa1*, and *Tacstd2*. Importantly, expression of these fetal markers was also enriched in tissue samples from ulcerative colitis patients, suggesting that fetal-like reprogramming may play a role in human intestinal pathologies.

Subsequent studies have confirmed the presence of a fetal-like transcriptional state in response to a wide spectrum of ISC/crypt injuries, including ionizing radiation, diphtheria toxin-mediated ISC ablation, and chemotherapy[6,9,21,29,45] (Figure 1B; Table 1). The use of bulk and single-cell RNA-seq technologies has helped to further refine the fetal-like transcriptional signature and elucidate the kinetics of this regenerative response. Many genes that were initially identified as part of the fetal organoid gene signature[17] are recurrently upregulated or enriched in different injury contexts (Figure 1C). However, it remains to be determined exactly which members of this signature are commonly expressed across all intestinal injuries and which ones may be unique to specific types of regeneration.

In addition to injuries that primarily affect the crypt, fetal-like reversion has also been described in a villus model of intestinal injury. Using poly(I:C) treatment to mimic acute viral gastroenteritis, the authors showed that regenerating villi contain IECs that are morphologically distinct from mature enterocytes found in control-treated mice.[52] These "atrophy-induced villus cells" (aVECs) exhibit a fetal-like transcriptional program, which is co-expressed with enterocyte-specific markers. Additionally, a study demonstrated that the luminal stage of *Hp* infection, in which *Hp* adult parasites reside among SI villi, also activates a fetal-like gene signature marked by *Clu*, *Anxa1*, *Il1rn*, and *Msln* expression[53] (Table 1). Overall, these results indicate that adult intestinal cells in both crypt and villus domains can reactivate gene expression programs also present during intestinal development and that conversion to a fetal-like state represents a core program in the context of intestinal regeneration.

SIGNALING PATHWAYS THAT INDUCE FETAL-LIKE REVERSION

Since the identification of fetal-like reversion, considerable attention has been directed toward uncovering the signaling pathways that drive this process. Interferon (IFN)-γ signaling was identified initially as a mediator of this state.[18] IFN-γ$^+$ lymphocytes accumulate in *Hp* granulomas, and IFN-γ is required for induction of *Ly6a*, a key marker of the fetal-like state (Table 1). However, IFN-γ signaling was not implicated in the loss of adult ISC genes, as *Lgr5* expression was still downregulated in IFN-γ-null mice during *Hp* infection, indicating that other signaling pathways cause loss of mature epithelial identity. In the DSS-damaged colon, fetal-like gene expression coincided with upregulated integrin signaling and elevated expression of focal adhesion kinase and steroid receptor coactivator (FAK/Src) and extracellular matrix (ECM) components (Table 1).[20] These data suggest that regenerating cells may sense the altered mechanical properties of DSS lesions, which are surrounded by a dense network of collagen I. Indeed, YAP/TAZ, the transcriptional mediators of the mechanosensing Hippo signaling pathway, were activated (i.e., YAP displayed nuclear localization) in the regenerating epithelium (Table 1). In line with a role for mechanical properties in the induction of the fetal-like phenotype, culturing SI organoids in collagen I resulted in a fetal-like spheroid phenotype *in vitro*. As with SI spheroids generated from GACs, spheroids that formed in collagen I cultures expressed fetal-like markers (*Sca1*, *Anxa1*) and had decreased expression of adult ISC and differentiated IEC lineage genes. The addition of Wnt3a was critical for spheroid growth in collagen I cultures. These findings extend the previously described interplay between YAP and Wnt signaling in intestinal regeneration.[48] After radiation damage, regenerating crypts had high levels of nuclear YAP localization, and this led to repression of Wnt targets and ISC genes (*Lgr5*, *Olfm4*) and activation of YAP targets including *Clu, Il1rn*, and *Areg*. Importantly, these genes are often co-expressed by

cells expressing *Ly6a, Anxa1*, and other fetal culture markers.[21] In fetal-like reversion following villus injury, Hippo signaling was also implicated as a key driver of regeneration, as nuclear YAP and expression of YAP target genes were enriched in aVEC cells, and villus recovery was impaired in YAP-deficient epithelium (Table 1).[52] Overall, these observations are consistent with data demonstrating that activation of YAP is required for the maintenance of the fetal epithelial state and that its expression is transiently required in intestinal development and regeneration.[48,55–57]

