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Thyroid hormone regulation of adult intestinal stem cells: Implications on intestinal development and homeostasis

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Abstract Organ-specific adult stem cells are essential for organ homeostasis, tissue repair and regeneration. The formation of such stem cells often takes place during postembryonic development, a period around birth in mammals when plasma thyroid hormone concentration is high. The life-long self-renewal of the intestinal epithelium has made mammalian intestine a valuable model to study the function and regulation and adult stem cells. On the other hand, much less is known about how the adult intestinal stem cells are formed during vertebrate development. Here, we will review some recent progresses on this subject, focusing mainly on the formation of the adult intestine during *Xenopus* metamorphosis. We will discuss the role of thyroid hormone signaling pathway in the process and potential molecular conservations between amphibians and mammals as well as the implications in organ homeostasis and human diseases.

Keywords Thyroid hormone receptor · Stem cell · Metamorphosis · *Xenopus laevis* and *tropicalis* · Postembryonic development · Intestine

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1 Introduction

Adult organ-specific stem cells are critical for organ-homeostasis, tissue-repair and regeneration. The adult mammalian intestine, especially the mouse intestine, has been a valuable model system to study adult organ-specific stem cells largely because of their constant self-renewal of the intestinal epithelium throughout adult life [1–6]. In the intestine, the stem cells residing at the bottom of the crypts, proliferate and their daughter cells differentiate into different epithelial cell types as they migrate along the crypt-villus axis, and eventually undergo apoptosis at the tip of the villus, thus completing the self-renewing cycle once every 1-6 days in adult mammals [2, 7, 8]. Similar processes occur in the intestine in all vertebrates, including amphibians, with self-renewing once every 2 weeks in *Xenopus laevis* [9]. Such interesting properties together with the development of a number of technologies, such as transgenesis and knockout as well as in vitro cultures, have enabled extensive studies that have revealed important mechanistic insights on the function and properties of the adult stem cells, including many molecular pathways governing stem cells [2, 10]. On the other hand, much less is known about when and how such adult intestinal stem cells are formed during vertebrate development, largely due to the difficulty to manipulate uterus-enclosed mammalian embryos.

Early studies suggests that in mouse, the formation of adult intestinal stem cells takes place shortly after birth when plasma thyroid hormone (T3) level high [3, 11–13], suggesting that T3 plays an important role in the formation of adult intestinal stem cells. Furthermore, TR deficiency leads to defects of the intestinal development, underlining the importance of this hormone. It is, however, difficult to study the role of T3 on intestinal maturation in mammals because of the dependence of the mammalian embryos or even neonates on the maternal supply of nutrients, making it difficult to separate the direct vs.

indirect effects of T3 on the embryos or neonates. Interestingly, this postembryonic developmental period in mammals resembles anuran metamorphosis in many aspects [14, 15]. Importantly, amphibian metamorphosis offers a number of advantages to study T3 action in vertebrate development. First, its total dependence on T3 makes it easy to manipulate this process in both intact animals and organ/primary cell cultures [14–16]. Second, extensive earlier studies have provided detailed biochemical, morphological, cytological, and molecular information on the metamorphic transformation of different organs/tissues [14–16]. Finally, the development of transgenic, gene knockout and knockin technologies have made it possible to carry out genetic studies in amphibians, especially the widely used, highly related species *Xenopus laevis* and *tropicalis* [17–26].

Intestinal remodeling during amphibian metamorphosis bears many similarities to the maturation of mammalian intestine during the neonatal period, also referred to as the postembryonic development [15]. In the *Xenopus laevis* and *tropicalis,* the tadpole intestine is a simple tubular structure made of mainly larval epithelial cells with little connective tissue or muscles, except in the single epithelial fold, the typhlosole, where connective tissue is abundant (Fig. 1) [27, 28]. During metamorphosis, the tadpole epithelium degenerates with the vast majority of the cells undergoing apoptosis. Some larval epithelial cells, however, dedifferentiate into highly proliferative cells that express well-known markers of adult mammalian intestinal stem cells, such as leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5) and Musashi-1 (Msi-1) [29–31]. These adult stem cells

