Cellular and Molecular Life Sciences (2022) 79: 476
https://doi.org/10.1007/s00018-022-04503-y

REVIEW

Thyroid hormone signaling in the intestinal stem cells and their niche

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Received: 1 April 2022 / Revised: 18 July 2022 / Accepted: 22 July 2022 / Published online: 10 August 2022

Abstract

Several studies emphasized the function of the thyroid hormones in stem cell biology. These hormones act through the nuclear hormone receptor TRs, which are T3-modulated transcription factors. Pioneer work on T3-dependent amphibian metamorphosis showed that the crosstalk between the epithelium and the underlying mesenchyme is absolutely required for intestinal maturation and stem cell emergence. With the recent advances of powerful animal models and 3D-organoid cultures, similar findings have now begun to be described in mammals, where the action of T3 and TRα1 control physiological and cancer-related stem cell biology. In this review, we have summarized recent findings on the multiple functions of T3 and TRα1 in intestinal epithelium stem cells, cancer stem cells and their niche. In particular, we have highlighted the regulation of metabolic functions directly linked to normal and/or cancer stem cell biology. These findings help explain other possible mechanisms by which TRα1 controls stem cell biology, beyond the more classical Wnt and Notch signaling pathways.

Keywords Colon cancer · Intestinal epithelium · Thyroid hormone · Thyroid hormone receptor · Stem cell · Stem cell niche

Introduction

The thyroid hormones (THs) and their nuclear receptors TRs play multiple roles in the development, homeostasis and metabolic processes in several organs and organisms [rev. in 1, 2]. Their function in intestinal development was described about a hundred years ago based on observations of amphibian metamorphosis [3]. During this postnatal maturation program, increased circulating TH levels are responsible for gut remodeling, including the first phase of apoptosis and shortening of the gut length followed by an increase in cell proliferation [4]. Interestingly, it has been reported that these maturation steps in gut tadpoles depend on complex signaling between different cell types, leading to the emergence of stem cells (SCs) and the establishment of the adult epithelium [5, 6]. In the mammalian intestine, it is well established that continuous epithelium renewal and SC maintenance depends on complex cell interactions and on signaling pathways that globally define and contribute to the SC niche [7, 8]. Similar to amphibians, TH signaling is also important for mammalian intestinal postnatal development and SC biology and the establishment of an SC niche [9–11]. The focus of this review will be on TH-dependent intestinal SC niche regulation and on how the alteration of this signal can lead to cell transformation and cancer.

The thyroid hormones and their nuclear receptors

THs are synthesized by the thyroid gland in a process finely regulated by the hypothalamus–pituitary–thyroid axis [12]. The hypothalamus synthesizes and secretes thyrotropin-releasing hormone (TRH) which is transported via axons to the pituitary gland where it interacts with its receptor and stimulates the synthesis of thyroid-stimulating hormone (TSH). TSH binds to its receptor located in the follicular cells of the thyroid, the thyrocytes, inducing the production of the hormones L-Thyroxine (T4) and 3,3′,5-Triiodo-L-thyronine (T3). T4 levels tend to be about 40-fold higher compared to T3 [12, 13]. TH synthesis is strictly regulated and subject to a negative feedback loop, resulting in TH-dependent negative regulation of TSH and TRH production [12, 13]. Thyrocytes secrete THs into the bloodstream and are transported to distal organs by serum proteins such as thyroid binding protein (TBP), transthyretin and albumin [14, 15]. It is important to note that, in addition to the central control of TH production, there is a local mechanism for controlling hormone levels. This involves the presence of

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plasma membrane transporters [16, 17], which ensure TH entry into cells, as well as the presence of deiodinase selenoenzymes, which activate and/or inactivate the THs [18].

Inside the cells THs, in particular T3, act through binding to the nuclear hormone receptors TRs, which are members of a large protein family of transcription factors [19]. T3 is considered the active form of TH because it binds TRs with 10–15 fold higher affinity than T4 [20, 21]. The gene regulation by TRs through direct DNA-binding on target genes is the classical bimodal switch, or type 1 regulation [22]. Other types of TR-mediated regulations, however, have been described. They include TRs participating in multi-protein complexes independent of DNA binding or TRs recruitment to DNA that is not required to regulate transcription [22]. Finally, it is important to note that THs can function independently of TRs and directly bind to other proteins such as integrin αvβ3 [22]. The TRs have a modular organization, typical of the family members (Fig. 1A) [23]. The A/B N-terminal domain allows the binding of protein co-factors and contains a T3-independent activation function 1 (AF1) region. The C domain contains two zinc finger structural units that bind specific DNA elements within target genes. The D domain is a hinge region linking the C and E domains and also includes a nuclear localization signal. The E domain contains the ligand- and protein co-factor-binding regions, which modulate the downstream transcriptional response. The AF-2 region in this domain allows T3-dependent transcriptional control. The TRs are present in numerous tissues and within several vertebrate species including mammals, amphibians, fishes, and birds [24]. Inside of cells, they are mainly located in the nucleus and, unlike other nuclear hormone receptors, TRs do not have an "inactive" form in the cytoplasm.

In mammals, the *THRA* and *THRB* genes code for TRα and TRβ protein isoforms. The *THRA* locus is located on human chromosome 17 and encodes for two major isoforms, TRα1 and TRα2, but only TRα1 is a true T3 nuclear receptor because it has both DNA- and ligand-binding domains, whereas TRα2 only displays the DNA- but not the ligand-binding domain [25, rev. in 26]. In addition to TRα1 and TRα2, the *THRA*/*Thra* locus generates two short isoforms, TRΔα1 and TRΔα2, that lack both the DNA- and ligand-binding domains [27]. These isoforms can function as dominant negative proteins vis-à-vis of the TR receptors and their function has been highlighted in the murine intestine [28]. The *THRB* locus is located on chromosome 3 and encodes TRβ1 and TRβ2 major isoforms, both acting as T3 nuclear receptors [rev. in 26]. The role of TRα1 is of importance during development [rev. in 11, 25] and in certain adult organs such as the heart, brain and intestine [29]. TRβ1 and/or TRβ2 act principally in the liver, retina, developing inner ear and at the level of the hypothalamus-pituitary axis (i.e., TRH neurons and the pituitary gland) [26, 30]. TRs modulate the expression of target genes by binding to specific genomic regulatory regions called thyroid hormone response elements (TREs) [30]. TREs consist of repeated hexameric nucleotide sequences organized in half-sites as direct repeats separated by four nucleotides (DR4) or as palindromes, direct or inverted [30] (Fig. 1B). The type 1 modulation of gene transcription by TRs involves protein complexes acting as co-activators or co-repressors, depending on the presence or the absence of T3 [31] (Fig. 1C).

