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Review **OPEN ACCESS**

Crosstalk among Wnt, Notch, EGF/ErbB, and BMP signaling pathways in intestinal stem cell fate

Ziasmin Khatun[1]*, Shoaib Saikat[2], Shaila Haque[1]

[1]Department of Biochemistry and Biotechnology, University of Barishal, Barishal-8254, Bangladesh; [2]One Health Laboratory, Infectious Diseases Division, icddr,b, Bangladesh

Abstract

Background Intestinal stem cell (ISC) proliferation and differentiation are tightly regulated by signaling crosstalk to maintain epithelial homeostasis.

Objectives This review synthesizes current evidence on the roles and interactions of Wnt, Notch, EGF/ErbB, and BMP pathways in governing ISC maintenance, self-renewal, and lineage fate decisions.

Methods This narrative review was synthesized from recent experimentally validated evidence from in vivo (mouse models, knockout/knock-in systems) and in vitro (intestinal organoid cultures, enteroids) studies. Key findings were extracted from research employing CRISPR/Cas9 gene editing, lineage tracing, immunohistochemistry, and pathway-specific activation or inhibition assays. The selection focused on molecular and cellular mechanisms governing the roles and crosstalk of Wnt, Notch, EGF/ErbB, and BMP signaling pathways in regulating intestinal stem cell fate decisions.

Results Canonical Wnt signaling maintains ISC stemness and self-renewal, whereas non-canonical Wnt drives cell motility and migration. Notch signaling balances absorptive versus secretory cell fates by modulating ATOH1 expression. Progenitor cells proliferation is further enhanced by EGF and ErbB signaling in synergy with Wnt. Conversely, a spatial BMP gradient suppresses ISC expansion, establishing differential gene expression along the crypt–villus axis. Microenvironmental stress, such as injury, inflammation, and aging, dynamically reshapes Wnt–Notch–EGF/BMP signaling to regulate regeneration and stem cell plasticity.

Conclusion Coordinated crosstalk among Wnt, Notch, EGF/ErbB, and BMP pathways forms a dynamic regulatory network that dictates ISC fate, providing strategic targets for regenerative medicine and intestinal disease interventions.

Keywords Intestinal stem cell | signaling pathways | crosstalk | regulation of fate

Introduction

The intestinal epithelium serves as a barrier against beneficial and dangerous bacteria found in the intestinal lumen. Crypts are created by the intrusion of intestinal epithelial cells, and the villi are the finger-like extensions of the layers of epithelial cells that emerge from the crypts. The colon does not have villi like the small intestine. Instead of villi, there are flattened layers that contain epithelial cells (Barker, 2014; Sancho *et al.,* 2004).

Figure 1 (A and B) illustrates the organization of intestinal epithelium and stem cell niche. Crypts contain intestinal stem cells (ISCs) located in the crypt base, and transient amplifying (TA) cells, which are also known as proliferating progenitor cells. ISCs generate TA cells that experience terminal differentiation into a variety of specialized cell types, including enterocytes, goblet cells, enteroendocrine cells, and Paneth cells. Enterocytes receive nutrients and release hydrolyzing enzymes, goblet cells produce fluid to form a protective mucus layer on the outside of the epithelium; enteroendocrine

*Corresponding author Email: ziasmin.bio@gmail.com

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cells produce hormones; and Paneth cells create antimicrobial substances such as cryptdins and enzyme-like lysozyme (Barker, 2014; Sancho *et al.,* 2004; Sato *et al.,* 2011).

As illustrated in **Figure 1**, Paneth cells are located at the crypt base between ISCs, whereas most other differentiated epithelial cells migrate upward toward the villus before being shed into the intestinal lumen. In the healthy colon, Paneth cells are generally absent, and deep crypt secretory (DCS) cells contribute to the supportive niche at the crypt base (Rothenberg *et al.,* 2012).

The epithelial compartment is further associated with specialized populations including M (or microfold) cells and tuft cells, as shown in **Figure 1**A (Gerbe *et al.,* 2012). M cells found in the human and mouse small intestine are associated with antigen sampling over Peyer's patch (Zhang *et al.,* 2022b) and tuft cells found in the human and mouse small intestine, but very sparse release immunomodulatory substances and offer protection from helminths and protozoan (Hendel *et al.,* 2022). The underlying mesenchymal and immune compartments, also depicted in **Figure 1**A, provide additional signals that contribute to epithelial homeostasis and ISC regulation (Clevers *et al.,* 2019).

The intestinal epithelium undergoes continuous renewal through a balance of ISC self-renewal, progenitorcell proliferation, differentiation, and cell loss (Santos *et al.,* 2018). In addition to actively cycling ISCs, reserve or quiescent stem/progenitor populations can contribute to regeneration after injury, highlighting the plasticity and dynamic nature of the ISC compartment (Barker, 2014). Abnormal mucosal repair and compromised barrier function in intestinal epithelium are fundamental features of intestinal pathology, particularly prolonged intestinal inflammation such as inflammatory bowel disease (IBD), which is characterized by ulcerative colitis and Crohn's disease (Horiguchi *et al.,* 2017; Martens *et al.,* 2018; Torres *et al.,* 2017).

The work by Wang, Qu, and Cui reviews several signaling mechanisms that affect ISCs (Wang *et al.,* 2023). Another review paper discusses how immune cells, Paneth cells, and mesenchymal cells release different substances that regulate ISCs and their function (Choi & Augenlicht, 2024). According to a review by Meyer *et al.* (2022), stress or radiation harms stem and progenitor cells, but reservoir stem cells, also known as quiescent stem cells, can use Bmi1, Lrig1, Hopx, or mTert triggers to regenerate active stem cells.

Several signaling pathways, including Wnt, Notch, EGF, and BMP signaling pathways, have also been examined as being involved in the control of intestinal stem cells during radiation enteropathy (Chen *et al.,* 2024). The crosstalk between various intestinal epithelial cells has reportedly been shown through various signaling pathways in which one cell expresses a particular ligand, and another cell has the associated receptor (Yu *et al.,* 2024). The previous review of ISC signaling has become outdated and does not adequately cover recent advances, particularly in the understanding of pathway crosstalk (Takahashi & Shiraishi, 2020). Although key mechanisms have been described, how spatially and temporally coordinated Wnt, Notch, EGF/ErbB, and BMP signals are integrated to determine ISC self-renewal, proliferation, lineage commitment, and regenerative plasticity remains insufficiently explored. Although the interaction of signaling pathways in ISCs was discussed in an earlier study, the findings are now relatively dated (Vanuytsel *et al.,* 2013).

This narrative review provides an updated overview of the major pathways regulating ISC fate—Wnt, Notch, EGF, and BMP with emphasis on their crosstalk, both spatially and temporally. We aimed to clarify how these coordinated networks control ISC maintenance, proliferation, and differentiation. We further highlighted recent key unanswered questions that may guide future investigations on intestinal regeneration and disease.

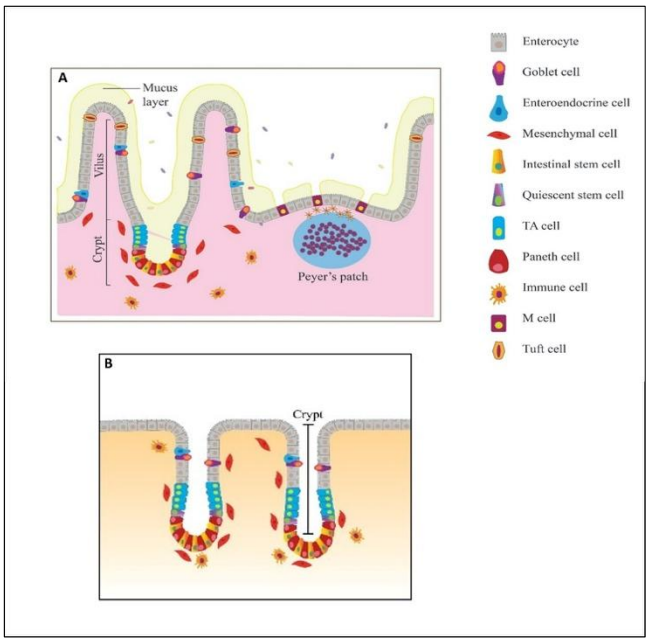

Figure 1 Architecture of intestinal epithelium and stem cell niches. (A) Small intestine displaying crypt-villus organization. Crypt base contains intestinal stem cells, Paneth cells, progenitor cells, and quiescent stem cells, supported by underlying stromal and immune cells. Villi are lined with absorptive enterocytes and secretory cells (goblet, enteroendocrine, tuft, and M cells). (B) Colon architecture featuring a flat surface with deep crypts, lacking villi and Paneth cells, with deep crypt secretory (DCS) cells residing at the crypt base.

Wnt signaling pathway

Wnt signaling regulates cellular proliferation, differentiation, migration, and apoptosis by controlling intestinal stem cell functions (Flanagan *et al.,* 2015; Kabiri *et al.,* 2014; Korinek *et al.,* 1998; Sansom *et al.,* 2004). Ligands of the Wnt and R-spondin (R-spo) family trigger signals via the canonical, non-canonical Wnt/PCP, and Wnt/Ca2+ pathways (Flanagan *et al.,* 2018; Sarabia-Sánchez & Robles-Flores, 2024) (**Figure 2**).

On the plasma membrane of a cell, Wnt protein binds to its receptors, Frizzled (Fzd) and low-density lipoprotein receptor-related protein 5/6 (LRP5/6). The intracellular Dishevelled (Dvl) protein is drawn to the intracellular location of the receptor following binding. By preventing a group of proteins from forming a complex, the Dvl protein within the cell prevents β-catenin from being destroyed in the canonical Wnt pathway. Adenomatous polyposis coli (APC), casein kinase I (CKI), glycogen synthase kinase 3β (GSK3β), and Axin make up this protein complex.

After blocking the destruction complex, β-catenin accumulates in the cytoplasm and moves to the nucleus, where it interacts with the transcription factors T-cell factor (TCF) and lymphoid enhancer factor (LEF) to promote the expression of Wnt target genes. Without Wnt ligands, β-catenins are phosphorylated by the destruction complex and targeted to ubiquitin-mediated degradation (**Figure 2**).

In the Wnt/PCP signaling pathway, the Dvl-associated activator of morphogenesis (DAAM)/ Ras homolog family member A (RHOA)/ Rho-associated protein kinase (ROCK) axis is activated by the Wnt/Fzd receptor and the Ror1/2 co-receptor, which also activates c-Jun N-terminal kinase (JNK) via Ras-related C3 botulinum toxin substrate 1 (Rac1). JNK activates Jun, which leads to gene expression, while the DAAM/RHOA/ROCK axis regulates actin dynamics and cell polarity (**Figure 2**). In the Wnt/Ca2+ pathway, phospholipase C (PLC) releases calcium from the endoplasmic reticulum, which activates calcineurin and calmodulin-dependent protein kinase II (CaMKII), and protein kinase C (PKC) through the PLC triggers cytoskeletal reorganizations by activating PKC, which in turn activates cell division cycle 42 (Cdc42) (**Figure 2**). The canonical Wnt pathway is adversely regulated by PLC and CaMKII. Conversely, calcineurin triggers nuclear factor of activated T-cells (NFAT), a family of transcription factors that results in gene transcriptional activation.