Recent research has shed a light on the upstream factors that induce fetal-like reprogramming. Along with mechanical forces,[58] paracrine factors from mesenchymal cells regulate YAP activity during intestinal regeneration. Multiple studies have highlighted the role of prostaglandin E2 (*PGE2*) as a regulator of YAP in the intestine.[59] PGE2 is secreted by a stromal population of pericryptal prostaglandin-endoperoxide synthase 2 (PTGS2)-expressing fibroblasts, signals through Prostaglandin E Receptor 4 (PTGER4), and drives the expression of *Ly6a* and other fetal markers by promoting the dephosphorylation and nuclear translocation of YAP (Table 1).[49] The importance of PGE2 signaling has also been characterized in wound-associated epithelial cells in the colonic epithelium[54], which share features with cells undergoing fetal-like reversion (e.g., expression of *Clu* and other members of the fetal gene signature and nuclear YAP localization) and in villus injury repair.[52] Furthermore, in the absence of mesenchymal PGE2 production, epithelial-autonomous production of PGE2 induces dedifferentiation to a developmental state.[60] During injury response following fluorouracil (5-FU) treatment, pericryptal mesenchymal cells also upregulate the proteoglycan asporin (*Aspn*), which promotes fetal-like reversion and tissue regeneration (Table 1). *In vitro*, recombinant ASPN induces spheroid morphology, SCA1 expression, and activates a fetal-like transcriptional profile.[45]

Fibroblast-derived EGF family ligands neuregulin 1 (NRG1) and epiregulin (EREG) are also implicated in fetal-like reprogramming during intestinal regeneration.[47] Upon DSS damage or irradiation, the expression of NRG1 and EREG is upregulated (Table 1). EREG is expressed by stromal and epithelial cells, whereas NRG1 expression is restricted to stromal fibroblasts. *In vitro* experiments involving the treatment of SI organoids with NRG1, but not EREG or EGF, resulted in increased expression of fetal-like markers *Ly6a*, *Sprr1a*, and *Areg* and led to an enrichment of a YAP-induced gene set. However, NRG1 did not induce spheroid morphology or activate *Clu* expression, and NRG1-treated organoids remained dependent on R-spondin1, indicating that NRG1 alone is not sufficient to fully convert intestinal cells to a fetal-like state.[47] Another study also identified elevated levels of NRG1 following radiation and 5-FU injury (Table 1). In this context, *Nrg1* expression was upregulated in PDGFRα+ mesenchymal cells but also in macrophages and Paneth cells, suggesting that signals from stromal, immune, and epithelial compartments can synergize during crypt regeneration.[51]

Beyond IFN-γ, additional immune cell-secreted inflammatory signals have been implicated in reparative processes. Interleukin 6 (IL-6), a pro-inflammatory cytokine produced by myeloid cells during injury, signals through receptor gp130 and Src family of kinases (SFKs) to activate YAP and Notch during colonic regeneration[46] (Table 1). Notch signaling is activated in intestinal regeneration following DSS[61] and radiation,[40] and ectopic activation of this pathway plays a role in Paneth cell dedifferentiation and regeneration in the SI.[40,41] In intestinal organoid cultures, activation of Notch signaling via expression of the Notch-intracellular-cleaved domain (NICD) in the context of p53 loss results in a fetal-like reversion phenotype, including spheroid morphology, increased proliferation, downregulation of ISC markers (*Lgr5*, *Ascl2*), upregulation of fetal/regenerative markers and nuclear YAP localization.[62] Expression of gp130 cytokines (IL6, IL11) is also increased during villus regeneration in the SI[52] (Table 1). Transforming growth factor β1 (TGF-β1), secreted by monocyte/macrophages during SI repair of radiation damage, contributes to fetal-like reprogramming.[50] TGF-β1 signals through TGFBR2 on epithelial cells to activate a YAP-SOX9 circuit that is both necessary and sufficient to induce regeneration and fetal-like reversion (Figure 1B; Table 1). Importantly, treatment of intestinal organoids with TGF-β1 induces spheroid morphology and improves organoid engraftment efficiency in DSS-damaged colon tissue, indicating that activation of fetal-like reversion through inflammatory or other signals may be a potential avenue for improving cellular therapies for intestinal pathologies. Mesenchymal *Aspn* signaling also activates TGF-β signaling via CD44,[45] which is upregulated by epithelial cells during injury response, suggesting that immune and mesenchymal signals work together to induce fetal-like reversion in the epithelium.