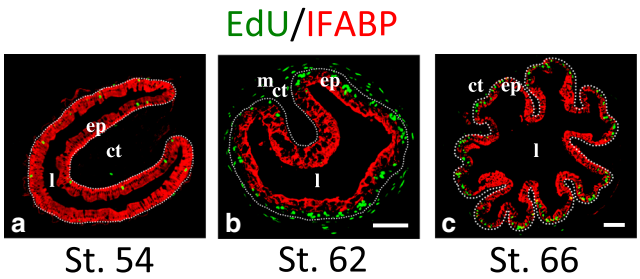

Fig. 1 Intestinal metamorphosis involves the formation of clusters of proliferating, undifferentiated epithelial cells at the climax. Tadpoles at premetamorphic stage 54 (**a**), climax (**b**, stage 62), and end of metamorphosis (**c**, stage 66) were injected with EdU one hour before being sacrificed. Cross-sections of the intestine from the resulting tadpoles were double-stained for EdU (5-Ethynyl-2'-deoxyuridine, labeling newly synthesized DNA) and IFABP (intestinal fatty acid binding protein, a marker for differentiated epithelial cells) by immunohistochemistry. The *dotted lines* depict the epithelium-mesenchyme boundary. Note that the EdU-labeled proliferating cells in the epithelium were few and expressed IFABP at premetamorphosis (**a**) and increased in form of clustered cells (proliferating adult stem cells) that lacked IFABP at the climax of metamorphosis (**b**). At the end of metamorphosis, EdU-labeled proliferating cells were localized mainly in the troughs of the epithelial folds where IFABP expression was low (**c**). ep, epithelium. ct, connective tissue. m, muscles. l, lumen. See [29] for more details

subsequently proliferate and differentiate to form the adult epithelium. Concurrently, the connective tissue and muscles also develop extensively. The resulting frog intestine contains numerous epithelial folds that resemble the crypt-villus structure in mammals and are surrounded by thick layers of connective tissue and muscles [1, 27, 28, 32, 33]. As in adult mammals, throughout adult frog life, the stem cells localized in the trough of the fold proliferate and the daughter cells differentiate into different epithelial cells as they migrate up toward the crest of the fold, where they undergo apoptosis [27].

2 T3 regulation of adult intestinal stem cell development during *Xenopus* metamorphosis

Like during mammalian postembryonic development, T3 levels peak during amphibian metamorphosis with little T3 present in premetamorphic tadpoles [14, 34]. More importantly, blocking the synthesis of endogenous T3 prevents metamorphosis while addition of physiological levels of T3 to the rearing water of premetamorphic tadpoles or even organ cultures derived from premetamorphic tadpoles induces precocious metamorphosis, indicating that T3 plays a causative role on amphibian metamorphosis [14, 34]. Thus, T3-treatment of premetamorphic tadpoles leads to precocious remodeling of the intestine, including the formation of adult intestinal stem cells [27]. Importantly, this process is organ-autonomous as T3 can even induce the formation of adult intestinal stem cells as well as the adult intestinal epithelium when the intestinal organ cultures from premetamorphic tadpoles are treated with physiological levels of T3 [1, 35–38]. Making use of the ability to generate transgenic animals expressing GPF and carrying out recombinant intestinal organ cultures, we have demonstrated that adult epithelial stem cells induced by T3 treatment have their origin in the larval epithelium [32]. Since there has been no evidence for the existence of epithelial stem cells in the larval epithelium [27, 39], these findings suggest that T3 induces some larval cells to develop into adult intestinal stem cells.

3 Mechanism of gene regulation by TR and an essential role of TR in *Xenopus* development and adult stem cell formation

T3 has both genomic and non-genomic effects. The non-genomic effects are mediated by cell surface and cytoplasmic binding proteins, including TRs, although their role in vertebrate development, if any, is unknown [40–45]. At the genomic level, T3 regulates gene transcription through T3 receptors or TRs [14, 40–42, 44, 46]. TRs can both activate and repress gene transcription. For genes that are induced by T3, TR mainly functions as heterodimers formed with 9-cis retinoic acid receptors (RXRs), members of the nuclear

hormone receptor superfamily that also include TRs [40, 42, 44, 46, 47]. TR/RXR heterodimers bind to T3-response elements (TREs) in target genes constitutively to regulate target gene expression in a T3-dependent manner [40, 42, 44, 47–50]. In the absence of T3, TR binds to histone deacetylase-containing corepressor complexes to repress transcription [51–67]. When T3 is available, TR binds coactivator complexes, such as those containing histone acetyltransferases SRC (steroid receptor coactivator) 1-3 and histone methyltransferase PRMT1 (protein arginine methyltransferase 1), to facilitate epigenetic modification and gene transcription [42, 56, 68–89]. Molecular studies such as chromatin immunoprecipitation (ChIP) assays have shown that TR and RXR are indeed bound to T3-inducible genes constitutively in pre- and metamorphosing *Xenopus laevis* and *tropicalis* tadpoles and recruits corepressor and coactivator complexes in a T3 dependent manner in vivo [67, 81, 86–94]. This leads to corresponding changes in local chromatin structure and histone modifications, accompanying changes in gene transcription [93–98].