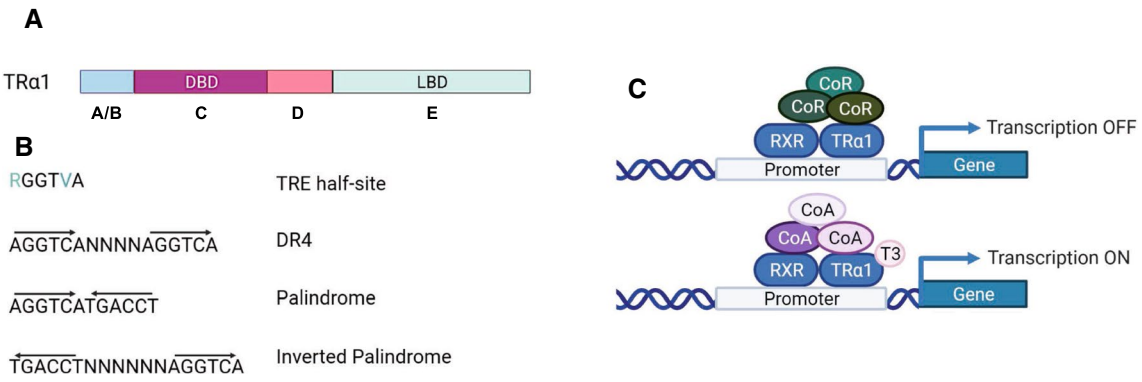


Fig. 1 TRα1 structure and mode of action. **A** Modular organization of the TRα1 nuclear receptor, including DNA-binding (DBD) and ligand-binding (LBD) domains. A/B, C, D and E indicate the typical structural domains of the nuclear receptors. **B** Typical organization of thyroid hormone-responsive elements (TREs) on target genes constituted by two repetitions of half-sites organized in different manners, as indicated. **C** Model of TR action on target genes. For a gene positively regulated by T3, in the absence of T3, co-repressors are recruited resulting in the inhibition of transcription. Upon T3 binding, co-activators bind to TR inducing transcription. The figure was created with BioRender.com (agreement number: QC23PTXLWH)

The mammalian intestinal epithelium and its organization

The intestinal epithelium has a peculiar vertical organization all along the anteroposterior axis, that correlates with specific functional compartmentalization [7, 32] (Fig. 2). Indeed, a proliferation zone is devoted to SC activity and progenitor proliferation, while a differentiation zone defines the region where differentiated cells reside [32, 33].

The intestinal SCs have been the focus of active investigations during the last 15 years and we benefited from a strong increase in the knowledge in this field [7, 33, 34]. They are located at the bottom of the small intestine and colon crypts and cycle rapidly to maintain a continuous turnover of epithelial cells. Crypt-base columnar cells (CBCs), originally described by Cheng and Leblond [35], express the cell surface marker LGR5 and are now considered the active SCs of the intestinal epithelium [36]. CBCs can generate both an SC or a progenitor that enters the transit-amplifying zone and differentiates while migrating toward the top of the vertical axis. Differentiated cells finally die by apoptosis and are shed into the lumen [32,