In summary, activation of the fetal-like transcriptional signature can be triggered by many upstream signals that are produced by epithelial and stromal cell types and appear dependent on the type of injury. These signals seem to converge upon the activation of YAP, a central driver of the fetal-like transcriptional signature.

EPIGENETIC REPROGRAMMING IN FETAL-LIKE REVERSION

During intestinal development and differentiation of adult ISCs into mature IECs, intestinal cells undergo changes in gene expression that are underpinned by changes in chromatin structure, histone modifications, and methylation patterns. This progression has been elegantly described in a study that profiled, in parallel, the transcriptional programs and chromatin remodeling events of the developing (E12.5, E14.5) and differentiating (adult ISC, adult villus) mouse intestinal epithelium.[63] The authors defined an ''embryonic epithelium signature'' of 1,070 genes, which were expressed during fetal development and downregulated in adult IECs. As development progressed, many of these genes lost histone marks associated with active gene expression (H3K27Ac, H3K4me3), whereas only a subset of these genes gained repressive marks (H3K27me3), and very few genes were silenced by DNA methylation. These data suggest that the epigenetic landscape of the adult intestinal epithelium remains relatively permissive to reactivation of embryonic gene expression programs.

Differences between fetal and adult transcriptional programs and epigenetic landscapes have also been explored using *in vitro* fetal spheroid and adult organoid models. Fetal and adult intestinal organoids have a similar 3D chromatin structure and

few changes in promoter accessibility but display differences in enhancer usage (i.e., methylation or accessibility at enhancers). These enhancers show enrichment for transcription factor (TF) binding sites corresponding to distinct TF networks between fetal and adult tissues; fetal epithelium shows enrichment for motifs associated with Activator Protein-1 (AP1), Transcriptional Enhanced Associate Domain (TEAD), SOX, and nuclear factor κB (NF-κB) TFs,[55] which are known to form complexes with YAP/TAZ.[64] In adult SI organoids in which fetal-like reversion was induced with recombinant TGF-β1 treatment, genomic regions with increased accessibility were also enriched in binding sites for many of the same TF families (SOX, TEAD, SMAD),[50] highlighting parallels between TF networks that regulate gene expression programs in the developing and regenerating intestine.

Histone modifiers have also been implicated in regulating intestinal maturation and fetal-like reversion. Lysine-specific histone demethylase 1A (LSD1) has been identified as a repressor of fetal/neonatal gene expression, as epithelial cells from SI crypts of *Lsd1*-knockout mice displayed an enrichment of fetal-like gene signatures.[65] Comparison of gene expression in *Lsd1*-knockout epithelium to embryonic and early postnatal timepoints showed that LSD1 loss renders the epithelium "stuck" in an early postnatal stage, likely through regulating H3K4me1/2 levels of developmental genes.[65] Furthermore, this study showed that *Lsd1* expression is decreased during radiation injury response. Similarly, aberrant activity of histone methyltransferase polycomb repressive complex 2 (PRC2), induced by NF-Kappa-B Inhibitor Alpha(IκBα)-deficiency, causes a fetal-like phenotype in ISCs, resulting in increased expression of fetal-like genes and spheroid formation *in vitro*.[66]