To study the role of TRs in *Xenopus* development, we and others first used transgenic approach to overexpress mutant receptors to show that TR is both necessary and sufficient to mediate the metamorphic effects of T3 [45, 98–112]. To specifically determine the involvement of TR in the formation of adult intestinal stem cells, we generated recombinant organ cultures of the isolated intestinal epithelium and the non-epithelium (the rest of the intestine) from wild type and transgenic animals expressing a dominant positive TR (dpTR) under the control of a heat shock-inducible promoter [102, 113]. This dpTR functions like constitutively liganded TR except that it does not bind to T3. We observed that when dpTR was induced to express in all tissues of the intestine, intestinal metamorphosis, including larval epithelial cell death and adult stem cell formation, took place even in the absence of T3 [113]. More importantly, we showed that expression of dpTR in the larval epithelium alone is able to induce the dedifferentiation of larval epithelial cells to upregulate sonic hedgehog gene, which is highly expressed in the proliferating adult epithelial progenitor/stem cells. Interestingly, such cells fail to upregulate the expression of well-known adult stem cell markers, such as Msi-1, and the formation of the stem cells expressing such markers also requires the expression of dpTR in the rest of the intestinal tissues (the non-epithelium) in the recombinant organ cultures (Fig. 2) [113]. Theses findings indicate that TR is necessary and sufficient for T3-induction of stem cell formation and that this process requires T3 action in both epithelium and non-epithelium, with the latter likely contribute to the formation of the so-called stem cell niche [35, 107, 113, 114]. They further suggest that T3-regulated genes in both the epithelium and non-epithelium are required for stem cell development. Many such tissue-specific T3-regulated genes have been identified and the analyses of the spatio-temporal expression profiles of some of the epithelial genes indeed support their involvement in adult stem cell formation/proliferation [115–120].

4 A role of PRMT1 in thyroid hormone-dependent intestinal stem cell development in *Xenopus*

Among the T3-regulated genes during intestinal metamorphosis is PRMT1, which has been shown to function as a TR coactivator [79]. PRMT1 binds to SRC1-3 and is capable of methylating histone H4 arginine 3 (H4R3) [121]. Consistently, during intestinal remodeling, PRMT1 is recruited by TR to endogenous target genes and transgenic overexpression of PRMT1 enhances TR target gene expression and accelerates metamorphosis in *Xenopus laevis* [81].

More importantly, PRMT1 is highly upregulated specifically in the developing/proliferating adult intestinal stem cells during metamorphosis and that its upregulation is one of the earliest events during the dedifferentiation of the larval epithelial cells in their transformation into adult stem cells (Fig. 3), suggesting a role of PRMT1 in this process. In support of this, heat shock treatment of transgenic tadpoles which had transgenic wild type PRMT1 under the control of a heat shock-inducible promoter resulted in an increased number of intestinal stem cells during metamorphosis and knockdown the endogenous PRMT1 with antisense morpholino oligonucleotide reduced the number of such stem cells [13]. It is likely that PRMT1 affects the formation and/or proliferation of adult intestinal stem cells during metamorphosis by enhancing T3 signaling. In addition, PRMT1 may also act as a coactivator for other transcription factors to affect gene expression or influence the function of other proteins through methylation during stem cell development and proliferation.

5 Conservation of T3-dependent intestinal stem cell development in vertebrates

As indicated in the introduction, the maturation of the intestine occurs around the time when plasma T3 levels are high in other vertebrates such as mammals, a period resembling amphibian metamorphosis. Furthermore, T3 or TR deficiency in mouse leads to abnormal intestinal morphology, a decrease in the number of epithelial cells along the crypt-villus axis and in proliferating crypt cells [122–125]. It has also been shown that TRα1 controls intestinal development during maturation at weaning as well as intestinal homeostasis in adulthood by activating the proliferation of intestinal progenitors in the crypt [126]. Thus, T3 and TR may have conserved roles in regulating the formation of vertebrate adult intestinal stem cells. Studies on PRMT1 expression during mouse and zebrafish development support this conservation. Little PRMT1 or no expression is present in the larval/neonatal intestine in zebrafish or mouse when plasma T3 levels were low.