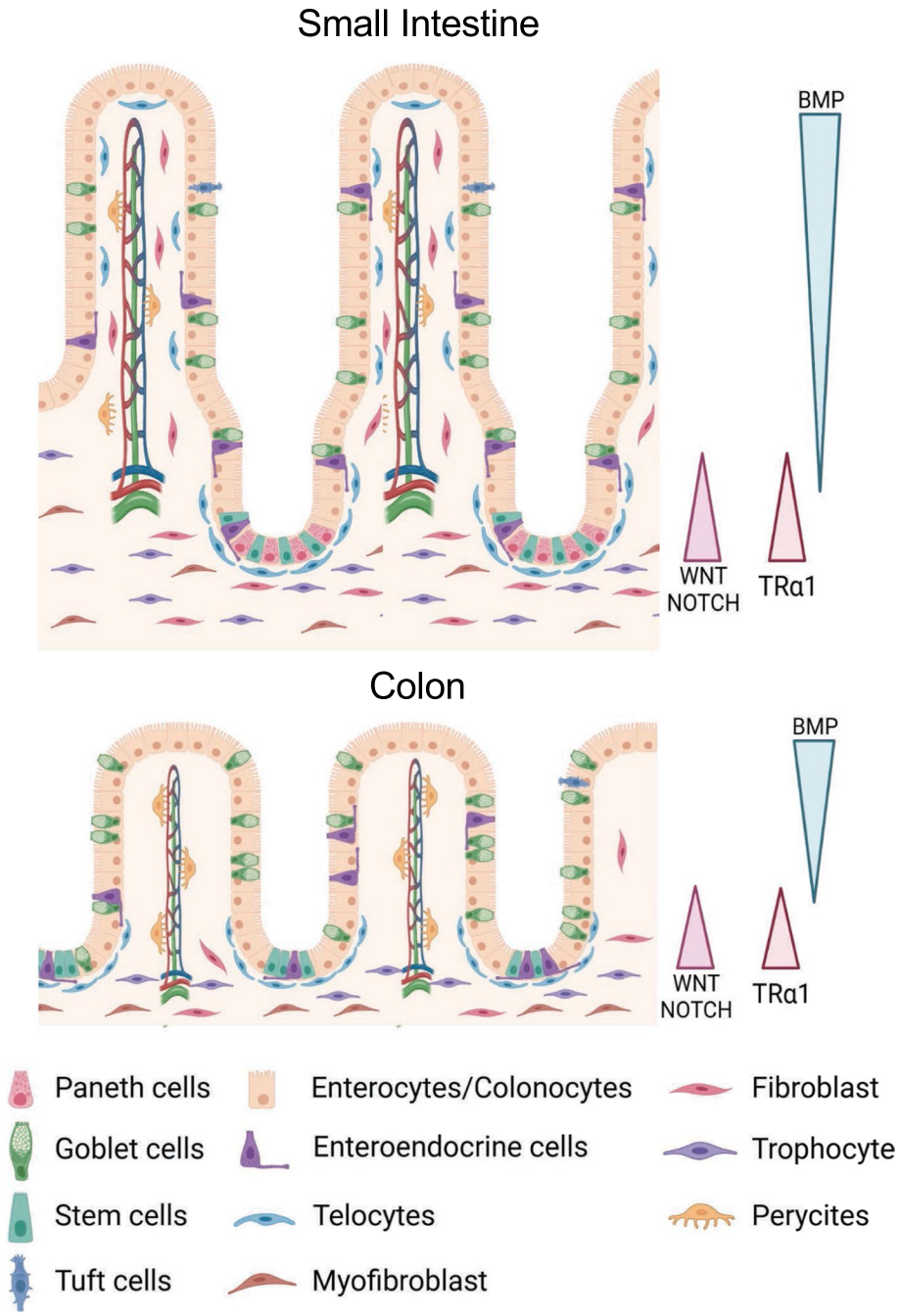


Fig. 2 Functional organization of the small intestine and colon epithelia. Organization of the intestinal mucosa in the small intestine (*upper* panel) and colon (*middle* panel), showing the vertical epithelial axis. At the bottom of the axis reside stem/progenitor cells while in the higher part of the vertical axis are located differentiated cells. It is interesting to note that TRα1 has a gradient of expression similar to Wnt and Notch pathway activities, while the BMP pathway presents an opposite gradient. In the *bottom* panel are depicted the different cell types present in the mucosa, including epithelial and mesenchymal-derived cells. The Figure was created with BioRender.com (agreement number: QC23PTXLWH)

33]. This entire process is completed within 3–5 days in murine tissue depending on the anterior–posterior intestinal region [32].

The intestinal epithelium hosts two major cell lineages generated from absorptive- and secretory-committed progenitors [7, 32]. Absorptive progenitors differentiate into enterocytes/colonocytes which have a brush border that enlarges their cell surface and facilitates efficient nutrient and water absorption [32]. Microfold cells (M cells) sample gut contents and transport, by trans-cytosis, luminal antigens to the underlying immune cells present in the Peyer's patches, thereby controlling immune responses [7, 32]. The secretory progenitors, on the other hand, give rise to Paneth/Paneth-like, enteroendocrine (EEC), tuft and goblet cells [7, 32]. Paneth (small intestine) and Paneth-like (colon) cells are the only differentiated cells present at the bottom of the crypts and produce antimicrobial compounds and niche factors important for SC maintenance and activity [37, 38]. EECs, the hormone-producing cells of the intestine, secrete hormones that regulate physiological processes in response to food intake [32, 39]. Tuft cells are chemo-sensors and mediate immune responses [40] while goblet cells secrete mucus that helps to protect the epithelium from the aggressive luminal content [32, 41].

Interestingly, several studies have described other cell populations within the intestinal epithelium with stem characteristics and these have been collectively called "reserve stem cells" as opposed to the active Lgr5-expressing SCs [32, 33]. Depending on the reports, they have been referred to as "quiescent, slow-cycling, revival or facultative", described and debated as candidate SC-like populations localizing within the SC/progenitor zone [42]. These cells express the markers Bmi1 [43], Tert [44], Hopx [45], Lrig [46], Msi1 [47] and Clu [48] and can regenerate the epithelium after injury and loss of active SCs [43–48]. These plastic and dynamic regeneration capacities are, however, not only restricted to SCs since there is evidence showing that lineage-specific committed progenitors have the capacity to de-differentiate and acquire SC properties [8, 49, 50].

Finally, it is important to emphasize that several signaling pathways are involved in the organization of the vertical axis of the intestinal epithelium and in defining the SC zone, by actively participating in the SC niche. This includes Wnt, Notch and epidermal growth factor (EGF) pathways which show a higher gradient of activity in the CBC zone [32] (Fig. 2). The bone morphogenic protein (BMP) and hedgehog (Hh) pathways show an opposite gradient and are highly active at the top of the axis, where they define a no SC/progenitor zone [8, 32]. Collectively, these signaling pathways control the epithelial vertical zonation, the balance between cell proliferation and cell differentiation, as well as between SC self-renewal and commitment [8, 32].

The intestinal epithelium stem cell niche

In 2009, Sato et al. cultured for the first time murine intestinal organoids from isolated Lgr5-expressing crypt SCs [51]. The culture was established in the absence of mesenchymal cells but included growth factors that define "the minimal stromal niche" of necessary signals for the viability and activity of the SCs [51]. Indeed, single Lgr5-expressing cells give rise to 3D multi-budded organoids containing all lineages when supplemented with EGF, R-spondin (a Wnt signaling amplifier) and Noggin (a BMP inhibitor) embedded in an extracellular matrix-like gel [51]. These three niche factors and the complex semi-solid matrix are necessary and sufficient for SC biology and well recapitulated the in vivo situation. In fact, in vivo, the niche surrounds SCs at the bottom of the crypts and sustains their identity, maintenance and activity by supplying Wnt proteins, R-spondins, EGF and BMP inhibitors [8, 32]. The niche is composed of several cell types, including Paneth cells and stromal/subepithelial mesenchymal cells (subepithelial myofibroblasts, non-muscle fibroblasts, telocytes, trophocytes, endothelial cells and pericytes) [52–54]. Immune cells may also contribute to the intestinal SC niche through action on Paneth and M cells [53, 54]. Moreover, extracellular matrix proteins that form the basal lamina are involved in complex metabolic signaling at the crypt's bottom and are essential niche elements [55]. Finally, ingested nutrients and diets show a prominent capacity to modulate SCs and this dietary-adaptation capacity has recently been proposed as a hallmark of SC activity [34]. The different cell types and factors described above have been summarized in several reviews [32, 33, 53, 55, 56] and will be discussed here only in relation to THs/TRs.

TH/TR in intestinal physiopathology

As already mentioned, THs and TRs play an important role in intestinal physiology in amphibians, mice and humans, as well as in intestinal tumor biology. Importantly, several studies have attempted to establish a link between THs and intestinal tumor development. However, a consensus has not been reached, and both anti- or pro-tumoral effects of THs have been described [57, 58; rev. in 59–61], as summarized in Table 1. Experimental data from models clearly shows a pro-tumoral action of high TH levels [62–65]. Moreover, studies that have monitored the thyroid axis in patients have reported a clear association between low TSH and high THs with cancers, including colorectal cancers (CRCs) [57, 58, 66]. Finally, some epidemiological studies have been performed in patients treated with either TH-deprivation or TH-supplementation therapies to normalize TH levels and analyzed tumor incidence under these conditions [66–68].