Pharmacological manipulation of histone-modifying enzymes is sufficient to induce fetal-like reversion in adult intestinal organoids. An organoid culture system with a defined 8 component medium ("8C") prompted striking changes to organoid morphology, including hyperplastic crypts, reduced expression of mature IEC lineage markers, and induction of a fetal-like gene signature *in vitro*. Using this model, two components—Valproic Acid (VPA) and EPZ-6438, inhibitors of histone deacetylases and histone methyltransferase EZH2, respectively—were identified as the major drivers of this phenotype.[67] Treatment of SI organoids with these compounds led to a global reduction in H3K27 trimethylation and an increase in H3K27 acetylation. Specifically, H3K27me3 was reduced at YAP target genes, suggesting that epigenetic mechanisms contribute to YAP-dependent fetal-like reprogramming. Interestingly, in the context of IκBα-deficiency, inhibition of EZH2 with EPZ-6438 led to an upregulation of ISC and mature IEC genes and partially restored crypt budding *in vitro*.[66] The discrepancy between the effect of EPZ-6438 treatment in these two studies suggests that, although histone-modifying enzymes play an essential role in developmental reprogramming, their effect is dependent on the genetic or signaling context. An *in vitro* study comparing fetal and adult organoids also highlighted a role for chromatin remodelers *Smarca4* and *Smarcc1*, members of the SWI/SNF complex, as gatekeepers of intestinal maturation.[68] Genetic inactivation of these factors in fetal spheroid cultures led to downregulation of fetal genes (*Ly6a*, *Anxa1*, and *Tacstd2*) and upregulation of markers of mature epithelium. Whether the SWI/SNF complex is also implicated in chromatin remodeling during fetal-like reversion of adult epithelium remains to be explored.

Epigenetic reprogramming is known to underlie Yamanaka factor (*Oct4*, *Sox2*, *Klf4*, and *c-Myc*; OSKM)-mediated dedifferentiation of somatic cells into induced pluripotent stem cells.[69] Transient activation of OSKM in the intestinal epithelium mimics an injury response, leading to a hyperplastic state marked by increased proliferation, reduced expression of adult ISC and mature lineage markers, enrichment of a fetal-like signature, and induction of spheroid morphology *in vitro*.[60] Forced expression of these factors in adult intestinal epithelium induces two distinct fetal-like cell states *in vivo*, one that mirrors the classic fetal-reversion state observed in crypt injury models (*Ly6a*, *Clu*, *Anxa1*) and one that retains a villus ("aVEC-like") epithelial identity. These findings suggest that the same transcriptional regulators can induce reprogramming into two distinct fetal-like states based on the affected cell's pre-existing epigenetic context or signaling environment along the crypt-villus axis. Further characterization of epigenetic regulators in fetal-like reversion of adult IECs and their pharmacological manipulation during injury response represent exciting future directions for the field. How upstream signal transduction pathways orchestrate epigenetic reprogramming machinery to achieve fetal-like reversion is an important open question.

FETAL-LIKE REVERSION MEDIATES REGENERATION ACROSS TISSUES AND SPECIES

Compared with mammals, other vertebrate lineages, such as salamanders and teleost fishes, have a more extensive ability to regenerate tissues, including whole limbs. Studies in these model organisms have demonstrated that developmental transcriptional programs are activated during tissue regeneration. During axolotl limb regeneration, heterogeneous cells from the adult connective tissue reprogram themselves into a homogeneous and transient blastema progenitor state, in which adult gene expression programs are lost, whereas embryonic limb marker expression is activated, particularly in later stages of regeneration[70] (Figure 2A). In zebrafish, which have a robust regenerative capacity in several tissues, including the heart, regeneration also proceeds via developmental reprogramming. Following ventricular apex resection or cryoinjury, embryonic regulators of cardiogenesis (e.g., *Gata4*) are re-expressed,[71] and regenerating adult cardiomyocytes activate gene expression and metabolic programs similar to those observed in embryonic cardiomyocytes[72] (Figure 2B).

Although the regenerative capacity in mammals is less extensive and differs across organs, multiple lines of evidence indicate that tissues beyond the intestine reactivate developmental programs during injury repair. For example, enrichment of a fetal-like signature during regeneration has been observed in the epidermis. Transcriptomic comparison of the developing epidermis (E13.5) with adult skin collected 7 days after biopsy wounding showed a significant overlap between E13.5 and wound-edge gene signatures.[73] The shared signature was driven by SOX11 and SOX4, and genes regulated by these TFs encode important players in ECM organization, cell migration, and embryonic morphogenesis (Figure 2C).