A 7-transmembrane receptor called leucine-rich repeat-containing G-protein-coupled receptor 5 (Lgr5) binds R-Spo and inhibits the E3 ligases Znrf3/Rnf43, which normally pro-

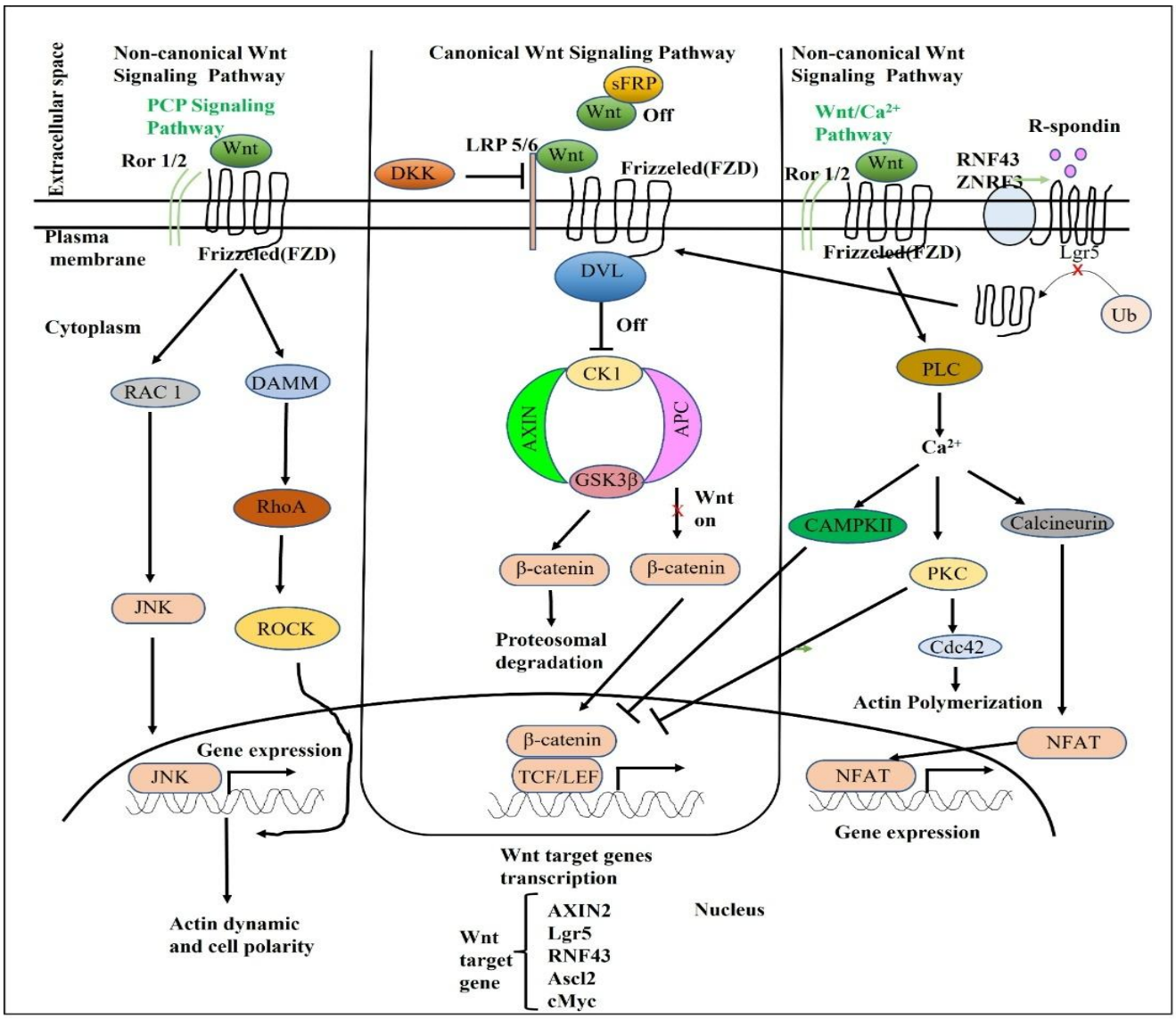

Figure 2 Schematic representation of Wnt signaling pathways. The middle diagram illustrates the β-catenin–mediated canonical Wnt signaling pathway. The Wnt/calcium (Wnt/Ca^{2+}) and Wnt/planar cell polarity (Wnt/PCP) pathways are examples of non-canonical signaling. In the Wnt/Ca^{2+} pathway, phospholipase C (PLC) induces calcium release from the endoplasmic reticulum, which activates calcineurin and CaMKII. Calcium-dependent activation of protein kinase C (PKC) contributes to cytoskeletal reorganization, including modulation of small GTPases such as Cdc42 and Rac. Components of the Wnt/Ca^{2+} pathway can antagonize canonical Wnt signaling through cross-talk mechanisms. Calcineurin activates NFAT, leading to transcriptional regulation of target genes. In the Wnt/PCP pathway, RhoA, Rac, and JNK are activated, influencing cytoskeletal dynamics and gene expression. Dkk1 inhibits canonical Wnt signaling by binding LRP5/6 and promoting its internalization via the co-receptor Kremen. Secreted Frizzled-related proteins (sFRPs) bind Wnt ligands and inhibit both canonical and non-canonical Wnt signaling. Lgr5 binds R-spondin (R-Spo), which inhibits the E3 ubiquitin ligases Znrf3/Rnf43 responsible for Fzd receptor degradation, thereby stabilizing Fzd on the cell surface and enhancing Wnt signaling.

mote ubiquitination and degradation of Fzd receptors. This inhibition stabilizes the Fzd receptor on the cell surface and increases Wnt signaling (Hao *et al.,* 2012; Koo *et al.,* 2012). By forming a complex with Kremen protein and LRP, Dickkopf-1 (Dkk1) prevents canonical Wnt signaling by internalizing LRP. Conversely, the Wnt protein is directly bound and neutralized by secreted Fzd-related proteins (sFRPs), which stop both canonical and non-canonical Wnt signaling (**Figure 2**) (Mah *et al.,* 2016).

Wnt signaling in the regulation of ISC fate

Paneth cells and specialized mesenchymal cells can provide Wnt ligands that contribute to ISC maintenance, although the relative contribution of epithelial- and mesenchymal-derived Wnt varies according to intestinal region and experimental context (Farin *et al.,* 2012; Sato *et al.,* 2011; Zou *et al.,* 2018). The Wnt signaling pathway appears to be active in ISCs, as Frzld5 and Frzld7, two receptors among the ten Frzld receptors, are found in ISCs and binds to Wnt ligands. Deletion of the cell-specific Frzld receptor revealed fewer ISCs in the intestine (Flanagan *et al.,* 2015; Mu *et al.,* 2025). These findings support a role for Wnt signaling in ISC maintenance, stemness, and proliferative activity.

Wnt signaling is dynamically controlled over time. In organoid model, high Wnt condition medium maintains ISCs pool. Removal of Wnt gives rise to differentiation of ISCs (Yang *et al.,* 2024). Loss of B-catenin function by tamoxifen-induced Cre-recombinases reportedly showed loss of ISCs and progenitor cells with increased enterocytes (Fevr *et al.,* 2007). The loss of ISCs and TA cells proliferation and secretory lineages was caused by conditional genetic deletion of TCF4 and intestinal epithelial-specific Dkk1 transgenic expression. However, polyposis and excessive intestinal epithelial proliferation can be caused by a mutation in the APC gene and ongoing β-catenin triggering, particularly in ISCs (Mah *et al.,* 2016).

Lgr5 receptor is present in stem cells, and the release of R-spo by mesenchymal cells promoted the growth of ISCs in the presence of Wnt signaling, which is mediated by a unique priming and regeneration factor (Yan *et al.,* 2017), suggesting R-spo potentiates Wnt signaling. ISCs are functionally heterogeneous, i.e., not all stem cells are functional stem cells; some might be non-cycling cells. These quiescent (non-cycling) cells have different gene expression profiles and activation triggers compared to active ISCs (Böttcher *et al.,* 2020).

On the other hand, RhoA-mediated actin remodeling was the outcome of pathogen infection-induced intestinal injury in Drosophila or localized tissue damage brought on by laser-activated Wnt/PCP signaling in intestinal stem cells. Stem cells multiply and replenish epithelial cells after or during migration, and this remodeling assists in the creation of protrusions in stem cells and their repositioning in wounded sites (Hu *et al.,* 2021).

These findings suggest that Canonical Wnt/β-catenin signaling primarily supports ISC maintenance and proliferative activity, while its intensity and interaction with other pathways influence lineage differentiation. In contrast, non-canonical Wnt/PCP signaling contributes to cell polarity, cytoskeletal remodeling, migration, and tissue repair.

Notch signaling pathway

Notch signaling plays an important role in cell proliferation, differentiation, and maintenance of stem cells during embryonic and adult development (Andersson *et al.,* 2011; Borggrefe & Oswald, 2009). This signaling pathway is triggered by communication between intestinal epithelium's niche cells, which express ligands, and stem cells, which receive signals (Liang *et al.,* 2019). The Notch signaling pathway includes four transmembrane receptors (Notch1-4) and three canonical delta-like protein ligands (Dll1, Dll3, Dll4), as well as two canonical Jag-1and Jag-2 ligands.

The non-canonical ligands include integral delta like membrane protein, Dlk1 and DNER ((Delta/Notch-like epidermal growth factor (EGF)-related receptor), GPI-linked membrane bound protein, F3/contactin1 and NB3/contactin6, and soluble proteins CCN3, also known as NOV (nephroblastoma overexpressed), MAGP-1 (Microfibril-Associated Glycoprotein 1), MAGP-2 ((Microfibril-Associated Glycoprotein 2), TSP2 (Thrombospondin 2), Y-box (YB) protein-1, EGFL7 (EGF-like domain-containing protein 7) (D'Souza *et al.,* 2010). Each Notch receptor contains heterodimeric subunits. One subunit is found on the totally extracellular side, and it has three cysteine-rich Lin12/Notch repeats (LNR) after epidermal growth factor-like repeats at its most extracellular position for ligand binding. Another subunit comprises the extracellular domain, transmembrane domain, and intracellular domain, which contains a nuclear localization signal (NLS). The two subunits come together to produce a fully functioning receptor (**Figure 3**).

Like Notch receptors, canonical Notch ligands have an extracellular domain of DSL (Delta, Serrate, Lag-2) that has a single cysteine-rich motif after EGF-like repeats. However, jagged proteins differ from Delta-like ligands in that they have an additional von Willebrand factor type C domain (VWC domain) before the EGF-like repetitions. In contrast, non-canonical ligands, Dlk1 and DNER, are structurally related to delta-like proteins but lack the DSL domain.

In the canonical Notch Pathway, the Notch receptor undergoes a conformational change upon ligand engagement, exposing the S2 cleavage site close to the extracellular side of the plasma membrane to the protein ADAM/TACE-containing metalloproteinases (Wu *et al.,* 2007). The Notch intracellular domain (NICD), which is released as a result of the subsequent S3 cleavage by γ-secretase within the transmembrane domain of the Notch receptor, moves into the nucleus and forms a heterotrimer with DNA-binding proteins CSL (CBF1/RBP-Jκ/Suppressor of Hairless (Hes)/LAG-1) and mastermind-like protein (MAML) to start target genes (Hes1 and Hey) transcription. NICD transforms the previously stated DNA-binding proteins from transcriptional repressors to transcriptional activators via this interaction (**Figure 3**) (Arai *et al.,* 2018; D'Souza *et al.,* 2010; Liang *et al.,* 2019; Wu *et al.,*