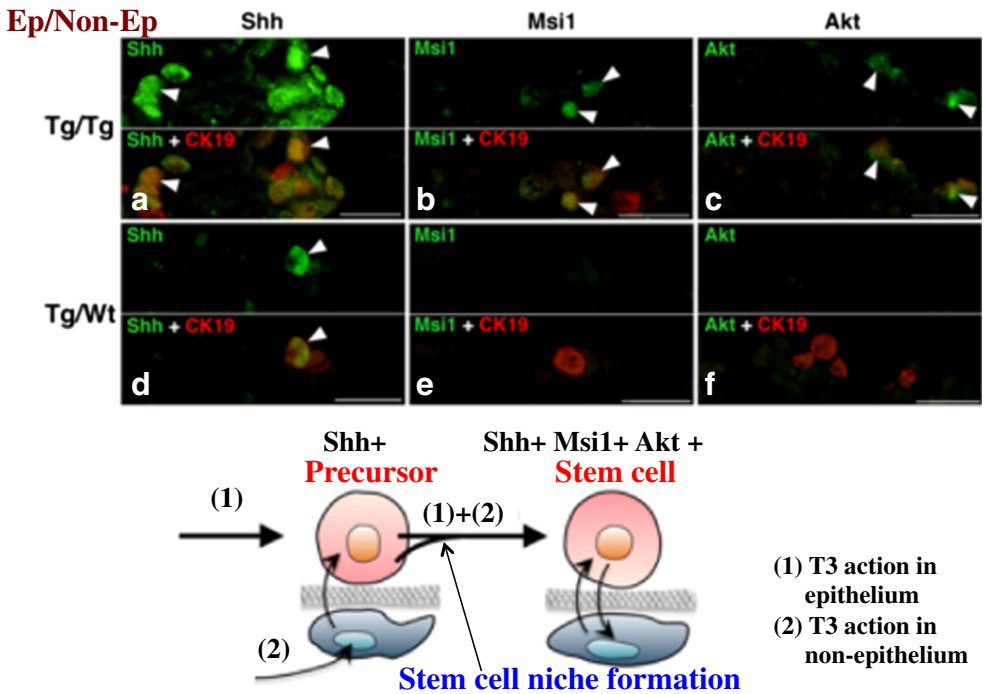

Fig. 2 *Top*. Recombinant intestinal organ culture studies using dpTR-expressing transgenic (Tg) and wild type (Wt) tadpoles indicate that only when both the epithelium (Ep) and non-Ep (the rest of the intestine) are derived from Tg animals, i.e., Tg/Tg, are true stem cells formed. Recombinants made of Tg Ep and Tg non-Ep (Tg/Tg) and Tg Ep and Wt non-EP (Tg/Wt) of premetamorphic intestines were cultured with heat shock treatment for 5 days in vitro. Cross sections were double-immunostained with anti-Shh (*green*, sonic hedgehog, an adult stem cell precursor marker) and anti-CK19 (red, cytokeratin-19, which is expressed in epithelial cells), or anti-Msi-1 (green, Musashi-1, a stem cell marker of the vertebrate adult intestine) and anti-CK19 (red), or anti-Akt (green, a stem cell marker of the vertebrate adult intestine) and anti-CK19 (red) antibodies. In both Tg/Tg (arrowheads) and Tg/Wt intestines, cells positive for Shh and CK19 become detectable among cells expressing, indicating the Shh positive cells can be induced by cell-autonomous action of activated TR in the epithelium. Cells positive for Msi1 and Akt are also detected among CK19- immunoreactive cells in Tg/Tg intestine (*arrowheads*) but not in Tg/Wt intestine. Thus, activation of TR in the non-epithelial tissues is also required for the stem cell formation. Not shown here is that most of the epithelial cells undergo apoptosis when dpTR is expressed in either the EP or non-EP or both, just like that during metamorphosis when T3 binds to TR. See [113] for details. *Bottom*: A model for T3 actions during stem cell development in *Xenopus laevis* intestine. During metamorphosis, T3 acts directly (*1*) on the larval epithelium as well as (*2*) on the rest of the intestine (the non-epithelium), mostly the connective tissue. The vast majority of the larval epithelial cells are induced to undergo programmed cell death but a small number of the larval cells within the larval epithelium undergo dedifferentiation upon receiving the T3 signal (*1*) to dedifferentiate into Shh positive precursor cells. However, T3 action in the non-epithelium (*2*) is required for these cells to develop into stem cells expressing Msi1 and Akt, with the T3 action in the non-epithelium likely contributes to the establishment of the stem cell niche