In the stomach, there are parallels between fetal gastric epithelium and regenerating adult stomach tissue, with similar

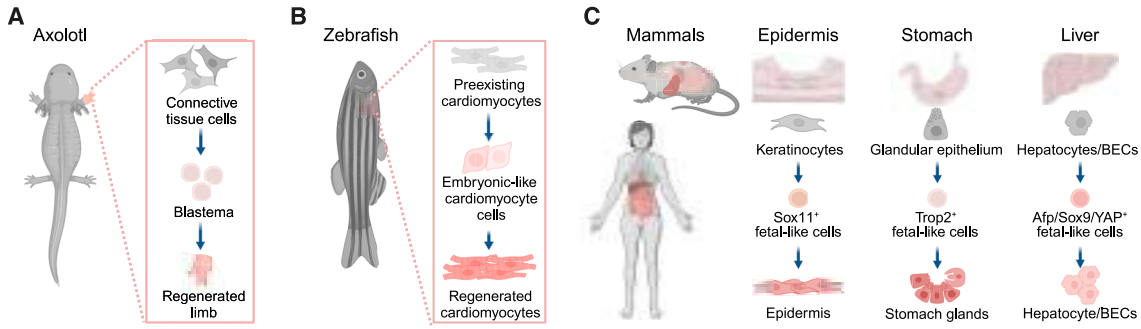

Figure 2. Fetal-like reversion during tissue regeneration is conserved across species and organs

(A) An embryonic-like blastema forms through the dedifferentiation of connective tissue fibroblasts during axolotl limb regeneration.

(B) In zebrafish heart regeneration, surviving cardiomyocytes dedifferentiate into an embryonic-like state, evident at gene expression and metabolic levels.

(C) In mammals, the process of adult epithelial cells undergoing developmental reprogramming into a fetal-like state contributes to regeneration in various tissues, including the epidermis, stomach, and liver.

markers and phenotypes as those observed in the intestine.[74] During development, cells expressing *Tacstd2* (also known as TROP2) isolated from the distal fetal stomach generate spheroids when cultured *in vitro*. In adult mice, TROP2 expression becomes undetectable in homeostatic tissue but is reactivated after LGR5^{+} stem cell loss or indomethacin-induced injury. TROP2^{+} cells in the regenerating adult stomach display an embryonic transcriptional signature (Figure 2C). Examination of injury repair in multiple tissues of the digestive tract, including the stomach and pancreas, led to the identification of a regenerative mechanism termed "paligenosis," which shares features with fetal-like reversion.[75,76] Studies of gastric and pancreatic metaplasia following injury have identified a coordinated program driven by modulation of mTORC1 expression. During injury repair, downregulation of mTORC1 promotes autophagy to degrade cellular machinery of differentiated cells, whereas subsequent upregulation allows cells to exit their differentiated state and re-enter the cell cycle.[75] In the pancreas and stomach, this process is dependent on two genes, *Ddit4* and *Ifrd1*.[77] Paligenosis also involves reactivation of embryonic or wound-healing genes, including well-characterized markers of intestinal fetal-like reversion, such as *Sox9*, *Clu*, *Cd44*, and nuclear YAP.[78] It remains to be determined whether all features of paligenosis, including *Ifrd1* and *Ddit4* expression, perturbations in mTORC1 expression, and activation of autophagy coordinately orchestrate intestinal regeneration in the same way as in the stomach and pancreas. However, several lines of evidence suggest that these genes and pathways are important for the intestinal injury response. For example, *Ifrd1* levels are increased following jejuno-ileal resection,[79] and loss of *Ifrd1* results in a "blunted" regenerative response, characterized by decreased crypt proliferation, crypt depth, and villus height, after partial SI resection.[80] *Ddit4* also seems to play a role in intestinal regeneration following chemotherapy, as *Ddit4*$^{-/-}$ mice display poorer regeneration following doxorubicin treatment compared with wild-type mice.[81]