Table 1 Representative literature on TH/TR and CRCs

	Cancer type; organism; details	Observations and comments	TR involved	References
Protection by THs	CRC; Colon and Rectum/sigmoid; Human; Epidemiology; Replacement therapy	Hypothyroid patients received Levothyroxine to normalize TH levels. Reduced risk of CRC, not always significant	ND	Rennert et al. [66], Friedman et al. J. Natl. Cancer Inst. 2011 Nov 2;103(21):1637–9
	CRC; Human; Epidemiology	Patients suffering Grave's disease (hyperthyroid). Patients very probably treated to cure hyperthyroidism	ND	Cheng et al. Thyroid 2013, 23(7):879–84
	CRC; Human epidemiology; Replacement therapy; Hypothyroid patients	Hypothyroid patients treated with THs replacement have less risk of CRC. Hypothyroid patients had increased risk of CRCs compared with those receiving replacement therapy	ND	Boursi et al. [68]
	Colon; Human epidemiology	Lower risk of colon cancer in hyperthyroid patients	ND	L'Hereux et al. [57]
	Metastatic CRC; Human; Low circulating T3	High T3 in patients with metastatic CRCs. No causal proof between metastasis and T3	ND	Rose et al. Arch. Intern. Med. 1981, 141:116–1164
	Human adenomas and adenocarcinomas; D3 and local hypothyroidism	Association between D3 expression and tumors at early stages	ND	Dentice et al. [103]
	CRC; Human primary tumor cells; D3 and intracellular hypothyroidism	In vitro T3 increases chemosensitivity	TRβ1	Catalano et al. [104]
	CRC; Human	Strong TRβ1 down-regulation	TRβ1	Markowitz et al. [73]
	CRC; Human	Higher TRβ1 expression in more differentiated tumors	TRβ1	Horkko et al. [74]
Worsening by THs	Rectal; Human epidemiology	Lower risk of rectal cancer in hypothyroid patients	ND	L'Hereux et al. [57]
	CRC; Human epidemiology; Replacement therapy; Hyperthyroid patients	Hypothyroid patients treated with THs replacement has less risk of CRC. Hyperthyroid patients had increased risk of CRCs compared with those receiving replacement therapy	ND	Boursi et al. [68]
	CRCs; Human epidemiology; Low TSH and high THs	Increased CRC incidence in hyperthyroid patients, but limited number of cases	ND	Hellevik et al. [58]
	Colon; Rat; Chemical induced tumors	T4 increases tumor number in an AOM chemical carcinogenesis model	ND	Iishi et al. [65]
	CRCs; Human; Transcriptomics	TRα1 increased in several CMS. THs status unknown	TRα1	Uchuya-Castillo et al. [63]
	Intestine and colon cancer; Mouse	TRα1 overexpression in intestinal epithelium induces hyperproliferation and adenomas. Proliferation is further increased by TH injections. In mutant Apc mice, TRα1 overexpression increases speed of tumor formation, their number and metastatic capacity	TRα1	Kress et al. [62]
	Colon adenocarcinoma cell lines	THs stimulates growth of explants and metastasis spreading. Effect mediated by integrin avb3 that can be inhibited by TETRAC (competes with T4 and blocks signaling)	ND	Lin et al. [133]
	Colorectal; Human epidemiology; Replacement therapy	Levothyroxine replacement therapy is associated with higher risk of CRCs in women but not in men	ND	Wandell et al. [67]

ND, not determined

However, these treatments do not mimic hypo- or hyperthyroidism and, paradoxically, show highly diverse results, strongly contributing to the lack of consensus in this matter. Altogether, these findings clearly indicate the complexity of the field and would deserve a specific focus.

Regarding the TRs, it has been shown that mutation or altered expression of TRs may be linked to tumorigenesis [69, 70]. Unlike the intestine, TRβ1 has been shown to control cell proliferation in the liver [71], and increased TRβ1 expression is strongly correlated with tumor invasion in hepatic cancer cell lines [72]. In the case of the colon, TRβ1 expression is greatly reduced in cancer due to hypermethylation [73]. Accordingly, TRβ1 is associated with a more differentiated phenotype and its loss of expression is linked to malignant transformation [73, 74]. TRα1 has been reported to be associated with the proliferation of pancreatic cells [75], while another study showed that its expression was associated with a poor prognosis in breast tumors with a mutated *BRCA1* gene [76]. Interestingly, the expression of TRβ1 in this same study was inversely associated with a favorable prognosis [76]. Our own functional studies of the TRα1 receptor in mouse models highlighted its role in controlling both intestinal development and homeostasis [rev. in 9, 11]. These properties result from the ability of TRα1 to regulate the Wnt and Notch pathways and to modulate the expression of various cell division and cell cycle regulators [77, 78; rev. in [79]. The importance of these mechanisms was validated by experimentally up-regulating TRα1 expression in intestinal epithelial cells in vivo (*vil*-TRα1 mice), and we demonstrated the induction of hyperproliferative and hyperplastic crypts [62]. Moreover, according to the assumption of SC-driven tumorigenesis, the overexpression of TRα1 in an *Apc*-mutated tumor-prone model (*vil*-TRα1/$Apc^{+/1638N}$ mice) increases tumor incidence, accelerates the intestinal tumorigenic process and induces metastasis dissemination [62]. Conversely, loss of TRα1 expression ($TR\alpha^{0/0}$/$Apc^{+/1638N}$ mice) drastically reduces tumor incidence [63]. Among the mechanisms at work, the control of [78, 80] or the functional interaction with the Wnt pathway [81] appear to be key processes. Finally, recent findings in human CRCs clearly indicated an up-regulation of *THRA* gene expression in tumors, a direct correlation with Wnt activity and an association with consensus molecular signature CRC subtypes [63, 82]. Collectively, these observations have clear clinical implications.

In the following paragraphs, we will summarize recent findings in the field of TH/TRs and SC biology, including the SC niche in normal intestines and tumors.

Lessons from amphibian metamorphosis

In amphibians, primary culture approaches have shown that the action of THs in non-epithelial cells is required for the appearance of adult epithelium and the emergence of the intestinal SCs [5, 6]. These results underline the importance of TH-dependent epithelial-connective tissue interactions in the establishment of an intestinal SC niche in the developing amphibian intestine [83, 84]. Both TRα and TRβ receptors are important for this developmental program [84–87] and finely regulate the cell cycle, apoptosis and the remodeling of the extracellular matrix, notably by the induction of metalloproteases [88].