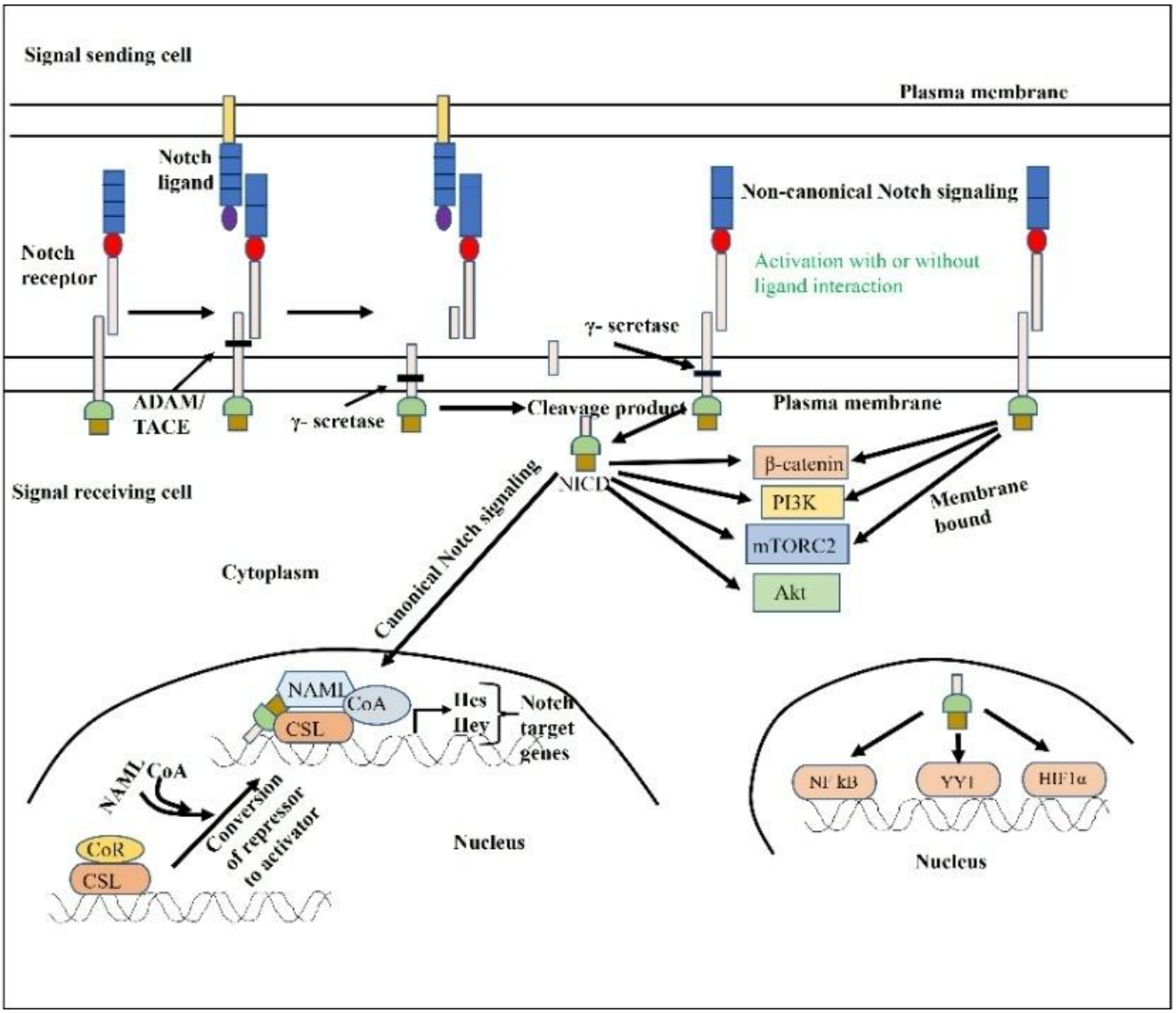

Figure 3 Schematic representation of the Notch signaling pathway. In canonical Notch signaling, ligand-receptor binding triggers ADAM/TACE metalloproteases and γ-secretase cleavage, releasing NICD. Translocated NICD complexes with CSL and MAML in nucleus to activate target genes (such as Hes1 and Hey). Non-canonical Notch signaling proceeds via ligand- or γ-secretase-independent mechanismes, modulating downstream PI3K, AKT, Wnt, and NFκB networks at the cytoplasmic and nuclear levels.

2007). In contrast, both reliant and devoid of ligand contact, non-canonical Notch signaling can occur.

Non-canonical Notch signaling can be either autonomous or reliant on γ-secretase, with the former responding as membrane-bound Notch. Instead of interacting with CSL/RBPJκ, non-canonical Notch signaling comes into contact with the cytoplasmic and/or nuclear levels of the PI3K (phosphoinositide 3-kinase), mTORC2 (mammalian target of rapamycin complex 2), AKT (Serine/Threonine kinase), Wnt, NFκB, YY1 (Ying Yang 1), or HIF-1α (Hypoxia-inducible factor 1-alpha) pathways (**Figure 3**) (Ayaz & Osborne, 2014).

Notch signaling in the regulation of ISC fate

ISCs express Notch 1 and Notch2 receptors, while adjacent Paneth cells, located within the stem cell niche, express their ligands, Dll1 and Dll4 (Demitrack & Samuelson, 2016). Genetic evidence identifies DLL1 and DLL4 as the principal physiological ligands sustaining Notch activity in intestinal stem and progenitor cells; combined ligand loss disrupts crypt homeostasis and promotes secretory differentiation (Pellegrinet *et al.,* 2011). On the other hand, impairment of Notch1 and Notch2 signaling leads to the loss of intestinal stem and progenitor cells, accompanied by an increase in goblet cells (Demitrack & Samuelson, 2016).

In ulcerative colitis mice, Notch activity is abnormally high, resulting in loss of secretory cell differentiation (Ning *et al.,* 2023). Notch activation reportedly induces Hes1 expression, which inhibits Atonal bHLH transcription factor 1 (ATOH1) expression (also known as MATH1) (Carulli *et al.,* 2015). The loss of ATOH1 results in the inhibition of secretory lineage differentiation, which consequently shunts cells towards the enterocyte fate under canonical Notch signaling conditions (Carulli *et al.,* 2015). When Notch 1 and 2 function is impaired in intestinal stem cells, Hes1 expression is lost, and stem cells differentiate into secretory cell lineages (Demitrack & Samuelson, 2016).

Ablation of Notch1 alone resulted in increased secretory cells but no loss of proliferation of stem cells; however, deletion of Notch1 and Notch2 together showed decreased proliferation of stem cells, which is redundant for the formation of differentiated goblet cells, suggesting that Notch1 is the primary receptor regulating stem cells (Carulli *et al.,* 2015). Additionally, it has been shown that genetically blocking additional components of the Notch pathway, such as the DLL1 and DLL4 ligands, Notch receptor protease ADM10, or the NICD binding partner RBPJ, can reduce progenitor cell proliferation or ISCs' function (Demitrack & Samuelson, 2016).

These findings suggest that Notch signaling plays a crucial role in supporting ISCs. ATOH1 acts as a tumor suppressor gene in colorectal cancer. It suppresses the proliferation and increases their differentiation (Fu *et al.,* 2020). VanDussen *et al.* (2012) reported that inhibition of Notch caused the depletion of stem cells, with their differentiation into secretory cells such as Paneth cells and goblet cells.

Differentiation of stem cells into absorptive lineage is known to be ATOH1 independent, whereas differentiation into secretory cells is strictly ATOH1 dependent. This aligns with the established understanding that disruption of Notch signaling removes the suppression of, and consequently activates the ATOH1 transcription factor (VanDussen *et al.,* 2012). It has been reported that Notch inhibition increased the activity of ATOH1 to regenerate hair cells (Luo *et al.,* 2017).

It has been documented that Achaete-Scute complex gene expression is increased and binds to multiple sites within the C2H2-type zinc-finger transcription factor Chronophage (Cph) locus to promote its expression in intestinal progenitor cells, which directs its differentiation towards enteroendocrine cells and maintains intestinal stem cells (Redhai *et al.,* 2026). In contrast, knockout of atonal homolog reportedly increased the death of neuronal cells but does not cause complete loss of neuronal cells. Double knockout of atonal homolog and achaete–scute homolog complete loss of neuronal cells and directs the differentiation of progenitor cells towards the glial cells (Tomita *et al.,* 2000), suggesting that both homolog genes work together to control the fate decisions.

Collectively, Notch signaling maintains the proliferative ISC/progenitor compartment and promotes absorptive lineage specification primarily through the NICD–RBPJ–HES1 axis, which suppresses ATOH1-dependent secretory differentiation. Additional transcriptional regulators may further refine lineage-specific outcomes.

EGF signaling pathway

Epidermal growth factor (EGF) signaling triggers intestinal stem/progenitor cell proliferation and inhibits apoptosis (Suzuki *et al.,* 2010). Proteins containing common, similar EGF-like motifs are members of the EGF family and function as ligands for the receptor tyrosine kinase superfamily's ErbB subtype, which includes the EGF receptor (EGFR); (also known as ErbB1), ErbB2, ErbB3, and ErbB4. Amphiregulin (AREG), betacellulin (BTC), Epigen (EPGN), Epiregulin (EREG), EGF, Heparin-Binding EGF-Like Growth factor (HB-EGF), transforming growth factor alpha (TGF-α), and neuregulins 1, 2, 3, 4 (NRG 1, 2, 3, 4) make up the EGF Ligand family.

The members of this EGF ligand family can be divided into four subgroups according to their unique receptor binding characteristics: (1) ligands that excluseively bind to ErbB1 (EGF, TGFα, AREG, and EPGN); (2) ligands that bind to ErbB1 and ErbB4 (HB-EGF, EREG, and BTC); (3) ligands that are specific for ErbB3 and ErbB4 (NRG1 and NRG2); and (4) ligands that exclusively activate ErbB4 (NRG3 and NRG4).

Although several ligands bind the same ErbB family receptor, they exert different functions (Abud *et al.,* 2021; Wilson *et al.,* 2009). These ligands interact with different receptors (except ErbB2, for which no direct ligand is confirmed, but which acts as a critical co-receptor) to form receptor dimers that trigger the intrinsic kinase domain, phosphorylating certain tyrosine residues in the cytoplasmic tail. Janus kinase-signal transducer and activator of transcription (JAK-STAT), rat sarcoma and rapidly accelerated fibrosarcoma (RAS-RAF) protein kinase and mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase-AKT-mTOR (PI3K-AKT-mTOR), and other molecules and regulatory proteins use phosphorylated residues as docking sites (**Figure 4**) (Abud *et al.,* 2021; Hsu *et al.,* 2019; Wilson *et al.,* 2009).

EGF signaling in the regulation of ISC fate

Both ErbB3 and ErbB4 are found in intestinal epithelium (Lee *et al.,* 2009; McElroy *et al.,* 2014) as well as in regenerating enteroids (Almohazey *et al.,* 2014; Almohazey *et al.,* 2017). Studies on ErbB4-null enteroid cultures has shown a disruption of the ISC niche, as evidenced by decreased Paneth cell populations and the absence of the rapidly cycling stem cell marker Lgr5 (Almohazey *et al.,* 2014). Conversely, ErbB3-null enteroids and knockout mice showed increased Paneth cells with robust expression of the stem cell marker Lgr5 (Almohazey *et al.,* 2017). These results suggest a complex and distinct role for ErbB3 and ErbB4 in intestinal stem cell niche and influencing cell fate decisions.

ErbB3 null progenitor cells showed decreased PI3K-AKT and MAPK activity, whichinduced ATOH1 and Paneth cell marker, Lyz expression (Almohazey *et al.,* 2017). EGF and Neuregulin1 secreted from both Paneth cells and mesenchymal cells activated EGFR and ErbB3 receptors present in the intestinal crypt but not in Paneth cells. Activation of EGFR and ErbB3 receptors resulted in PI3K-AKT and MAPK activation, thereby inducing crypt formation and ISCs proliferation in organoids formed from isolated mouse intestinal crypts. However the number of crypts and ISCs was more robust in neuregulin 1 signaling (Jardé *et al.,* 2020).