The importance of mTOR signaling in the intestinal injury response has also been established. Following radiation damage, mTORC1 activity is increased during crypt repair through IGF1 signaling from mesenchymal cells.[82] Pharmacological inhibition of mTOR with rapamycin or intestinal-specific deletion of *mTOR* or *Rptor* impedes SI regeneration.[82,83] Surprisingly, however, calorie restriction, which also inhibits mTORC1 signaling, seems to have a protective or pro-regenerative effect on IECs following radiation or chemotherapy treatment.[81,84] Although these studies highlight the importance of mTORC1 in intestinal regeneration, they suggest that dynamic regulation of this signaling pathway is needed for proper repair. Interestingly, loss of mTORC1 signaling activates fetal-like reversion in intestinal organoid cultures.[85] Genetic deletion of *Rptor* in the intestinal epithelium (VilCre^{ERT2};Rptor$^{fl/fl}$) activated a ZAKα-SRC-YAP axis and led to spheroid morphology, loss of ISC and mature intestinal markers, and upregulation of fetal markers (*Tacstd2*, *Sca1*, *Spp1*, and *Cnx43*), in concert with metabolic rewiring.[85] Given this finding, it is likely that temporal control of mTORC1 levels is necessary to activate fetal-like reversion during regeneration and subsequently allow the tissue to return to homeostasis, as described in the paligenosis process in other tissues of the digestive tract.

Although not highly proliferative during homeostasis, the liver is one of the most regenerative mammalian organs. The most striking example of its regenerative capacity is partial hepatectomy (PHx), after which the liver can regenerate two-thirds of its mass in as few as 5–7 days in rodents and within 3 months in humans.[86] Epithelial cells of the liver also proliferate in response to chemical insults, and several studies point to a role for developmental reprogramming, mediated by YAP signaling, in this regenerative process. Single-cell RNA-seq profiling of liver epithelium following 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) treatment, a model of chronic liver injury, showed that regenerating biliary epithelial cells activate a YAP-driven transcriptional program.[87] These cells express high levels of *Tacstd2*, *Cd44*, and other Wnt target genes, and they downregulate expression of mature epithelial markers. Similarly, a subset of hepatocytes also upregulates YAP signaling and gets reprogrammed into a progenitor-like state. In a separate study comparing DDC-treated hepatocytes and fetal hepatocytes from E18 livers, the authors showed that regenerating cells downregulate expression of mature hepatocyte genes associated with metabolic and biosynthetic processes and coordinately upregulate neonatal-like genes associated with cell cycle and growth factor signaling.[88] Mechanistically, this process was driven by altered translation of splicing factors, which induced a neonatal-like splicing program, particularly in Hippo pathway

components. Alternatively, spliced isoforms found in development and after injury resulted in higher transcriptional activity of YAP1 and TEAD1, promoting proliferating during regeneration. Finally, reprogramming of hepatocytes to a developmental state termed "liver-progenitor-like cells" (LPLCs) has also been observed after DDC injury.[89] In this study, the authors showed that injury-induced LPLCs upregulated a transcriptional program similar to that observed in embryonic hepatoblasts, marked by expression of *Sox9*, *Sox4*, *Spp1*, and *Cd44*. The induction of this program was dependent on IL-6 secreted by macrophages, a signal that similarly induces dedifferentiation in the intestinal epithelium. In this context, IL-6 signaling activated STAT3, as well as YAP, though to a lesser extent. Interestingly, STAT3 has also been shown to interact with YAP during intestinal regeneration following DSS damage.[90]