As described earlier, several signaling pathways are important for intestinal development in mammals, such as Hh, WNT, BMP and Notch pathways. Interestingly, some of them are also necessary for the emergence of SCs in amphibians. For example, Shh is a member of the Hh signaling family and is one of the early T3 responsive genes in the metamorphosing amphibian intestine [89]. It is specifically expressed in the epithelium and highly transiently upregulated during the earliest events of metamorphosis. Some downstream components of Shh signaling, such as the receptors Patched, Smoothened and GLIs, are mainly expressed in the connective tissue, thereby responding to the epithelial-derived Shh signal [90]. In addition to Shh, BMP4 is another T3 target gene in the amphibian intestine, but it is specifically expressed in connective tissue and its expression temporally correlates with adult epithelium differentiation [91]. TH-induced BMP4 represses cell proliferation in connective tissue and promotes differentiation of adult epithelial cells through the epithelial-specific presence of its receptor [92]. Importantly, several TH-modulated genes associated with amphibian metamorphosis belong to the WNT pathway and are expressed in both the epithelium and the mesenchyme, directly participating in intestinal remodeling [93–95]. Indeed, under the influence of increasing TH levels and in the presence of both TRα and TRβ, the adult epithelium originates from a scattered population of larval absorptive epithelial cells expressing tyrosine kinase-like orphan receptor 2 (*Ror2*; a receptor for Wnt5a) or *Sfrp2* (a Wnt soluble modulator). The non-canonical Wnt5a/Ror2, the canonical sFRP2/Fzd and the hyaluronan/CD44 Wnt signaling, all stimulated by THs, are essential for larval epithelial cells to de-differentiate and generate the adult-type epithelium [93–95]. Altogether, the cell–cell interactions that involve WNT, Shh and BMP signaling have an important role in the establishment of the intestinal SC niche that is essential for the neo-generation of SCs of the adult-type epithelium.

Recently, a paper described the importance of TH signaling in tadpole telocytes. These stromal cells in the mammalian intestine surround the bottom of the crypts and are characterized by the marker Foxl1 [96, 97]. Hasebe et al., showed that Foxl1, which is also a marker of telocytes in amphibians, is indirectly upregulated by TH through Shh signaling from the epithelium. These signal exchanges between the epithelium and the Foxl1-expressing niche cells

are required for the emergence of SCs in the tadpole intestine [98]. The Notch pathway is activated through ligand-receptor interaction between adjacent cells and is upregulated by TH during metamorphosis [95, 99]. Several genes such as *Notch1*, *Hairy1*, *Delta-like 1 (Dll1)* and *Jagged 1* (*Jag1*) are directly or indirectly TH-responsive [99, 100]. While Dll1 is expressed in the adult epithelium, Jag1 is present in both larval epithelium and stromal fibroblasts beneath adult progenitor/SCs. These findings suggest different roles of the Notch elements in the developing or adult intestinal epithelium and SC niche [95, 99].

What do we know in mammals?

Contrary to amphibians, in mammals the role of TH and TRs in intestinal SCs and their niche is much less characterized. Recently, we showed the role of T3 and of TRα1 in murine intestinal SCs in vivo and in derived organoids. T3, in a TRα1-dependent manner, induced in organoids an increase in cell turnover affecting the commitment of progenitors into goblet cells [10]. In vivo, an increase of crypt cell proliferation upon T3 exposure was also present along with regulation of cell differentiation, but in this case, it was directed towards Paneth cells [10]. This study demonstrated for the first time the role of T3 and TRα1 in increasing the number of SCs and their markers, related to an effect on Paneth cells that, as we described in the previous section, are part of the SC niche [37]. TH/TR-dependent cell–cell interactions and instructive signal exchanges between the epithelium and connective tissue have not been formally demonstrated yet. Nevertheless, TH-dependent stimulation of ligands and receptors participating in Wnt, BMP, Hh and Notch pathways has been shown in several reports [63, 77, 78]. Thus, in the light of these findings, we can hypothesize that THs through TRα1 may also play a role in mesenchymal cells participating to the SC niche. This action might result in direct and indirect modulation of multiple signals in different cell types and tissues, similar to what has been shown in amphibians [96, 98].

The local TH/TR signaling has been investigated in the context of intestinal tumors and cancer stem cells (CSCs). The deiodinases, TH metabolizing enzymes, have been well studied both in normal physiology and in cancer [101]. The stroma of *Apc*-mutant mice has elevated expression of *Dio2*, a T3-activating enzyme. When the expression of Dio2 is inhibited in these cells, or when hypothyroidism is chemically induced, the growth of intestinal tumors is blunted. This is indicative of crosstalk between the epithelium and the connective tissue mediated by local or systemic TH levels. Importantly, this effect is accompanied by a reduction in angiogenesis [102]. High expression of *Dio3*, a T3-inactivating enzyme, has been reported in human CRCs [103]. The depletion of *Dio3* in adenocarcinoma cell lines or primary tumor cells indicated a pro-differentiation action of T3, through downregulation of Wnt and increase of BMP pathways [103–105]. The contrasting results between these reports may be due to the altered expression of these two enzymes in the stroma (Dio2) or in the epithelial tumor cells (Dio3).

These findings are also discordant with our data showing a positive regulation of TH/TRα1 on the Wnt pathway, cell proliferation, tumorigenicity and on SC activity [10, 62, 63, 78, 80]. While we lack explanations for these discrepancies, it is important to note that TH treatment in vivo and in organoids have different outcomes. Indeed, organoids are an epithelial-only model where T3 induces a "thyroid shock", which is not the case when treating the animals and perform analyses on the intestinal epithelium in its integrated physiological context [10].

In addition to mesenchymal derivatives, macrophages also participate in the intestinal SC niche and the CRC tumor microenvironment. In these cells, THs regulate the triggering receptor expressed on myeloid cells-2 (TREM2), a cell surface receptor on macrophages and microglia involved in immune suppression of the tumor microenvironment [106]. This finding is in line with previous data showing the influence of THs as immunomodulators with the potential of decreasing the physiological response against tumor cells [107]. We can affirm that TH/TRα1 influences intestinal tumor biology through its interaction with the Wnt/β-catenin and other signaling pathways [63, 108]. However, we should also consider a possible tumor-promoting role *via* CSC maintenance by an action on the tumor microenvironment (i.e., the CSC niche).