Studies in Drosophila provide additional evidence that EGF signaling can regulate ISC metabolism through RAS–RAF–MAPK signaling; however, the extent to which these mechanisms are conserved in mammalian ISCs remains unclear (Chen *et al.,* 2024; Zhang *et al.,* 2022a). EGF signaling increases the proliferation of immature putative intestinal stem/progenitor cells in fetal and adult mice, inhibites apoptosis. Directs their differentiation towards goblet cells, Paneth cells, enteroendocrine cells, and enterocytes indicates that the differentiation of stem cells and progenitor cells is par-

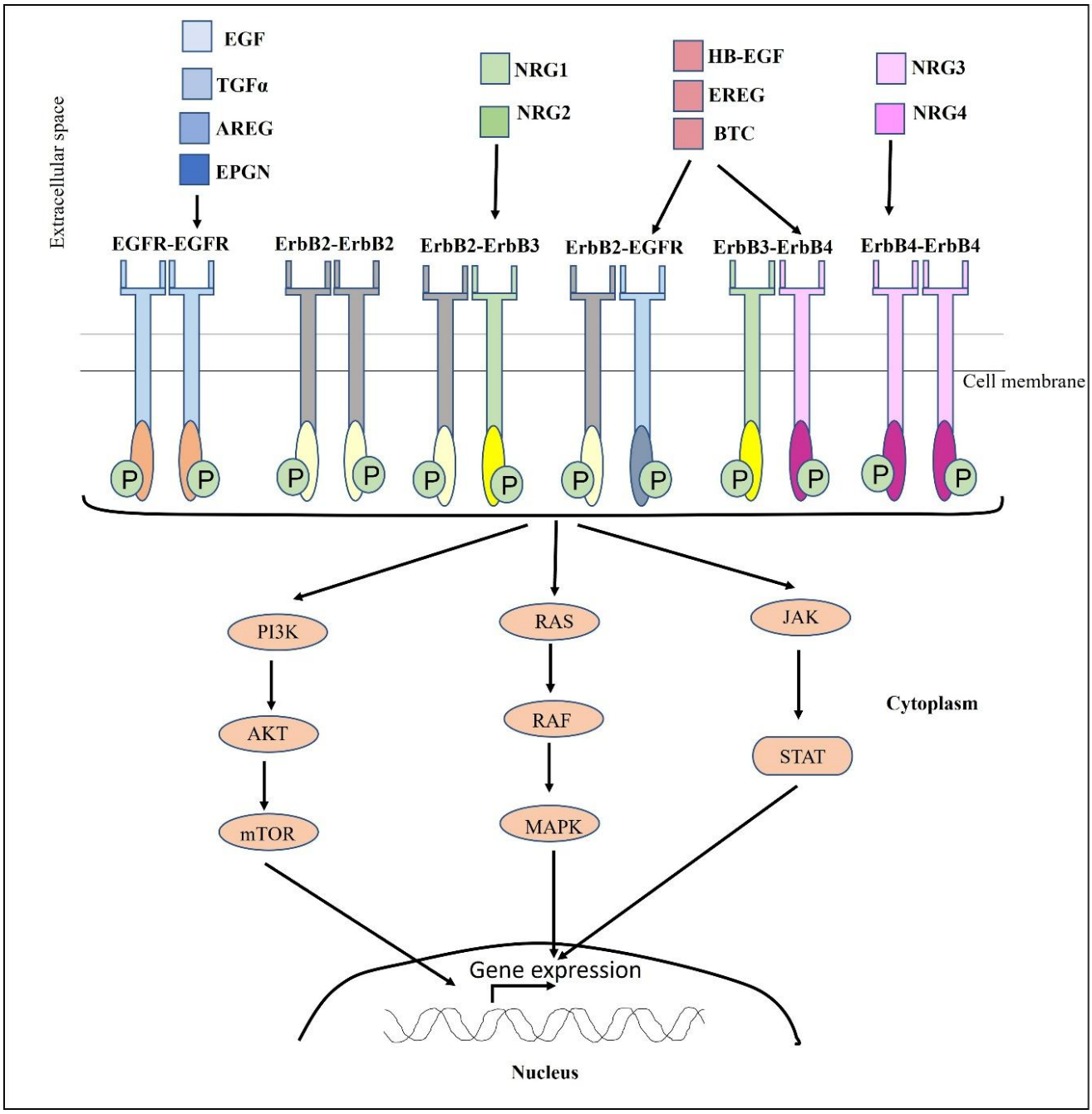

Figure 4 Schematic representation of EGF signaling pathway. The EGF ligand family activates EGF receptors (ErbB family), typically forming homo and heterodimers. ErbB2 serves as a crucial co-receptor, but has no direct ligand. These interactions activate the downstream signaling pathways such as JAK/STAT, PI3K/AKT-mTOR, and the RAS-RAF-MEK-ERK (MAPK) pathway and these pathways promote the transcription of genes involved in the proliferation, differentiation and survival of cells.

tially regulated by EGF signaling (Suzuki *et al.,* 2010).

In weaning piglets, EGF increased Atoh1 expression, which was attributable to increased β-catenin activity, thereby promoting differentiation towards secretory cells (Wang *et al.,* 2020). In contrast, a lower level of EGF increases intestinal stem cell proliferation and differentiation towards enterocytes by phosphorylating mTOR (Wang *et al.,* 2019). Collectively, these findings indicate that EGF/ErbB signaling regulates ISC proliferation, survival, and lineage differentiation through the PI3K–AKT and RAS–RAF–MAPK pathways, with effects that vary according to receptor composition, ligand availability, signaling intensity, and cellular context.

BMP signaling pathway

Bone morphogenic protein (BMP) signaling is important for intestinal disorders, advancement, and stem cell maintenance (Wang & Chen, 2018; Zhang & Que, 2020). BMP affects target gene transcription by means of intracellular signaling mediated by receptors. It was discovered that BMPs are members of the superfamily of transforming growth factor-β (TGF-β), which also comprises activins in addition to TGF-βs.

There are about 15 members of the BMP family. The most extensively studied are BMP 2, 4, 6, 7, 9, and 10 (Katagiri & Watabe, 2016). The cellular context influences the activity of

BMPs, a multifunctional protein (Morikawa *et al.,* 2016). In the form of dimers, BMPs interact with type I and type II cell surface receptors to trigger particular biological functions by activating the receptors' serine/threonine kinase.

There are three different BMP type II receptors (BMPRII, ActRIIA, and ActRIIB) and four different type I receptors (ALK1, ALK2 (also termed ActRI), ALK3 (also termed BMPRIA), and ALK6 (also termed BMPRIB)). Although BMPR-II is BMP-specific, ActRIIA and ActRIIB can interact with both activins and BMPs. While BMP9 and BMP10 are highly binding ligands for ALK1 but can also bind to ALK2, BMP2 and BMP4 bind with greater force to ALK3 and ALK6, while BMP6 and BMP7 bind strongest to ALK2. BMPs bind to a specific combination of BMPRIs and BMPRIIs (Katagiri & Watabe, 2016).

BMP signal transduction involves two distinct signaling pathways. In the canonical pathway, BMPRI recruits through adaptor protein endofin and phosphorylates Smad1, Smad5 (R-Smad). A heterotrimeric complex is formed by the combination of two phosphorylated R-Smads with a common Smad4 (Co-Smad). Translocating into the nucleus, the Smad heterotrimeric complex works with other transcription factors to alter the expression of the target gene (**Figure 5**). In the parallel pathway, the BMP receptor signal is connected to TAK1 by X-linked inhibitor of apoptosis (XIAP), and BMP-mediated TAK1 activation also requires TAK1 binding proteins (TAB1/2/3). TAK1 is a MAP3K which has multiple downstream targets, including MKK3/6, JNK and NF-kb (**Figure 5**)(Zhang & Li, 2005).

BMP signaling in the regulation of ISC fate

When BMPR1a is conditionally lost in the mouse intestine, stem/progenitor cells proliferate, and Wnt/β-catenin is released, suggesting a correlation between BMP signaling and the Wnt signaling pathway. Interestingly, evidence showed that BMP signaling suppressed Wnt/ β-catenin signaling through the PTEN-PI3k-Akt pathway (He *et al.,* 2004). In addition to this Wnt-dependent crosstalk, conditional deletion of BMPRI in mice ISCs resulted in expansion of Lgr5+ stem cells and crypt hyperplasia, which suggested the existence of Wnt-independent mechanisms (Qi *et al.,* 2017).

BMP signaling recruits Histon deacetylase 1 (HDAC1) through Smad1 and Smad4 to the promoter region of stem cells' signature gene Lgr5, indicating that the suppression of stem cells was a Wnt-independent pathway (Qi *et al.,* 2017). Inducible conditional deletion of ALK3 in mice and organoids upregulated the expression of Bcl11b in stem cells, which resulted in the expansion of ISCs with an increased number of crypts. DOX inducible upregulated Bcl11b disrupted the NurD repressive complex HDAC1, MBD2/3, RBBP4/7, GATAD2B, and MTA2 containing by interacting with it and promoted the interaction between β-catenin and TCF4, thereby increasing the number of stem cells and crypt formation (Li *et al.,* 2024).

Recent evidence showed that there is a gradient of BMP along the crypt villus axis, and this gradient is not due to cell autonomy. This BMP gradient is organized by sub-epithelial sources of essential agonists and antagonists. PDGFRA hi myofibroblast aggregates located up the crypt villus axis secretes BMP, which inhibits the intestinal supportive gene, Wnt, expression from pericryptal CD81$^-$ PDGFRA low stromal cells. CD81+ PDGFRA low trophocytes located just beneath the crypt base and peri-cryptal CD81− CD55hi located near the bottom of the crypt base secrete antagonist of BMP, Gremlin1, as well as secrete Wnt supporting niche factors (Kraiczy *et al.,* 2023; McCarthy *et al.,* 2020).

BMP gradient is needed to direct overall zonal differentiation and maturation along the crypt-villus axis. The lower BMP level in the crypts promotes the expression of stemness and secretory genes (such as mucus production in goblet cells), while the higher BMP level in the villi drives differentiation and the expression of mature enterocyte absorption genes. This zonal regulation was validated by knockout experiments of BMPR1 (Beumer *et al.,* 2022). Thus, an antagonist of BMP signaling makes a gradient in BMP signaling, and this gradient is responsible for zonated gene expression in enterocytes and goblet cells. Moreover, BMP signaling restricts intestinal stem cells and progenitor cell proliferation through suppression of Wnt target genes by reducing β-catenin transcriptional activity, and when cells migrate upward, increasing BMP signaling reduces the stemness of cells and increases their differentiation (Wang *et al.,* 2025).

Signaling crosstalk in intestinal stem cells to determine the fates

Signaling crosstalk in intestinal stem cells during fate determination is depicted in **Figure 6** and **Table 1**. Tight regulation of adult stem cells and differentiation through the integration of several signaling pathways is necessary for proper intestinal epithelial homeostasis. Both Notch and Wnt signaling are reportedly present in intestinal stem cells, which causes the proliferation of stem cells. Notch signaling is also present in TA cells. When Notch (NICD) is present, ATOH1 is absent. These results indicate that both Wnt and Notch signaling maintain intestinal stem and progenitor cells with absorptive cell lineages.

Notch signaling depletion with antibody treatment in mice resulted in differentiation of stem cells towards secretory cell lineages (Paneth cells) at the expense of absorptive cells, which resulted from derepressed Wnt signaling. Partial loss of Wnt signaling rescued the phenotype of Notch blockade with a reduction of intestinal stem cells (Tian *et al.,* 2015). In DSS-induced mice, epithelial damage by inflammation necessitates rapid regeneration by ISCs. During regeneration, canonical-Wnt and Dll1 mediated Notch pathways are activated and act cooperatively, not independently, to regenerate tissues (Ou *et al.,* 2024; Xue *et al.,* 2025).