Fetal-like reversion in hepatocytes has also been observed following acute chemical injury and PHx. After acetaminophen intoxication, hepatocytes at the interface of damaged and non-damaged zones of liver lobules showed a transient but distinct gene expression signature characterized by genes implicated in liver development (*Afp*, *Spp1*, and *Cdh17*).[91] Similarly, single-cell RNA-seq and ATAC-seq analysis of hepatocytes 48 h after PHx identified a subset of cells with fetal-like features.[92] These cells upregulated expression of developmental progenitor markers (*Afp*, *Sox9*, *Yap*, and *Igf2bp3*) and displayed enrichment in differentially accessible (DA) regions associated with embryonic development and cytoskeleton reorganization and a depletion in DA regions associated with biosynthetic and metabolic processes[92] (Figure 2C). Additionally, as in the case of the intestine, induced partial reprogramming of hepatocytes with OSKM also activated a fetal-like program, which mirrored many of the hallmarks observed during injury response in other models.[93] Transient OSKM activation in hepatocytes *in vivo* led to the downregulation of mature hepatocyte gene expression programs, upregulation of genes (*Afp*) and TFs (*Gata4*, *Gata6*, *Foxa2*, and *Sox9*) expressed during liver development, and improved regeneration after CCl_4-mediated acute liver injury.

On the opposite end of the regenerative spectrum from the liver, the mammalian adult heart exhibits very low regenerative capacity. However, reactivation of fetal-like programs in cardiomyocytes by overexpression of key TFs induces dedifferentiation and potentiates regeneration even in this tissue. As in the intestine[60] and liver,[93] transient activation of OSKM in adult cardiomyocytes induced a gene expression program that overlapped with that of embryonic (E14.5) cardiomyocytes, activated proliferation, and improved regeneration following myocardial infarction.[94] Strikingly, conditional overexpression of an active form of YAP (YAP5SA) was sufficient to reprogram cardiomyocytes to a proliferative, fetal-like state.[95] Overall, these studies highlight parallels between the hallmarks and molecular mediators of fetal-like reversion in the intestine and other tissues.

OUTSTANDING QUESTIONS AND FUTURE PERSPECTIVES

Even though many regulators of fetal-like reversion have now been identified, it remains unclear which cell lineages give rise to fetal-like cells during regeneration and how this state is resolved when the intestinal epithelium returns to homeostasis. Lineage-tracing studies have shown that the secretory cells marked by *Neurog3*[29] or *p57*[33] expression activate a fetal-like transcriptional program during dedifferentiation following crypt injury. Given that this regenerative program is conserved across many types of intestinal injury, it is likely that any epithelial cell exposed to the appropriate signals after damage can undergo fetal-like reversion. This hypothesis could help explain why such widespread plasticity has been observed using various Cre lineage-tracing models in the intestine. Possibly, cells of various lineages marked prior to damage transition through the fetal-like regenerative state and contribute to regeneration. However, whether all IEC lineages at the site of damage have equipotent potential to "revert" to a fetal-like state or whether certain cell types are more predisposed remains to be determined. Similarly, we do not know how the regenerative state is resolved and homeostatic lineage composition is restored. Answering these questions will require the coupling of advanced lineage-tracing tools with temporally resolved transcriptomic datasets to track cell fate transitions during regeneration. The use of mouse models with clonal barcode diversity should enable high-resolution study of lineage relationships and their molecular signatures in various injury contexts.[96] Additionally, spatial transcriptomics or proteomic methods offer promise for unraveling the molecular mechanisms that govern cell-cell and cell-niche interactions during intestinal regeneration. Although many upstream signals that activate the fetal-like transcriptional state have been uncovered, it remains unknown how this program is turned off once an injury is resolved. In intestinal crypts, this process likely requires a coordinated downregulation of YAP transcriptional activity and restoration of Wnt and Notch signals that sustain homeostatic ISCs.[97] Evidence from organoid studies also suggests that retinoid X receptor (RXR) signaling controls IECs' exit from the regenerative or fetal-like state[98]. However, the full ensemble of cell-intrinsic and -extrinsic mechanisms that orchestrate this process, especially *in vivo*, remain to be elucidated.