Finally, as previously stated, non-classical TH functions have been described. These are primarily dependent on integrin αvβ3, a transmembrane receptor capable of binding T3 and T4 independently of TRs [109]. Other non-genomic actions are associated with the 30 or 43 kDa TRα isoforms, which are N-terminally truncated proteins located in the plasma membrane and mitochondria, respectively [110]. Interestingly, these non-classical and non-genomic actions may result in SC maintenance *via* niche factors [111]. These regulations include the control of COX2, hypoxia-inducible factor 1 (HIF1), fibroblast growth factor 2, NOS2, MMP9, and genes related to glucose and lipid metabolism such as sterol regulatory element-binding protein 1 (SREBP-1) [111] and CD47 [109]. Importantly, actions of THs in the tumor stroma via hypoxia induction, tumor microenvironment recruitment and stimulation of angiogenesis have been shown in hepatocellular carcinoma [112, 113].

TH/TR and metabolic regulations in intestinal SC/CSC and their niche

Several reviews have summarized the roles of signaling pathways in relation to TH/TR in the normal intestine and in cancers [9, 11, 70, 81]. Here we have focused on

metabolic regulation, given the increasing interest on the role of metabolism in normal tissues and tumors. In the intestine, particularly in the field of gut SCs and their niche, several studies have shown that nutrient availability and metabolic pathways can directly regulate or instruct cellular function [114–116]. The various cell types within the intestinal crypt and the cells participating in the niche preferentially use different metabolic pathways and, depending on the cell type or on the cell state, a metabolic switch can occur. For instance, active SCs rely highly upon oxidative phosphorylation (OXPHOS) whereas Paneth cells rely on glycolysis (Fig. 3A) [117, 118].

Importantly, THs are critical regulators of metabolic processes and positively or negatively control the transcription of anabolic and catabolic gene subsets that affect energy homeostasis and metabolism [119]. Hyperthyroidism promotes a hypermetabolic state characterized by increased resting energy expenditure, weight loss, reduced cholesterol levels, increased lipolysis and gluconeogenesis. Conversely, hypothyroidism is associated with the opposite effects. THs influence key metabolic pathways that control energy balance by regulating energy storage and expenditure as described in the brain, white fat, brown fat, skeletal muscle, liver and pancreas [119].

In addition to TRs, other nuclear hormone receptors, including peroxisome proliferator-activated receptor alpha (PPARα), PPARγ and liver X receptor (LXR) share a similar structure and mode of action and heterodimerize with the retinoid X receptor (RXR). These similarities have suggested potential functional interactions in the control of metabolic gene expression [120]. PPARs and LXRs are ‘‘permissive’’ RXR partners that bind dietary lipids with low affinity and activate enzymes involved in lipid metabolism [120]. TRs, on the other hand, are "non-permissive" RXR heterodimers, bind to T3 with high affinity and mediate feedback regulation of their ligand [119, 120]. T3-liganded TRs dominate the interaction with RXR and may have a stronger effect in co-regulated genes than nutrient signals acting through PPAR and LXR. Furthermore, THs control the expression of SREBPs [121, 122], key regulators of lipid metabolism and long-chain fatty acids [123]. It has been shown, at least in vitro, that SRPBs can inhibit T3 binding to TRs, suggesting another level of gene regulation through competition between nutrient signaling and T3 binding to TRs [120].

The role of THs and TRs in lipid and carbohydrate metabolism has been extensively studied in the liver, where TRβ1 is the major TR isoform responsible for these actions [2, 120]. In the intestine, TRα1 is the isoform present in the crypt compartment, while TRβ is expressed in differentiated cells of the villi [9]. Within the crypts, TRα1 is enriched in SCs compared with progenitors, whereas Paneth cells express low TRα1 levels [10]. These findings point to a complex T3-mediated metabolic interplay between the various crypt cell types, which eventually influence SC biology (Fig. 3A). In intestinal tumors, the expression of TRα1 is upregulated [63] while the *THRB* gene is strongly silenced [73, 74], indicating that metabolic controls in this context rely exclusively on TRα1.

Carbohydrate metabolism and mitochondrial activity

TH status influences glucose metabolism. Excess of THs stimulate hepatic glucose production and increases the expression of the glucose transporters GLUT4 and SLGT1 in skeletal muscle and intestine, respectively [119]. Liganded TRα1 impairs glucose-stimulated insulin secretion by acting directly at the level of the pancreatic islets [119]. A further link between glucose metabolism and TH signaling is the T3-dependent induction of the carbohydrate response element-binding protein (ChREBP). This transcription factor stimulates the expression of genes involved in glycolysis and lipogenesis in response to glucose and insulin [120]. In a TRα- and TRβ-dependent manner, THs reduce insulin levels, regulate the expression of genes in the liver and skeletal muscle and stimulate ChREBP expression, which in turn influences glucose response and insulin secretion [120].

In the intestine, THs increase alkaline phosphatase and peptidase activities in a dose-dependent manner in vivo and inhibit γ-glutamyltransferase in vitro [124, 125]. In addition, studies in TRα-knockout animals showed that lactase, sucrase, aminopeptidase and FABP expression and activities are decreased [126], indicating a regulation by the TRα1 receptor of diverse metabolic processes in this organ. More recently, we also showed that T3 impacts the metabolic activity of intestinal organoids by upregulating all enzymes involved in glycolysis, pyruvate metabolism and OXPHOS [10]. This T3-induced metabolic change is parallel to an alteration in SC renewal by favoring secretory progenitor lineages [10]. We can assume that THs via TRα1 control the metabolic state of the SCs and, in consequence, regulate their self-renewal capacity and the fate determination of progenitor cells. The fine-tuned mechanisms at the basis of these complex regulations remain, however, to be fully elucidated, as schematized in Fig. 3.

The Notch/FOXO/mitochondria axis regulates goblet and Paneth cell lineages, with mitochondrial fission as a requisite for inducing differentiation [127]. Mitochondrial dysfunctions are central in the development of inflammatory bowel diseases and cancer, and affect intestinal SCs and Paneth cells by modifying the cellular phenotypes and lineage commitment [128]. Interestingly, THs and TRα1 have been implicated in mitochondrial biogenesis and activity in mammals [129, 130] and the mitochondrial fission is also a key process for the amphibian TH-dependent intestinal maturation and the emergence of SCs [131]. The pyruvate

dehydrogenase kinase *PDK4* gene expression had been shown to be modulated in the rat liver by T3 [132]. This finding suggests that T3, by modulating the mitochondrial metabolic pathways, may direct the differentiation of SCs towards secretory lineages, as it has been shown in mouse organoids [10] (Fig. 3B). Thus, it is possible that in both mammals and amphibians an interplay occurs between classical cell signaling and metabolic pathways and both share the mitochondria as an essential regulator of SC maintenance and differentiation potentialities.