It has been reported that the 36 extracellular EGF-like repeats that the ΔEGF_N1 construct lacked prevented ligand binding and obscured the S2 cleavage site, trapping the Notch protein in the membrane of HCT116 cells. This trapped Notch receptor was unable to trigger the production of a reporter gene that was dependent on RBPj. On the other hand, the NICD construct, which only consists of the intracellular domain, was only detected in the nucleus and strongly stimulated transcription that is dependent on RBPj. By interacting with Deltex, Notch1 can sequester β-catenin and counteract

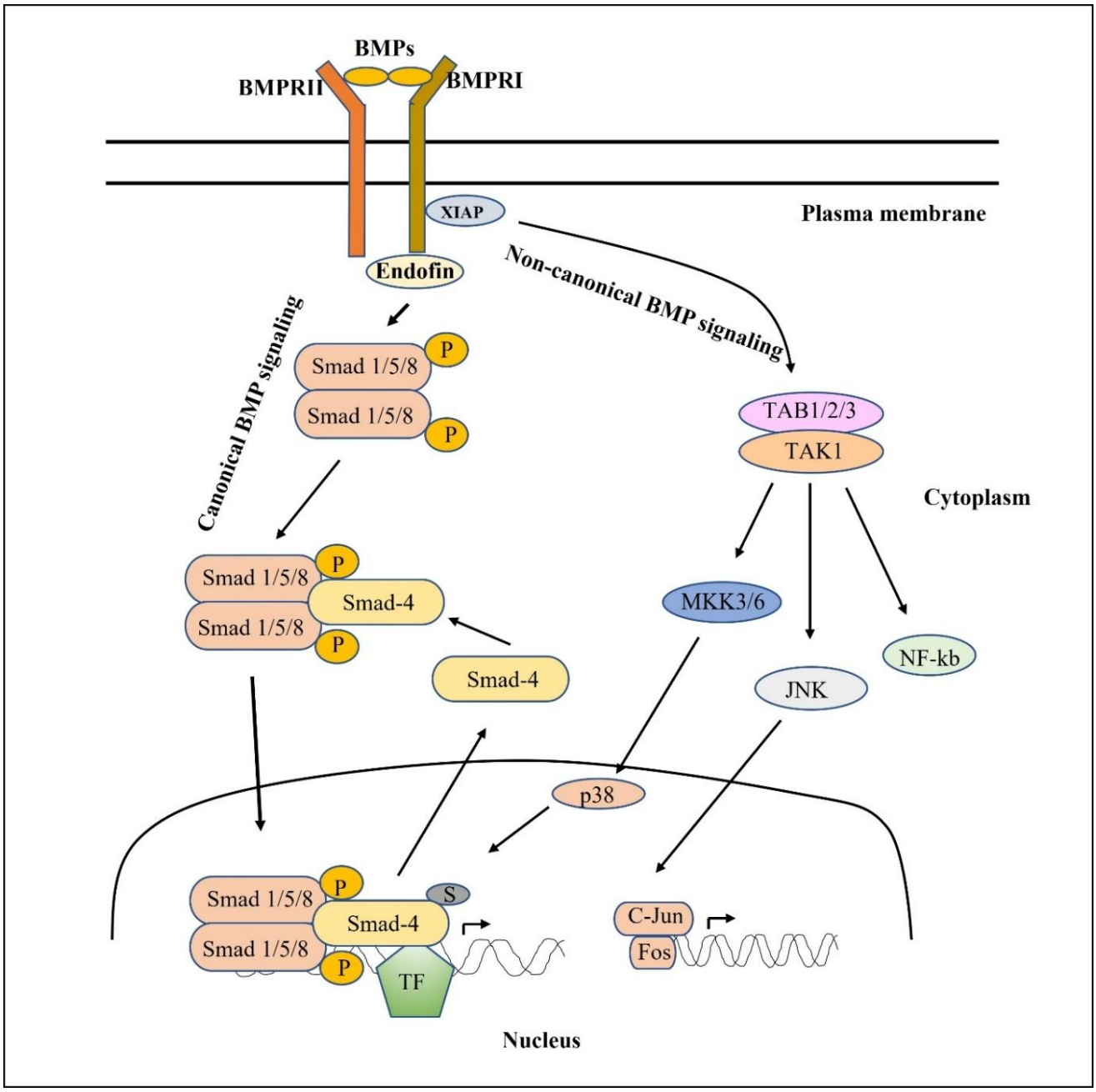

Figure 5 Schematic representation of the BMP signaling pathway. BMP ligands bind as dimers to type II (BMPRII) and type I (BMPRI) receptors. Upon ligand binding, BMPRII phosphorylates and activates BMPRI. In the canonical pathway, activated BMPRI phosphorylates receptor-regulated Smads (R-Smads: Smad1/5/8), which often form a heterotrimeric complex with a common mediator Smad4 (Co-Smad). This complex translocates into the nucleus and cooperates with other transcription factors to regulate target gene expression. In the non-canonical (parallel) pathway, BMP receptor signaling activates the MAP3K TAK1 through interaction with X-linked inhibitor of apoptosis (XIAP) and TAK1 binding proteins (TAB1/2/3). TAK1 subsequently activates multiple downstream pathways, including MKK3/6-p38 MAPK, JNK, and NF-kB.

its activity at the membrane without the use of DSL ligands. By forming a complex that necessitates its interaction with RBPjκ, the intracellular domain of Notch1 can also inhibit β-catenin-induced transcription within the nucleus (Acar *et al.,* 2021; Xue *et al.,* 2025). Thus, Notch limits the Wnt/β-catenin activity in cells through a crosstalk mechanism that is necessary for maintaining balance between stem cells' self-renewal (driven by Wnt) and the initiation of lineage specification (regulated by both pathways, favoring the absorptive lineage under normal conditions).

EGF reportedly plays a supportive role in intestinal stem cell proliferation, but it is not essential for determining stemness until Wnt signaling is active and BMP signaling is suppressive (Li *et al.,* 2018). Without EGF and Wnt in the medium, only GSK and BMP inhibitors were sufficient to maintain intestinal stem cells, but the proliferation of stem cells was lower. These results suggest that EGF synergizes with Wnt-β-catenin signaling to support intestinal stem cell proliferation. Additionally, it has been reported that EGFR transactivates β-catenin through PI3K-Akt kinase and Wnt ligand transactivates EGFR through Frzld receptor (Chege & Finney, 2025).

APC1 loss in intestinal stem cells in Drosophila adult midgut, β-catenin upregulated EGF-like ligand Spitz in intestinal stem cells autonomously and interleukin-like ligand Upds non-autonomously in enterocytes. The secreted Upds causes proliferation of stem cells through the JAK-STAT signaling

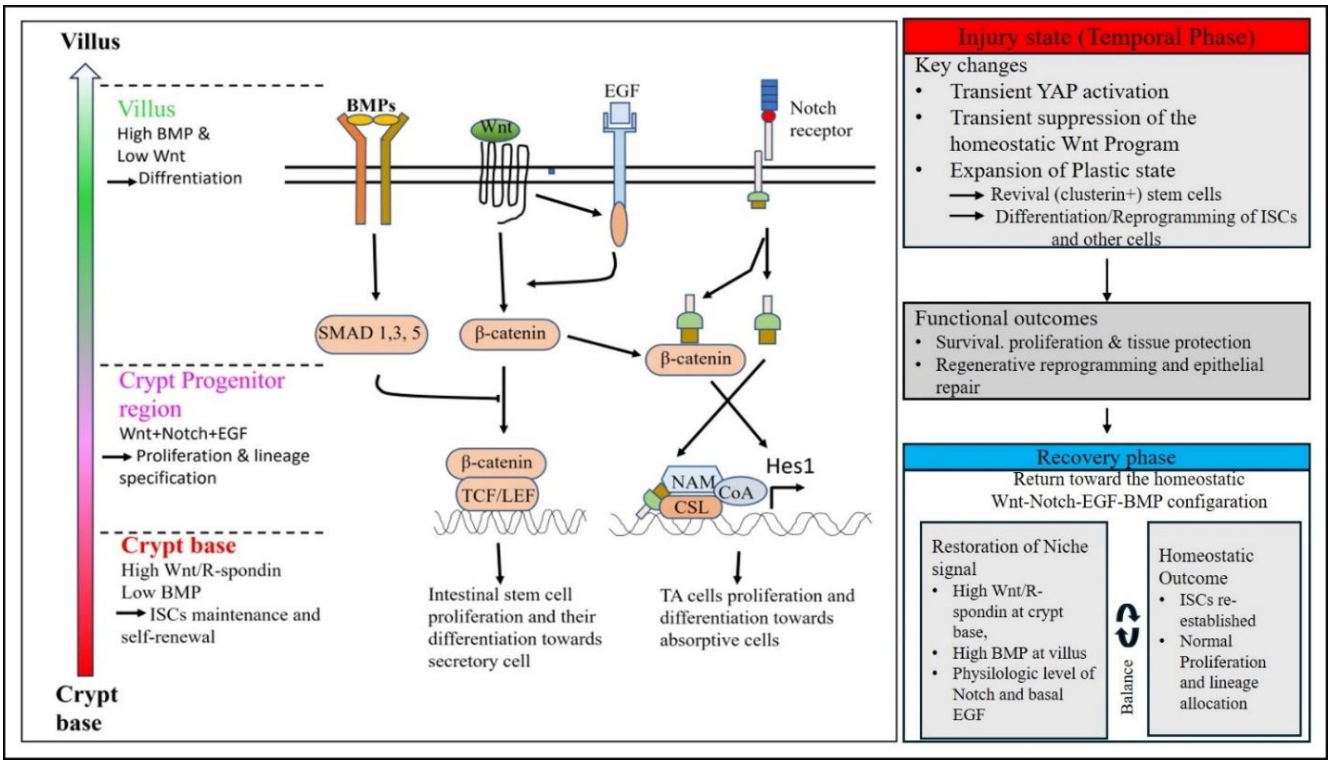

Figure 6 Spatial and context-specific temporal cross-talk among Wnt, Notch, EGF, and BMP signaling Pathways in ISC that regulate their fate decisions, including differentiation into absorptive or secretory lineages.

pathway, and Spitz causes proliferation of stem cells through the EGFR in a paracrine manner. This result indicates that EGF secreted from epithelial niche cells supports intestinal epithelial homeostasis through the Wnt-driven signaling pathway (Cordero *et al.,* 2012). It has been mentioned earlier that in weaning piglets, EGF increased ATOH1 expression, which was attributable to the increased β-catenin activity, thereby promoting their differentiation towards secretory cells (Wang *et al.,* 2020).

Wnt and EGF signals work together to form a cooperative network in the intestinal stem cell niche. While EGF promotes progenitor cell proliferation, Wnt maintains stemness, and their interactions primarily support the absorptive lineage fate or maintain the undifferentiated state of rapidly cycling cells. It has been mentioned earlier that BMP signaling inhibits the intestinal stem cell proliferation and their differentiation to secretory cells by suppressing the interaction of β-catenin with TCF4, suggesting a crosstalk between BMP and Wnt signaling (Li *et al.,* 2024; Wang *et al.,* 2025).

The output of the Wnt-Notch-EGF/BMP network is also reshaped by tissue mechanics and the injury state. Following damage, YAP can transiently suppress the homeostatic Wnt program while promoting survival and regenerative reprogramming of Lgr5-positive ISCs (Gregorieff *et al.,* 2015). In the colon, extracellular-matrix remodeling activates YAP/TAZ-dependent fetal-like epithelial reprogramming, linking stromal changes to regenerative cell states (Yui *et al.,* 2018). Single-cell analysis has further identified clusterin-positive revival stem cells that expand in a YAP1-dependent manner after irradiation, Lgr5-positive-cell ablation, or DSS injury and subsequently reconstitute the homeostatic stem-cell compartment (Ayyaz *et al.,* 2019). These findings indicate that pathway crosstalk is state-dependent, and signaling combinations that maintain homeostatic stemness are temporarily reweighted during repair.

Recent lineage-tracing evidence also challenges the strictly Lgr5-centered model of intestinal stemness. In mice, proliferative isthmus progenitors contribute substantially to homeostatic epithelial turnover and can support regeneration after injury, indicating that stem-cell competence is distributed across crypt cell states rather than confined to a single marker-defined population (Malagola *et al.,* 2024). Human organoid and primary-tissue studies further show that mature proliferative tuft cells can survive irradiation, reacquire multipotency, and generate all major epithelial lineages; their expansion is enhanced by Wnt and type-2 cytokine signals (Huang *et al.,* 2024). These findings place Wnt-dependent plasticity within a broader, species- and injury-dependent regenerative network.