During the transition to the adult intestine when T3 levels are high [127, 128], PRMT1 mRNA is upregulated specifically in the bottom of the developing epithelial fold or crypt in the intestine of zebrafish or mouse, respectively, suggesting that T3 regulates the development of the adult epithelial stem cells in zebrafish and mouse intestine in a process that requires high levels of PRMT1, similar to that during *Xenopus* metamorphosis. The findings also argue that the embryonic/neonatal mouse intestinal stem cells are molecularly distinct from those in the adult mouse intestine.

Two subsequent mouse genetic studies on the transcriptional repressor, B lymphocyte-induced maturation protein 1 (Blimp1) have also provided evidence to support that mouse adult intestinal stem cells are distinct from the embryonic/neonatal epithelial or stem cells [11, 12]. Blimp1 is strongly expressed throughout the intestinal epithelium of embryonic and newborn mice when there are no crypts. Shortly after birth as the intestine matures into the adult form with crypt-villus axis, Blimp1 expression is down-regulated in the intervillus pockets where crypts begin to develop, while its expression in the rest of the epithelial cells persists. As the crypts develop, all cells in the newly formed crypts lack Blimp1 expression and eventually, Blimp1 expression is absent throughout the epithelium in the adult intestine. Thus, the loss of Blimp1 expression in the developing crypt is likely one of the early events for the embryonic/neonatal epithelial cells to develop into the adult stem cells, whose offspring subsequently populate the epithelium in the adult intestine. Subsequently, it has been shown that Blimp1 helps to maintain neonatal tolerance during postembryonic intestinal maturation [129]. These findings suggest that Blimp1 is important for maintaining the natal stage of the intestine and the delay of the formation of adult