Aside from direct regulation of target genes, THs can also modulate the expression of several genes by non-genomic actions. TH binding to integrin αVβ3 in colon adenocarcinoma cell lines has been shown to favor an increase of AMPK and the inhibition of mTOR resulting in increased tumor cell aggressivity [133]. In the mitochondria, the truncated TRα isoforms or the hormones T3 or T2, generated from the deiodination of T3, modulate the activity of several components of the respiratory chain leading to an overall increase in OXPHOS [134]. Moreover, THs can regulate the expression of several enzymes and transporters, like the intestinal fructose transporter GLUT5 [135] and PKM2 enzyme, involved in the generation of acetyl-CoA that favors OXPHOS metabolism [136]. Future research will need to focus on characterizing the cell types in which these regulations take place for a better understanding of the integrated processes.

Lipid metabolism

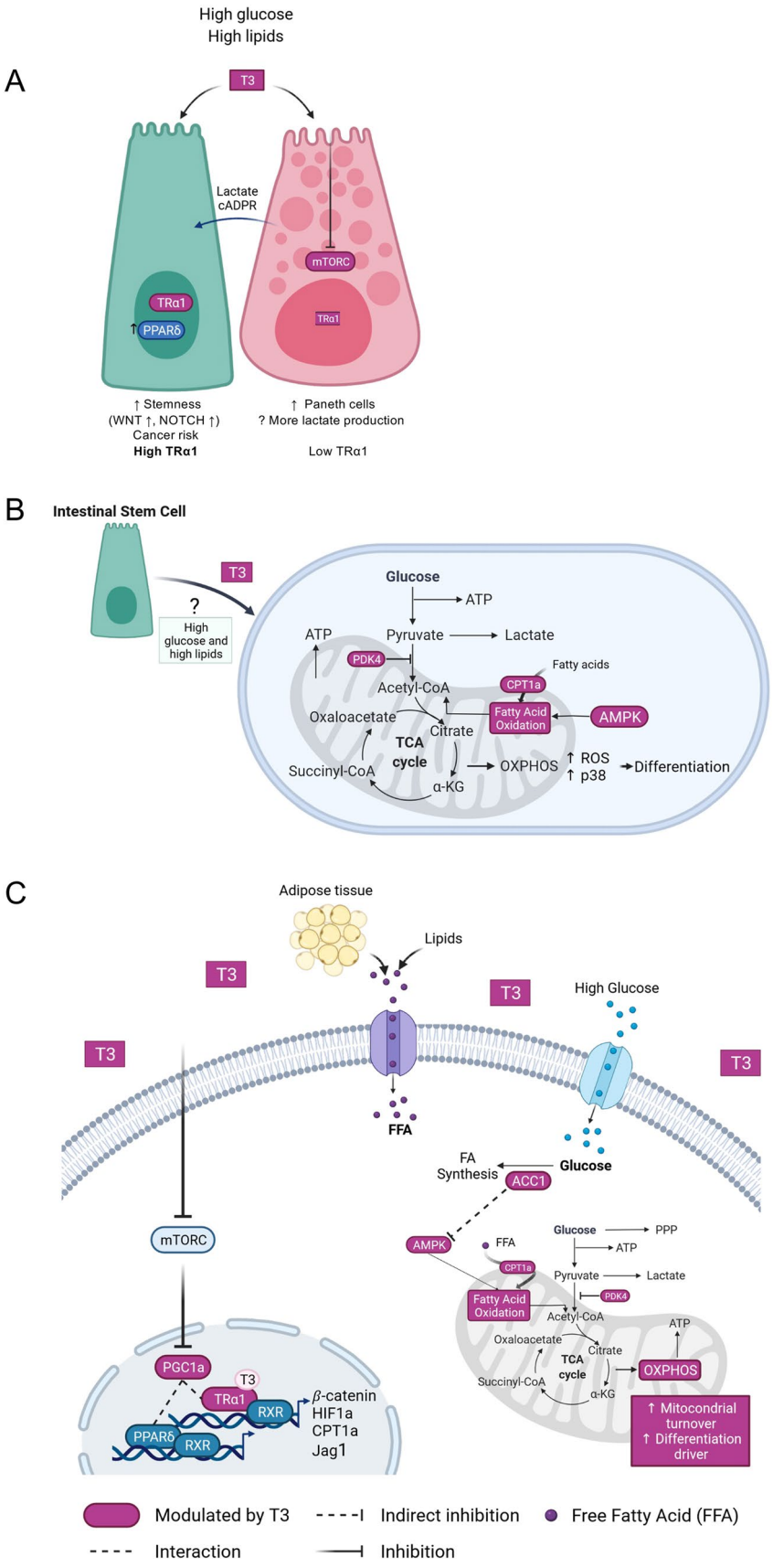
Mouse models with TRα and TRβ gene point mutations show a range of metabolic phenotypes, including impairment of cholesterol metabolism, fatty acid oxidation, lipolysis and increased cholesterol and triglyceride serum levels [120].

THs stimulate lipolysis, lipogenesis and cholesterol reduction by regulating the expression of SREBPs. The SREBP-1c isoform, involved in the fatty acid synthesis and glucose metabolism, is repressed by THs, while the SREBP-2 isoform, which is a lipid sensor important in cholesterol metabolism, is induced by THs. In addition, both TREs and sterol regulatory elements (SREs) are required for the activation of human acetyl–CoA carboxylase [35] and low-density lipoprotein receptor genes [36]. Thus, THs directly regulate SREBPs but also control genes harboring close TREs and SREs in their regulatory regions [137, 138]. Interestingly, SREBPs have SC- and tumorigenic- promoting activities in the intestine [139, 140], indicating another possible functional link between TRα1 and SREBPs. TRs can also bind to LXR-responsive elements in the intestinal *ABCA1* gene, affecting the cholesterol efflux through suppression of the LXR-dependent ABCA1 expression [119]. In addition, a crosstalk between TRs and PPARγ has been shown in the regulation of lipid metabolism, in particular the induction of carnitine palmitoyltransferase 1 (CPT1a) enzyme, through peroxisome proliferator-activated receptor gamma co-activator (PGC-1α), a TH-target gene [141]. CPT1a is the key enzyme involved in fatty acid oxidation (FAO) as it exchanges the acyl group of the fatty acid for carnitine, so it can enter the mitochondria to be oxidated [142] (Fig. 3B).