Inflammatory and aging-associated signals can also reset the response of ISCs to the core Wnt–Notch–EGF/BMP network. Persistent inflammation induces metabolic and epigenetic changes in Lgr5-positive ISCs that impair later differentiation and regenerative performance even after the initial insult has resolved (Zhao *et al.,* 2024). During aging, increased lamina-propria-derived IFN-γ activates STAT1 in ISCs, biases secretory-lineage priming, and reduces regenerative capacity, demonstrating that immune-state-dependent inputs modify canonical fate decisions (Omrani *et al.,* 2023). Therefore, the biological output of the four core pathways should be interpreted according to cell identity, anatomical region, species, age, and injury or inflammatory context.

Table 1 The pivotal signaling crosstalk in ISCs to determine the fates

Ref.	Model	Perturbation / Approach	Pathway crosstalk	ISC fate outcome	Limitation
(He *et al.,* 2004)	Mouse intestine	BMPR1A deletion and BMP signaling manipulation	BMP suppresses Wnt/β-catenin signaling through PTEN–PI3K–Akt pathway	Restricts ISC self-renewal and proliferation	Limited consideration of other pathways and injury-related signaling in regulating BMP–Wnt crosstalk
(Tian *et al.,* 2015)	Mouse intestine	Notch blockade with anti-Notch antibodies and Wnt reduction By LRP6 blocking antibodies	Notch restrains Wnt activity during lineage specification	Secretory-cell expansion whereas partial Wnt reduction rescues the phenotype	Limited insight into how other pathways modify Notch–Wnt crosstalk in vivo
(Acar *et al.,* 2021)	Human HCT116 cells	Notch receptor and NICD constructs expression	Notch inhibits β-catenin activity at both membrane and nuclear levels	Balances stem-cell maintenance and lineage commitment	Cancer-cell model rather than normal ISCs
(Li *et al.,* 2018)	Mouse Intestinal crypt derived organoids	Growth-factor-free culture with Wnt/BMP modulation	Wnt activity and BMP inhibition are sufficient for ISC maintenance; EGF enhances proliferation	Maintenance of stemness and crypt growth	The growth factor-free system may not fully reflect the complexity of the in vivo intestinal niche.
(Cordero *et al.,* 2012)	Drosophila adult midgut	APC1 loss	Wnt activation induces EGFR and JAK-STAT signaling	ISC hyperproliferation and epithelial expansion	Findings in Drosophila may not fully translate to mammalian intestinal stem cells.
(Kraiczy *et al.,* 2023)	Isolation of mouse intestinal crypts and mesenchymal cells. The Crypts derived organoids	Spatial analysis of stromal BMP signaling	BMP-producing and Gremlin1-producing stromal cells establish a BMP gradient that organizes the Wnt niche	Controls crypt stemness and villus differentiation	Limited understanding of how BMP–Wnt crosstalk changes during injury and regeneration.
(Li *et al.,* 2024)	Mouse intestine and organoids	ALK3 deletion and Bcl11b induction	BMP suppresses β-catenin/TCF4 activity through Bcl11b–NuRD complex	Restrains ISC expansion and crypt formation	Human relevance remains uncertain
(Ou *et al.,* 2024)	DSS-induced colitis mice	Intestinal injury model	Wnt and Notch act cooperatively during epithelial repair and regeneration	Regeneration of damaged intestinal epithelium	Injury-specific context
(Gregorieff *et al.,* 2015)	Mouse intestine	Injury-induced YAP activation	YAP transiently suppresses homeostatic Wnt signaling while promoting regeneration	Regenerative reprogramming of $Lgr5^{+}$ cells	Does not directly examine Notch, EGF, or BMP signaling crosstalk
(Ayyaz *et al.,* 2019)	Irradiated and DSS-injured mouse intestine	Single-cell transcriptomics	Revival stem cells emerge after injury and restore the ISC compartment	Injury-induced stem-cell plasticity	Mechanisms linking all pathways remain unresolved

Conclusion and Future Considerations

Current evidence suggests that intestinal stem cell (ISC) fate is controlled by an integrated signaling network rather than by individual pathways acting independently. Wnt/β-catenin signaling is central to ISC maintenance and self-renewal, Notch signaling regulates the balance between absorptive and secretory differentiation largely through the NICD–RBPJ–HES1–ATOH1 axis, and EGF/ErbB signaling supports progenitor-cell proliferation, survival, and regenera-

tion. BMP signaling provides an important spatial constraint on ISC expansion and differentiation through its gradient along the crypt–villus axis and through Wnt-dependent and Wnt-independent mechanisms.

These pathways do not function independently. Wnt interacts with Notch, EGF/ErbB, and BMP signaling at multiple levels, producing context-dependent effects on ISC behaviors. These findings support a model in which the intensity, timing, cellular source,and crosstalk of these signals determine ISC behavior.

Several aspects of this regulatory network remain unresolved. We still do not know exactly how a stem or progenitor cell combines the strength of these different signals to decide its fate, or how this signaling balance changes during normal tissue maintenance, injury, inflammation, and aging. During normal homeostasis, Wnt may mainly support ISC maintenance. However, after injury, Wnt, EGF/ErbB, Notch, and other regenerative signals may become strongly coordinated to promote epithelial repair.

Future studies should therefore combine lineage tracing, single-cell and spatial transcriptomic approaches, organoid and primary human intestinal models, and temporally controlled genetic manipulation to determine how these pathways interact during specific stages of regeneration. Studies incorporating inflammatory, aging, and injury models are also needed to determine whether mechanisms identified during homeostasis remain valid during disease-associated regeneration.

Therapeutic applications require careful consideration of disease context, pathway specificity, dosing, timing, and safety. Persistent or excessive activation of pathways such as Wnt or Notch may disrupt normal differentiation and tissue homeostasis and could have tumor-promoting consequences. Future approaches should aim to understand and precisely manipulate their context-dependent crosstalk to promote effective regeneration while preserving epithelial organization and safety.

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Author contribution ZK: conceptualization, visualization, investigation, data curation, analysis, writing-original draft, writing-review and editing; SS: visualization; SH: writing-review and editing.

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References

Abud HE, Chan WH, Jardé T. 2021. Source and impact of the EGF family of ligands on intestinal stem cells. *Frontiers in Cell and Developmental Biology*, 9: 685665. DOI: 10.3389/fcell.2021.685665.

Acar A, Hidalgo-Sastre A, Leverentz MK, Mills CG, Woodcock S, Baron M, Collu GM, Brennan K. 2021. Inhibition of Wnt signalling by Notch via two distinct mechanisms. *Scientific Reports*, 11(1): 9096. DOI: 10.1038/s41598-021-88618-5.

Almohazey D, Bernard J, Frey M. 2014. ErbB4 deletion compromises the murine small intestinal stem cell niche and sensitizes the epithelium to TNF-induced apoptosis (1119.6). *FASEB Journal*, 28(S1): 1119.6. DOI: 10.1096/fasebj.28.1_supplement.1119.6.

Almohazey D, Lo YH, Vossler CV, Simmons AJ, Hsieh JJ, Bucar EB, Schumacher MA, Hamilton KE, Lau KS, Shroyer NF, Frey MR. 2017. The ErbB3 receptor tyrosine kinase negatively regulates Paneth cells by PI3K-dependent suppression of Atoh1. *Cell Death & Differentiation*, 24(5): 855–865. DOI: 10.1038/cdd.2017.27.

Andersson ER, Sandberg R, Lendahl U. 2011. Notch signaling: simplicity in design, versatility in function. *Development*, 138(17): 3593–3612. DOI: 10.1242/dev.063610.

Arai MA, Akamine R, Tsuchiya A, Yoneyama T, Koyano T, Kowithayakorn T, Ishibashi M. 2018. The Notch inhibitor cowanin accelerates nicastrin degradation. *Scientific Reports*, 8(1): 5376. DOI: 10.1038/s41598-018-23698-4.

Ayaz F, Osborne BA. 2014. Non-canonical notch signaling in cancer and immunity. *Frontiers in Oncology*, 4: 345. DOI: 10.3389/fonc.2014.00345.

Ayyaz A, Kumar S, Sangiorgi B, Ghoshal B, Gosio J, Ouladan S, Fink M, Barutcu S, Trcka D, Shen J, Chan K, Wrana JL, Gregorieff A. 2019. Single-cell transcriptomes of the regenerating intestine reveal a revival stem cell. *Nature*, 569(7754): 121-125. DOI: 10.1038/s41586-019-1154-y.

Barker N. 2014. Adult intestinal stem cells: critical drivers of epithelial homeostasis and regeneration. *Nature Reviews Molecular Cell Biology*, 15(1): 19–33. DOI: 10.1038/nrm3721.

Beumer J, Puschhof J, Yengej FY, Zhao L, Martinez-Silgado A, Blotenburg M, Begthel H, Boot C, van Oudenaarden A, Chen YG, Clevers H. 2022. BMP gradient along the intestinal villus axis controls zonated enterocyte and goblet cell states. *Cell Reports*, 38(9): 110438. DOI: 10.1016/j.celrep.2022.110438.

Borggrefe T, Oswald F. 2009. The Notch signaling pathway: transcriptional regulation at Notch target genes. *Cellular and Molecular Life Sciences*, 66(10): 1631–1646. DOI: 10.1007/s00018-009-8668-7.

Böttcher A, Büttner M, Tritschler S, Sterr M, Aliluev A, Oppenländer L, Burtscher I, Sass S, Irmler M, Beckers J. 2020. Wnt/PCP-primed intestinal stem cells directly differentiate into enteroendocrine or Paneth cells. *bioRxiv*, 2020.2008.12.247585. DOI: 10.1038/s41556-020-00617-2.

Carulli AJ, Keeley TM, Demitrack ES, Chung J, Maillard I, Samuelson LC. 2015. Notch receptor regulation of intestinal stem cell homeostasis and crypt regeneration. *Developmental Biology*, 402(1), 98–108. DOI: 10.1016/j.ydbio.2015.03.012.

Chege N, Finney CAM. 2025. Mechanistic insights into intestinal stem cell disruption during infection. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, 329(3): G371–G389. DOI: 10.1152/ajpgi.00352.2024.

Chen SM, Guo BJ, Feng AQ, Wang XL, Zhang SL, Miao CY. 2024. Pathways regulating intestinal stem cells and potential therapeutic targets for radiation enteropathy. *Molecular Biomedicine*, 5: 46. DOI: 10.1186/s43556-024-00211-0.

Choi J, Augenlicht LH. 2024. Intestinal stem cells: guardians of homeostasis in health and aging amid environmental challenges. *Experimental & Molecular Medicine*, 56(3): 495–500. DOI: 10.1038/s12276-024-01179-1.

Clevers H, Conder RK, Li VSW, Lutolf MP, Vallier L, Chan S, Grikscheit TC, Jensen KB, De Coppi P. 2019. Tissue-engineering the intestine: The trials before the trials. *Cell Stem Cell*, 24(6): 855–859. DOI: 10.1016/j.stem.2019.04.018.

Cordero JB, Stefanatos RK, Myant K, Vidal M, Sansom OJ. 2012. Non-autonomous crosstalk between the Jak/Stat and Egfr pathways mediates Apc1-driven intestinal stem cell hyperplasia in the Drosophila adult midgut. *Development*, 139(24): 4524–4535. DOI: 10.1242/dev.078261.

D'Souza B, Meloty-Kapella L, Weinmaster G. 2010. Canonical and non-canonical Notch ligands. *Current Topics in Developmental Biology*, 92: 73–129. DOI: 10.1016/s0070-2153(10)92003-6.

Demitrack ES, Samuelson LC. 2016. Notch regulation of gastrointestinal stem cells. *Journal of Physiology*, 594(17): 4791–4803. DOI: 10.1113/jp271667.