Another pending question is how surviving epithelial cells sense the loss of ISCs or the disruption of the epithelial barrier. Undoubtedly, different types of damage produce distinct signals and cellular responses, but it is unclear whether specific metabolites might be released and sensed by IECs in distinct injury contexts. Since apoptosis is implicated in both crypt and villus injury models, it is plausible that cell death could be a triggering signal for dedifferentiation or fetal-like reversion. The molecules released by apoptotic cells act as messengers and mediate inflammatory reactions, cell survival, and tissue regeneration.[99] For example, in a colorectal tumor model, cells undergoing apoptosis caused by chemotherapy treatment released ATP, which mediated an mTOR-dependent pro-survival program in neighboring cancer cells.[100] Whether a similar mechanism is at play in normal epithelial cells during regeneration remains to be determined. Exploring fetal-like reversion through the lens of metabolomics could also offer important clues into the signals that activate this program. An air-liquid interface culture model of fetal-like reversion, which has already been used to describe a role for hypoxia and ER stress in this process in the colon,[19] could be used to investigate the role of specific metabolites and other environmental signals, including cytokines and microbe-secreted products.

There is debate as to whether the fetal-like gene signature constitutes a bona fide return to a developmental state or whether it is an ectopic state activated by injury.[29] The initial observations of fetal-like reversion after *Hp* infection and DSS injury were based on comparisons to a gene expression profile generated from fetal organoid cultures[17,43] rather than primary fetal tissue. Although both fetal and adult organoid cultures recapitulate the gene expression profiles of their *in vivo* counterparts,[55] the increasing availability of high-resolution single-cell datasets from embryonic intestine[101,102] will enable a more direct comparison between cell types found during development and those that arise during regeneration. Recent data[101] show that a subset of epithelial cells in development express the canonical fetal-like gene signature. The specific function of these cells in the embryo is unknown. A deeper characterization of the role of these cells, their location within the tissue, and their developmental trajectory may provide better insight into the function of the fetal-like signature during regeneration.

To date, most studies interrogating fetal-like reversion have been conducted in murine models, although studies suggest that human intestinal tissues can also activate a fetal-like program during intestinal regeneration.[20,50] Further exploring this phenomenon in the human context represents a critical future direction. Published single-cell datasets of human fetal intestine[103,104] will facilitate the definition of a human intestinal fetal gene signature, which can serve as a benchmark for investigating whether adult human tissue truly reverts to a fetal-like state. Irrespective of the degree of homology between the fetal and regenerating intestine, deeper characterization of the transcriptional and epigenetic mechanisms implicated in human development and intestinal injury responses will advance our understanding of intestinal pathologies and may lead to the identification of therapies that could augment intestinal regeneration.

Finally, it seems that many of the hallmarks of fetal-like reversion observed during intestinal regeneration are also found in other tissues, particularly those associated with the digestive tract (stomach, liver), and also in the skin. Additional comparisons of cell populations and transcriptional programs found in development and regeneration of other organs will allow us to better understand the shared and divergent features of fetal-like reprogramming across tissues and species. Recent studies[105,106] suggest that developmental reprogramming, mediated by YAP, is active in the human skin and liver during injury response. In the human skin, pharmacological YAP activation promoted regenerative repair of cutaneous wounds and induced phenotypes associated with "youthful" skin, suggesting that developmental reprogramming may be beneficial for regeneration.[105] By contrast, a dysregulated fetal-like program, marked by high expression of SOX9, YAP1, and IGF2BP3, was observed in human tissues from patients with acute liver failure.[106] This phenotype closely mirrored the fetal-like program that is activated in regenerating murine hepatocytes.[92] This and other studies suggest that activation of a fetal-like state can be a double-edged sword, which needs to be carefully regulated. It is likely that after an injury, reactivation of developmental gene expression programs that are utilized during the initial "construction" of tissues allows for rapid re-epithelization and maintenance of barrier integrity. However, failure to properly restore homeostatic function can lead to pathogenesis (i.e., organ failure, aberrant proliferation, and cancer).[48,59,76] In fact, several studies have demonstrated that fetal-like reprogramming is a feature of oncogenesis in the intestine, in both genetic and carcinogen-induced models.[49,62,107,108] Future studies investigating the process of fetal-like reversion and the mechanisms that regulate it will provide a deeper understanding of injury response and lead to therapeutic avenues that can promote tissue regeneration while preventing pathologies resulting from dysregulated tissue repair.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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