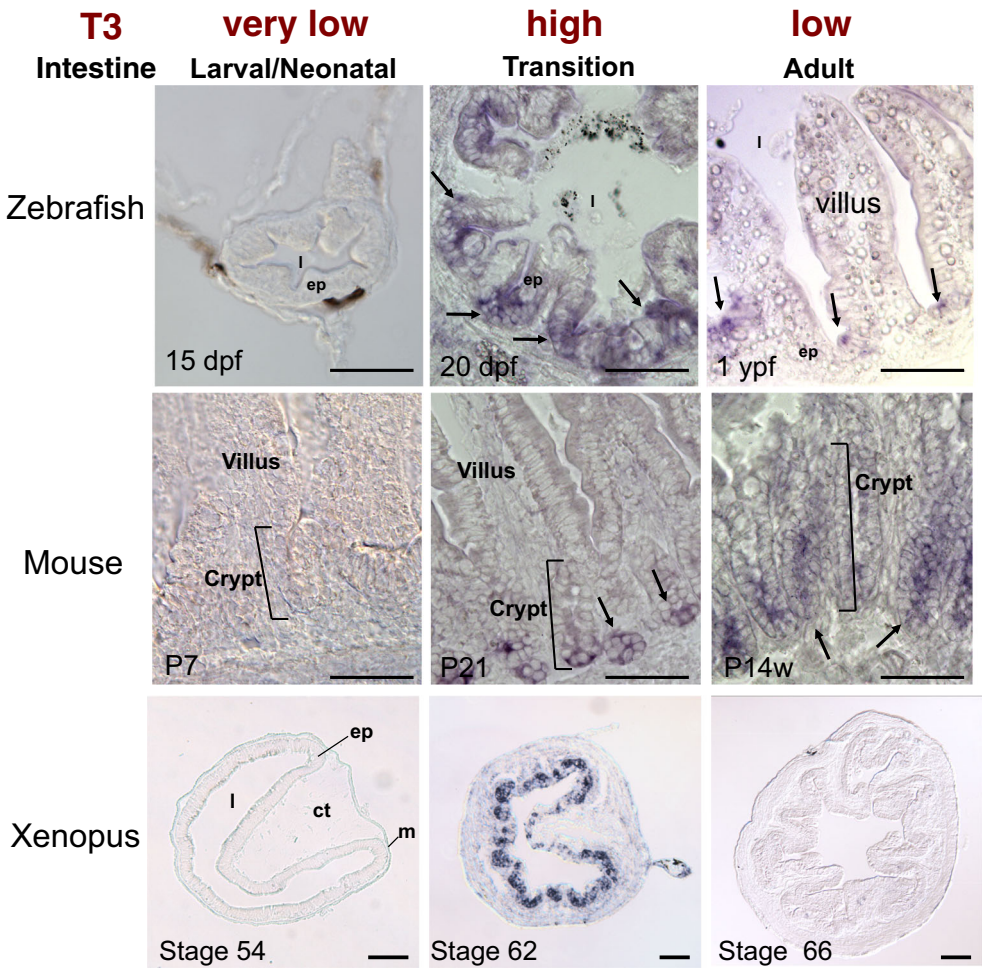

Fig. 3 PRMT1 has conserved spatiotemporal expression patterns during postembryonic intestinal development in *Xenopus laevis,* fish, and mouse. PRMT1 mRNA was analyzed by in situ hybridization in the intestines at three different developmental stages: larval/neonatal when plasma T3 level is low; larval to adult transition when T3 level is high, and end of the transition when T3 is low, in three different animal species. The stages were stage 54 (premetamorphosis), stage 62 (metamorphic climax), and stage 66 (end of metamorphosis for *Xenopus laevis*; 15 days post fertilization (dpf), 20 dpf and 1 year post fertilization (ypf) for zebrafish; and postnatal day 7 (P7), P21, and postnatal week 14 (P14w) for mouse, respectively. *Arrows* indicate PRMT1 positive cells in the intestinal epithelium of zebrafish and mouse. Note that there was little PRMT1 expression in the larval/neonatal stage prior to the transformation in all three species. As T3 level rose during intestinal transformation to the adult type, high levels of PRMT1 expression was detected only in the proliferating/stem cells located in the crypts in both mouse and zebrafish and in the clusters of cells in the epithelium at climax of metamorphosis in *Xenopus laevis*. ep, epithelium. ct, connective tissue. m, muscles. l, lumen. *Bars*, 50 μm for zebrafish and mouse, 100 μm for *Xenopus*. See [13] for details

stem cells while PRMT1 is important for the development of the adult intestinal stem cells and that the two genes may function to keep a balance during transition from the neonatal to adult stage.

6 T3 and adult intestinal physiology and diseases

Aside from its roles in development, T3 is also critical for normal physiological functions of most, if not all, organs in the adult vertebrates and T3 levels regulates metabolic rate [130–132]. T3 and/or T3 metabolism is known to affect stem cell function and regeneration in different tissues including muscle and neurons [133–137]. Similarly, a number of studies suggest that T3 signaling is also critical for adult intestinal physiology. First, recent discoveries of human patients with mutations in TRα revealed that disrupting liganded TRα function causes distinct pathological problems in human compared to similar mutations in the human TRβ [138–141]. In particular, such patients have constipations, suggesting intestinal defects due to the TRα mutations [139–141]. Second, altered T3 levels are associated with intestinal abnormalities and diseases. For example, increased rate of thyroid disorders has been observed in patients with inflammatory bowl diseases (IBD), such as ulcerative colitis and Crohn's disease [142]. Third, studies in mouse have shown that T3 deficiency or TRα knockout results in abnormal intestinal morphology

and a decrease in stem cell proliferation in the adult [122–126]. Finally, in thyroid patients with either hypothyroidism or hyperthyroidism, gastrointestinal manifestations are common signs of the disease. These include reduced motility in hypothyroidism vs. increased motility in hyperthyroidism, autoimmune gastritis, or esophageal compression [143]. Patients with hyperthyroidism can experience frequent bowel movements, diarrhea, nausea and vomiting, while those with hypothyroidism have overall decreased metabolic function accompanied by slow intestinal motility and constipation [144].