Farin HF, Van Es JH, Clevers H. 2012. Redundant sources of Wnt regulate intestinal stem cells and promote formation of Paneth cells. *Gastroenterology*, 143(6): 1518–1529.e1517. DOI: 10.1053/j.gastro.2012.08.031.

Fevr T, Robine S, Louvard D, Huelsken J. 2007. Wnt/beta-catenin is essential for intestinal homeostasis and maintenance of intestinal stem cells. *Molecular and Cellular Biology*, 27(21): 7551–7559. DOI: 10.1128/mcb.01034-07.

Flanagan DJ, Austin CR, Vincan E, Phesse TJ. 2018. Wnt Signalling in Gastrointestinal Epithelial Stem Cells. *Genes*, 9(4): 178. DOI: 10.3390/genes9040178.

Flanagan DJ, Phesse TJ, Barker N, Schwab RH, Amin N, Malaterre J, Stange DE, Nowell CJ, Currie SA, Saw JT, Beuchert E, Ramsay RG, Sansom OJ, Ernst M, Clevers H, Vincan E. 2015. Frizzled7 functions as a Wnt receptor in intestinal epithelial Lgr5(+) stem cells. *Stem Cell Reports*, 4(5): 759–767. DOI: 10.1016/j.stemcr.2015.03.003.

Fu Y, Yuan SS, Zhang LJ, Ji ZL, Quan XJ. 2020. Atonal bHLH transcription factor 1 is an important factor for maintaining the balance of cell proliferation and differentiation in tumorigenesis. *Oncology Letters*, 20(3): 2595–2605. DOI: 10.3892/ol.2020.11833.

Gerbe F, Legraverend C, Jay P. 2012. The intestinal epithelium tuft cells: specification and function. *Cellular and Molecular Life Sciences*, 69(17): 2907–2917. DOI: 10.1007/s00018-012-0984-7.

Gregorieff A, Liu Y, Inanlou MR, Khomchuk Y, Wrana JL. 2015. Yap-dependent reprogramming of Lgr5(+) stem cells drives intestinal regeneration and cancer. *Nature*, 526(7575): 715–718. DOI: 10.1038/nature15382.

Hao HX, Xie Y, Zhang Y, Charlat O, Oster E, Avello M, Lei H, Mickanin C, Liu D, Ruffner H, Mao X, Ma Q, Zamponi R, Bouwmeester T, Finan PM, Kirschner MW, Porter JA, Serluca FC, Cong F. 2012. ZNRF3 promotes Wnt receptor turnover in an R-spondin-sensitive manner. *Nature*, 485(7397): 195–200. DOI: 10.1038/nature11019.

He XC, Zhang J, Tong WG, Tawfik O, Ross J, Scoville DH, Tian Q, Zeng X, He X, Wiedemann LM, Mishina Y, Li L. 2004. BMP signaling inhibits intestinal stem cell self-renewal through suppression of Wnt-beta-catenin signaling. *Nature Genetics*, 36(10): 1117–1121. DOI: 10.1038/ng1430.

Hendel SK, Kellermann L, Hausmann A, Bindslev N, Jensen KB, Nielsen OH. 2022. Tuft cells and their role in intestinal diseases. *Frontiers in Immunology*, 13: 822867. DOI: 10.3389/fimmu.2022.822867.

Horiguchi H, Endo M, Kawane K, Kadomatsu T, Terada K, Morinaga J, Araki K, Miyata K, Oike Y. 2017. ANGPTL2 expression in the intestinal stem cell niche controls epithelial regeneration and homeostasis. *EMBO Journal*, 36(4): 409–424. DOI: 10.15252/embj.201695690.

Hsu PC, Jablons DM, Yang CT, You L. 2019. Epidermal Growth Factor Receptor (EGFR) Pathway, Yes-Associated Protein (YAP) and the Regulation of Programmed Death-Ligand 1 (PD-L1) in Non-Small Cell Lung Cancer (NSCLC). *International Journal of Molecular Sciences*, 20(15): 3821. DOI: 10.3390/ijms20153821.

Hu DJ, Yun J, Elstrott J, Jasper H. 2021. Non-canonical Wnt signaling promotes directed migration of intestinal stem cells to sites of injury. *Nature Communications*, 12(1): 7150. DOI: 10.1038/s41467-021-27384-4.

Huang L, Bernink JH, Giladi A, Krueger D, van Son GJF, Geurts MH, Busslinger G, Lin L, Begthel H, Zandvliet M, Buskens CJ, Bemelman WA, López-Iglesias C, Peters PJ, Clevers H. 2024. Tuft cells act as regenerative stem cells in the human intestine. *Nature*, 634(8035): 929–935. DOI: 10.1038/s41586-024-07952-6

Jardé T, Chan WH, Rossello FJ, Kaur Kahlon T, Theocharous M, Kurian Arackal T, Flores T, Giraud M, Richards E, Chan E, Kerr G, Engel RM, Prasko M, Donoghue JF, Abe SI, Phesse TJ, Nefzger CM, McMurrick PJ, Powell DR, Abud HE. 2020. Mesenchymal niche-derived neuregulin-1 drives intestinal stem cell proliferation and regeneration of damaged epithelium. *Cell Stem Cell*, 27(4): 646–662.e647. DOI: 10.1016/j.stem.2020.06.021.

Kabiri Z, Greicius G, Madan B, Biechele S, Zhong Z, Zaribafzadeh H, Edison, Aliyev J, Wu Y, Bunte R, Williams BO, Rossant J, Virshup DM. 2014. Stroma provides an intestinal stem cell niche in the absence of epithelial Wnts. *Development*, 141(11): 2206–2215. DOI: 10.1242/dev.104976.

Katagiri T, Watabe T. 2016. Bone morphogenetic proteins. *Cold Spring Harbor Perspectives in Biology*, 8(6): a021899. DOI: 10.1101/cshperspect.a021899.

Koo BK, Spit M, Jordens I, Low TY, Stange DE, van de Wetering M, van Es JH, Mohammed S, Heck AJ, Maurice MM, Clevers H. 2012. Tumour suppressor RNF43 is a stem-cell E3 ligase that induces endocytosis of Wnt receptors. *Nature*, 488(7413): 665–669. DOI: 10.1038/nature11308.

Korinek V, Barker N, Moerer P, van Donselaar E, Huls G, Peters PJ, Clevers H. 1998. Depletion of epithelial stem-cell compartments in the small intestine of mice lacking Tcf-4. *Nature Genetics*, 19(4): 379–383. DOI: 10.1038/1270.

Kraiczy J, McCarthy N, Malagola E, Tie G, Madha S, Boffelli D, Wagner DE, Wang TC, Shivdasani RA. 2023. Graded BMP signaling within intestinal crypt architecture directs self-organization of the Wnt-secreting stem cell niche. *Cell Stem Cell*, 30(4): 433–449.e438. DOI: 10.1016/j.stem.2023.03.004.

Lee D, Yu M, Lee E, Kim H, Yang Y, Kim K, Pannicia C, Kurie JM, Threadgill DW. 2009. Tumor-specific apoptosis caused by deletion of the ERBB3 pseudo-kinase in mouse intestinal epithelium. *Journal of Clinical Investigation*, 119(9): 2702–2713. DOI: 10.1172/jci36435

Li Y, Liu Y, Liu B, Wang J, Wei S, Qi Z, Wang S, Fu W, Chen YG. 2018. A growth factor-free culture system underscores the coordination between Wnt and BMP signaling in Lgr5(+) intestinal stem cell maintenance. *Cell Discovery*, 4: 49. DOI: 10.1038/s41421-018-0051-0

Li Y, Wang X, Huang M, Wang X, Li C, Li S, Tang Y, Yu S, Wang Y, Song W, Wu W, Liu Y, Chen YG. 2024. BMP suppresses Wnt signaling via the Bcl11b-regulated NuRD complex to maintain intestinal stem cells. *EMBO Journal*, 43(23): 6032–6051. DOI: 10.1038/s44318-024-00276-1

Liang SJ, Li XG, Wang XQ. 2019. Notch Signaling in Mammalian Intestinal Stem Cells: Determining Cell Fate and Maintaining Homeostasis. *Current Stem Cell Research & Therapy*, 14(7): 583–590. DOI: 10.2174/1574888x14666190429143734.

Luo WW, Han Z, Ren DD, Wang XW, Chi FL, Yang JM. 2017. Notch pathway inhibitor DAPT enhances Atoh1 activity to generate new hair cells in situ in rat cochleae. *Neural Regeneration Research*, 12(12): 2092-2099. DOI: 10.4103/1673-5374.221169.

Mah AT, Yan KS, Kuo CJ. 2016. Wnt pathway regulation of intestinal stem cells. *Journal of Physiology*, 594(17): 4837–4847. DOI: 10.1113/jp271754.

Malagola E, Vasciaveo A, Ochiai Y, Kim W, Zheng B, Zanella L, Wang ALE, Middelhoff M, Nienhüser H, Deng L, Wu F, Waterbury QT, Belin B, LaBella J, Zamechek LB, Wong MH, Li L, Guha C, Cheng CW, Wang TC. 2024. Isthmus progenitor cells contribute to homeostatic cellular turnover and support regeneration following intestinal injury. *Cell*, 187(12): 3056–3071.e3017. DOI: 10.1016/j.cell.2024.05.004.

Martens EC, Neumann M, Desai MS. 2018. Interactions of commensal and pathogenic microorganisms with the intestinal mucosal barrier. *Nature Reviews Microbiology*, 16(8): 457–470. DOI: 10.1038/s41579-018-0036-x.

McCarthy N, Manieri E, Storm EE, Saadatpour A, Luoma AM, Kapoor VN, Madha S, Gaynor LT, Cox C, Keerthivasan S, Wucherpfennig K, Yuan GC, de Sauvage FJ, Turley SJ, Shivdasani RA. 2020. Distinct mesenchymal cell populations generate the essential intestinal bmp signaling gradient. *Cell Stem Cell*, 26(3): 391–402.e395. DOI: 10.1016/j.stem.2020.01.008.

McElroy SJ, Castle SL, Bernard JK, Almohazey D, Hunter CJ, Bell BA, Al Alam D, Wang L, Ford HR, Frey MR. 2014. The ErbB4 ligand neuregulin-4 protects against experimental necrotizing enterocolitis. *American Journal of Pathology*, 184(10): 2768–2778. DOI: 10.1016/j.ajpath.2014.06.015.

Meyer, A. R., Brown, M. E., McGrath, P. S., & Dempsey, P. J. (2022). Injury-induced cellular plasticity drives intestinal regeneration. *Cellular and Molecular Gastroenterology and Hepatology*, 13(3): 843–856. DOI: 10.1016/j.jcmgh.2021.12.005.

Morikawa M, Derynck R, Miyazono K. 2016. TGF-β and the TGF-β Family: Context-Dependent Roles in Cell and Tissue Physiology. *Cold Spring Harbor Perspectives in Biology*, 8(5): a021873. DOI: 10.1101/cshperspect.a021873.

Mu Q, Ha A, Santos AJM, Lo YH, van Unen V, Miao Y, Tomaske M, Guzman VK, Alwahabi S, Yuan JJ, Deng L, Li L, Garcia KC, Kuo CJ. 2025. FZD5 controls intestinal crypt homeostasis and colonic Wnt surrogate agonist response. *Developmental Cell*, 60(3): 342–351.e345. DOI: 10.1016/j.devcel.2024.10.022.

Ning H, Liu J, Tan J, Yi M, Lin X. 2023. The role of the Notch signalling pathway in the pathogenesis of ulcerative colitis: from the perspective of intestinal mucosal barrier. *Frontiers in Medicine*, 10: 1333531. DOI: 10.3389/fmed.2023.1333531.