T3 and TRs have also been implicated to play a role in intestinal tumorigenesis. Transgenic overexpression of TRα in the intestinal epithelium leads to abnormal intestine that has increased cell proliferation and adenoma in wild type mice; TRα overexpression also synergizes with over-activation of WNT signaling caused by mutations in the WNT pathway to induce intestinal tumorigenesis [5, 145, 146]. Additionally, TRβ mutations and altered TR expression have been reported in intestinal tumors [147–149]. Since intestinal tumor development is likely due to neoplastic transformation of intestinal stem cells [150–152], T3 and TR presumably affect intestinal tumorigenesis by regulating adult intestinal stem cells, as suggested by the adult intestinal phenotypes caused by T3 or TR deficiency in mouse [122–126].

Many T3-regulated genes have also been isolated in the mouse intestinal crypts [124]. T3 may affect intestinal physiology and pathogenesis through these target genes. Of particular interests are genes in the Wnt and Notch signaling pathways, which are known to be important for adult intestinal stem cell function [124, 153, 154]. One such gene is the secreted frizzled-related protein 2 (sFRP2), which is strongly upregulated by T3 in the intestinal crypt and modulates cell fate by regulating Wnt signaling [153]. Similarly, TRα has been shown to directly regulate the transcription of Jag1 gene, a member of the Notch pathway [154]. Additionally, as indicated above, the TR coactivator PRMT1 is also highly upregulated in the developing adult intestinal stem cells during mouse postembryonic intestinal maturation [13]. It remains to be investigated whether PRMT1 plays role in T3-regulation of the Wnt and Notch pathways. On the other hand, our recent unpublished studies suggest that epithelial expression of PRMT1 is required for the proper maturation of the mouse intestine as well as intestinal repair (Roediger, J. and Shi, Y.-B., unpublished observation), supporting a role of PRMT1 in adult intestinal stem cell development and function. Additionally, PRMT1 is overexpressed in colon cancers as well as may other cancers and silencing PRMT1 expression suppresses cancer cell growth, suggesting that PRMT1 also play a role in intestinal cancers [155, 156]. Furthermore, PRMT1 has been associated with other intestinal diseases such as Hischsprung disease, also known as congenital megacolon [157], and lipopolysaccharide-induced intestine tissue inflammation [158]. Thus, proper spatiotemporal expression of PRMT1 is critical for ensuring normal intestinal physiology and preventing diseases, possibly through regulating adult intestinal stem cell function.

Given the involvement of T3 in intestinal diseases and physiology, one may expect that genes involved in T3 synthesis and metabolism also play a role. In particular, T3 is synthesized as through the deiodination of thyroxin (T4) and can be metabolized through further deiodination. There are three deiodinases, D1, D2, and D3, in vertebrates, with D1 and D2 capable of converting T4 to T3 while D3 inactivates T3. It has been shown that the expression of deiodinases is altered in several types of human cancers, including the overexpression of D3 in human colorectal cancers [159–161]. D3 is a direct downstream target of the Wnt/ β-catenin pathway and thus represents an interface between the β-catenin and T3 signaling pathways [160]. β-catenin stimulates D3 and reduces D2, the T4 activating deiodinase, leading to a decrease in intracellular T3. The reduction in T3 in turn promotes cell proliferation while inhibiting E-cadherin expression and cell differentiation. In colon cancer cells the activity of the Wnt/ β-catenin pathway is elevated and the expression of D3 is high, suggesting that hormone activation and inactivation pathways are critical in tumorigenesis [160, 162]. Furthermore, T3 treatment of colorectal cancer spheres represses Wnt pathway and inhibits tumorigenic potential, indicating that T3 signaling is a strong determinant in tumorigenesis [162].

7 Conclusion

The external development and total dependence of amphibian metamorphosis on T3 and TR has enabled easy manipulation of this process for molecular and genetic studies of postembryonic organ development in vertebrates [45, 93, 94, 97, 98, 100, 163]. In particular, the analyses of intestinal metamorphosis in *Xenopus laevis* and *Xenopus tropicalis* have revealed important mechanistic insights on how T3 induces the formation of adult intestinal stem cells and identified many candidate adult stem cell genes. These studies as well as those in other vertebrates, especially mouse, have revealed conserved roles and mechanisms in the intestinal development and also implicated a role of T3 in regulating adult intestinal stem cell functions during normal physiology and pathogenesis, especially tumorigenesis. Clearly, functional studies of the candidate stem cells genes in mouse and frogs are needed to determine their roles in these processes. The recent advancements in knockout and knockin technologies in *Xenopus* [19–26] further enhances the value of the amphibian model for studying the role of adult organ-specific stem cells in human intestinal homeostasis and diseases.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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