Omrani O, Krepelova A, Rasa SMM, Sirvinskas D, Lu J, Annunziata F, Garside G, Bajwa S, Reinhardt S, Adam L, Käppel S, Ducano N, Donna D, Ori A, Oliviero S, Rudolph KL, Neri F. 2023. IFNγ-Stat1 axis drives aging-associated loss of intestinal tissue homeostasis and regeneration. *Nature Communications*, 14(1): 6109. DOI: 10.1038/s41467-023-41683-y.

Ou W, Xu W, Wang Y, Hua Z, Ding W, Cui L, Du P. 2024. Cooperation of Wnt/β-catenin and Dll1-mediated Notch pathway in Lgr5-positive intestinal stem cells regulates the mucosal injury and repair in DSS-induced colitis mice model. *Gastroenterology Report*, 12: goae090. DOI: 10.1093/gastro/goae090.

Pellegrinet L, Rodilla V, Liu Z, Chen S, Koch U, Espinosa L, Kaestner KH, Kopan R, Lewis J, Radtke F. 2011. Dll1- and dll4-mediated notch signaling are required for homeostasis of intestinal stem cells. *Gastroenterology*, 140(4): 1230–1240.e1231-1237. DOI: 10.1053/j.gastro.2011.01.005.

Qi Z, Li Y, Zhao B, Xu C, Liu Y, Li H, Zhang B, Wang X, Yang X, Xie W, Li B, Han JJ, Chen YG. 2017. BMP restricts stemness of intestinal Lgr5(+) stem cells by directly suppressing their signature genes. *Nature Communications*, 8: 13824. DOI: 10.1038/ncomms13824

Redhai S, Hirschmüller N, Wang T, Bahuguna S, Leible S, Peidli S, Valentani E, Kharuk S, Holzem M, Bräckow L, Port F, Ibberson D, Huber W, Boutros M. 2026. Autoinhibitory feedback preserves intestinal stem cell maintenance and fate commitment. *EMBO Journal*, 45: 4636–4669. DOI: 10.1038/s44318-026-00808-x.

Rothenberg ME, Nusse Y, Kalisky T, Lee JJ, Dalerba P, Scheeren F, Lobo N, Kulkarni S, Sim S, Qian D, Beachy PA, Pasricha PJ, Quake SR, Clarke MF. 2012. Identification of a cKit(+) colonic crypt base secretory cell that supports Lgr5(+) stem cells in mice. *Gastroenterology*, 142(5): 1195–1205.e1196. DOI: 10.1053/j.gastro.2012.02.006

Sancho E, Batlle E, Clevers H. 2004. Signaling pathways in intestinal development and cancer. *Annual Review of Cell and Developmental Biology*, 20(1): 695-723. DOI: 10.1146/annurev.cellbio.20.010403.092805.

Sansom OJ, Reed KR, Hayes AJ, Ireland H, Brinkmann H, Newton IP, Batlle E, Simon-Assmann P, Clevers H, Nathke IS, Clarke AR, Winton DJ. 2004. Loss of Apc in vivo immediately perturbs Wnt signaling, differentiation, and migration. *Genes & Development*, 18(12): 1385–1390. DOI: 10.1101/gad.287404.

Santos AJM, Lo YH, Mah AT, Kuo CJ. 2018. The intestinal stem cell niche: homeostasis and adaptations. *Trends in Cell Biology*, 28(12): 1062–1078. DOI: 10.1016/j.tcb.2018.08.001.

Sarabia-Sánchez MA, Robles-Flores M. 2024. WNT Signaling in Stem Cells: A Look into the Non-Canonical Pathway. *Stem Cell Reviews and Reports*, 20(1): 52–66. DOI: 10.1007/s12015-023-10610-5.

Sato T, van Es JH, Snippert HJ, Stange DE, Vries RG, van den Born M, Barker N, Shroyer NF, van de Wetering M, Clevers H. 2011. Paneth cells constitute the niche for Lgr5 stem cells in intestinal crypts. *Nature*, 469(7330): 415–418. DOI: 10.1038/nature09637.

Suzuki A, Sekiya S, Gunshima E, Fujii S, Taniguchi H. 2010. EGF signaling activates proliferation and blocks apoptosis of mouse and human intestinal stem/progenitor cells in long-term monolayer cell culture. *Laboratory Investigation*, 90(10): 1425–1436. DOI: 10.1038/labinvest.2010.150.

Takahashi T, Shiraishi A. 2020. Stem Cell Signaling Pathways in the Small Intestine. *International Journal of Molecular Sciences*, 21(6): 2032. DOI: 10.3390/ijms21062032.

Tian H, Biehs B, Chiu C, Siebel CW, Wu Y, Costa M, de Sauvage FJ, Klein OD. 2015. Opposing activities of Notch and Wnt signaling regulate intestinal stem cells and gut homeostasis. *Cell Reports*, 11(1): 33–42. DOI: 10.1016/j.celrep.2015.03.007.

Tomita K, Moriyoshi K, Nakanishi S, Guillemot F, Kageyama R. 2000. Mammalian achaete-scute and atonal homologs regulate neuronal versus glial fate determination in the central nervous system. *EMBO Journal*, 19(20): 5460–5472. DOI: 10.1093/emboj/19.20.5460.

Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. 2017. Crohn's disease. *Lancet*, 389(10080): 1741–1755. DOI: 10.1016/S0140-6736(16)31711-1.

VanDussen KL, Carulli AJ, Keeley TM, Patel SR, Puthoff BJ, Magness ST, Tran IT, Maillard I, Siebel C, Kolterud Å, Grosse AS, Gumucio DL, Ernst SA, Tsai YH, Dempsey PJ, Samuelson LC. 2012. Notch signaling modulates proliferation and differentiation of intestinal crypt base columnar stem cells. *Development*, 139(3): 488–497. DOI: 10.1242/dev.070763.

Vanuytsel T, Senger S, Fasano A, Shea-Donohue T. 2013. Major signaling pathways in intestinal stem cells. *Biochimica et Biophysica Acta*, 1830(2): 2410–2426. DOI: 10.1016/j.bbagen.2012.08.006

Wang L, Zhu F, Yang H, Li J, Li Y, Ding X, Xiong X, Ji F, Zhou H, Yin Y. 2019. Epidermal growth factor improves intestinal morphology by stimulating proliferation and differentiation of enterocytes and mTOR signaling pathway in weaning piglets. *Science China Life Sciences*, 63: 259–268. DOI: 10.1007/s11427-018-9519-6.

Wang LX, Zhu F, Li JZ, Li YL, Ding XQ, Yin J, Xiong X, Yang HS. 2020. Epidermal growth factor promotes intestinal secretory cell differentiation in weaning piglets via Wnt/β-catenin signalling. *Animal*, 14(4): 790–798. DOI: 10.1017/s1751731119002581.

Wang S, Chen YG. 2018. BMP signaling in homeostasis, transformation and inflammatory response of intestinal epithelium. *Science China Life Sciences*, 61(7): 800–807. DOI: 10.1007/s11427-018-9310-7.

Wang X, Li S, Liu Y, Kuang X, Chen J, Yu P, Zhao L, Zhang Z, Huang M, Liu L, Zhang M, Wang Y, Ji W, Li J, Zhang L, Chen YG. 2025. Positional BMP signaling orchestrates villus length in the small intestine. *Nature Communications*, 16: 5461. DOI: 10.1038/s41467-025-60643-2.

Wang Z, Qu YJ, Cui M. 2023. Modulation of stem cell fate in intestinal homeostasis, injury and repair. *World Journal of Stem Cells*, 15(5): 354–368. DOI: 10.4252/wjsc.v15.i5.354.

Wilson KJ, Gilmore JL, Foley J, Lemmon MA, Riese DJ, 2nd. 2009. Functional selectivity of EGF family peptide growth factors: implications for cancer. *Pharmacology & Therapeutics*, 122(1): 1-8. DOI: 10.1016/j.pharmthera.2008.11.008.

Wu F, Stutzman A, Mo YY. 2007. Notch signaling and its role in breast cancer. *Frontiers in Bioscience-Landmark*, 12: 4370–4383. DOI: 10.2741/2394.

Xue C, Chu Q, Shi Q, Zeng Y, Lu J, Li L. 2025. Wnt signaling pathways in biology and disease: mechanisms and therapeutic advances. *Signal Transduction and Targeted Therapy*, 10: 106. DOI: 10.1038/s41392-025-02142-w.

Yan KS, Janda CY, Chang J, Zheng GXY, Larkin KA, Luca VC, Chia LA, Mah AT, Han A, Terry JM, Ootani A, Roelf K, Lee M, Yuan J, Li X, Bolen CR, Wilhelmy J, Davies PS, Ueno H, Kuo CJ. 2017. Non-equivalence of Wnt and R-spondin ligands during Lgr5(+) intestinal stem-cell self-renewal. *Nature*, 545(7653): 238–242. DOI: 10.1038/nature22313.

Yang L, Wang X, Zhao G, Deng L, Yin X. 2024. Leveraging Temporal Wnt Signal for Efficient Differentiation of Intestinal Stem Cells in an Organoid Model. *Stem Cells and Development*, 33(1-2): 11-26. DOI: 10.1089/scd.2023.0186.

Yu LE, Yang WC, Liang YC. 2024. Crosstalk Within the Intestinal Epithelium: Aspects of Intestinal Absorption, Homeostasis, and Immunity. *Biomedicines*, 12(12): 2771. DOI: 10.3390/biomedicines12122771.

Yui S, Azzolin L, Maimets M, Pedersen MT, Fordham RP, Hansen SL, Larsen HL, Guiu J, Alves MRP, Rundsten CF, Johansen JV, Li Y, Madsen CD, Nakamura T, Watanabe M, Nielsen OH, Schweiger PJ, Piccolo S, Jensen KB. 2018. YAP/TAZ-Dependent Reprogramming of Colonic Epithelium Links ECM Remodeling to Tissue Regeneration. *Cell Stem Cell*, 22(1): 35–49.e37. DOI: 10.1016/j.stem.2017.11.001.

Zhang C, Jin Y, Marchetti M, Lewis MR, Hammouda OT, Edgar BA. 2022a. EGFR signaling activates intestinal stem cells by promoting mitochondrial biogenesis and β-oxidation. *Current Biology*, 32(17): 3704–3719.e3707. DOI: 10.1016/j.cub.2022.07.003.

Zhang J, Li L. 2005. BMP signaling and stem cell regulation. *Developmental Biology*, 284(1): 1-11. DOI: 10.1016/j.ydbio.2005.05.009.

Zhang Q, Hao S, Li L, Liu M, Huo C, Bao W, Cheng H, Fung H, Wong T, Wu W, Leung P, Wang S, Li T, Zhang G, Li M, Zhao Z, Jia W, Bian Z, Mitchison T, Han Q. 2022b. M cells of mouse and human Peyer's patches mediate the lymphatic absorption of an Astragalus hyperbranched heteroglycan. *Carbohydrate Polymeres*, 296: 119952. DOI: 10.1016/j.carbpol.2022.119952.

Zhang Y, Que J. 2020. BMP signaling in development, stem cells, and diseases of the gastrointestinal tract. *Annual Review of Physiology*, 82: 251–273. DOI: 10.1146/annurev-physiol-021119-034500.

Zhao D, Ravikumar V, Leach TJ, Kraushaar D, Lauder E, Li L, Sun Y, Oravecz-Wilson K, Keller ET, Chen F, Maneix L, Jenq RR, Britton R, King KY, Santibanez AE, Creighton CJ, Rao A, Reddy P. 2024. Inflammation-induced epigenetic imprinting regulates intestinal stem cells. *Cell Stem Cell*, 31(10): 1447–1464.e1446. DOI: 10.1016/j.stem.2024.08.006.

Zou WY, Blutt SE, Zeng XL, Chen MS, Lo YH, Castillo-Azofeifa D, Klein OD, Shroyer NF, Donowitz M, Estes MK. 2018. Epithelial WNT ligands are essential drivers of intestinal stem cell activation. *Cell Reports*, 22(4): 1003–1015. DOI: 10.1016/j.celrep.2017.12.093.