T3 treatment of intestinal organoids causes downregulation of the lipid metabolism pathway, including most of the enzymes involved in FAO, compared to non-treated organoids, with the only exception of CPT1a [9]. AMPK, another major regulator of FAO, is regulated by THs [143] (Fig. 3B). In addition, the mitochondrial trifunction protein (MTP), which catalyzes three FAO reactions, is stabilized and modulated by the TRα p43 isoform [144]. MTP modulation was also observed in intestinal SCs during calorie restriction and fasting [116, 145], leading to an increase of SCs, Paneth cells and progenitors, which is similar to what happens in mice when treated with T3 [10]. During calorie restriction, it was shown that mTORC1 inhibition is important for intestinal regeneration and preservation of "reserve SCs" from DNA damage [146]. T3 treatment may have a similar role in this context, as it inhibits mTOR [10]. Moreover, TRα1 protects the epithelium from DNA damage [147], strongly supporting its role in epithelium regeneration upon injury, through action on "reserve SCs".

In the case of the high-fat diet, PPARδ activates the Wnt pathway and increases the intestinal SC number by modulation of metabolic responses and provoking SC self-renewal independently from Paneth cells, through the secretion of Jag1 [114]. A high-fat diet also has a tumor-inducing role via increased CPT1a [148], suggesting that THs and TRα1 may have a similar inducing role via CPT1a and FAO induction through Wnt or Jag1 modulation [10, 77, 78].

Altogether, the combination of classical cell signaling with metabolism and diet, nuclear receptors and hormones (like THs) help to maintain SC self-renewal and regulate differentiation through modification of mitochondrial metabolism both in SCs and the cells of their niche. It is worth highlighting that most of the studies to date have focused on the role of metabolism in SCs and Paneth cells. Therefore, additional studies on other cell types within the intestinal SC niche are necessary to fully understand the interrelation between different cell types in this complex metabolic interplay. Towards this end, newer studies have begun to investigate the role of adipocytes in CSCs and intestinal tumorigenesis. As mentioned above, THs have an important role in FAO and SC/CSC metabolism, resulting in increased stemness and tumorigenesis. They are also important in adipose tissue lipidic


A
High glucose
High lipids
T3
Lactate
cADPR
mTORC
TRα1
PPARδ
TRα1
↑ Stemness
(WNT ↑, NOTCH ↑)
Cancer risk
High TRα1
↑ Paneth cells
? More lactate production
Low TRα1
B
Intestinal Stem Cell
T3
?
High glucose and high lipids
Glucose
ATP
ATP
Pyruvate
Lactate
PDK4
Fatty acids
CPT1a
Acetyl-CoA
Fatty Acid Oxidation
AMPK
Oxaloacetate
Citrate
TCA cycle
Succinyl-CoA
α-KG
OXPHOS
↑ ROS
↑ p38
Differentiation
C
Adipose tissue
Lipids
T3
T3
High Glucose
T3
T3
FFA
FA Synthesis
ACC1
Glucose
mTORC
AMPK
FFA
Glucose
PPP
ATP
CPT1a
Pyruvate
Lactate
PDK4
Fatty Acid Oxidation
Acetyl-CoA
ATP
Oxaloacetate
Citrate
TCA cycle
OXPHOS
Succinyl-CoA
α-KG
PGC1a
T3
TRα1
RXR
β-catenin
HIF1a
CPT1a
Jag1
PPARδ
RXR
↑ Mitocondrial turnover
↑ Differentiation driver
Modulated by T3
Indirect inhibition
Free Fatty Acid (FFA)
Interaction
Inhibition

◂**Fig. 3** Proposed models recapitulating the integration of classical signaling and metabolic pathways depending on TH/TRα1 in intestinal crypts and colon cancer cells. **A** Differential outcome in SCs or in Paneth cells in response to T3, possibly inducing metabolic shifts. Accumulating data suggest that T3 through the TRα1 receptor modulates the stemness in crypts via regulation of the Wnt and Notch pathways. However, recent data also point to the induction of metabolic challenges stimulated by high glucose and high lipid metabolism, acting on the balance between self-renewal and differentiation [8, 32, 37]. Importantly, T3 also induces an increase of Paneth cells in the intestinal crypts [10]. Paneth cells are well known to act on stemness through Wnt and Notch, but also to produce lactate that once up-taken by SCs contributes to the oxidative phosphorylation (OXPHOS) metabolic pathway [115], participating in the maintenance of the stem phenotype. **B** Overview of the integrated glucose and lipid metabolism in the intestinal SCs under T3 treatment. We speculate that T3 might mimic a high glycolysis and high lipolysis condition increasing OXPHOS. Upon oxidation of fatty acids, stimulated OXPHOS can induce reactive oxygen species (ROS) and p38 expression. The stemness, stimulated by Wnt and Notch, or the differentiation induced by ROS/p38, depend on the balance between these two events. **C** Integrated view of the action of T3/TRα1 in a cancer context. Adipocytes are strongly mobilized in the cancer environment and considered as part of the cancer stem cell niche [56, 149, 150], releasing high levels of lipids that can be absorbed by cancer cells. The T3-induced transcriptional program includes genes involved in fatty acid oxidation, OXPHOS, and stemness together with mitochondrial turnover. The balance between these major events determines the extent of stem potential *versus* their differentiation. The Figure was created with BioRender.com (agreement number: PO23P-TXM00)

mobilization [119]. During calorie restriction, SCs and CSCs uptake fatty acids from the nearby adipocytes and promote the expression of CPT1a through PPARγ [149]. This same phenomenon was observed in organoids supplemented with fatty acids [114]. A similar role can be hypothesized for TRs, as both nuclear receptors engage in crosstalk in the regulation of lipid metabolism, adipogenesis, and tumorigenesis [150]. Colon tumors typically grow in an adipose tissue-enriched microenvironment, making adipocytes a key niche component for regulating cancer metabolism (Fig. 3C). The uptake of fatty acids from adipocytes renders colon cancer cells resistant to nutrient deprivation and favors a high level of Wnt signaling by acetylation of β-catenin [149]. It is therefore likely that THs and TRα1 contribute to the maintenance of CSCs in CRC by a positive induction of the Wnt signaling in CSCs and their niche by upregulating CPT1a and increasing the metabolism of fatty acids in adipocytes [10, 63, 78].

Chromatin remodelling

As described earlier, changes in nutrient availability can result in the reprogramming of cellular metabolism. Core metabolite pools such as ATP, S-adenosyl methionine, acetyl-CoA, NAD/NADP and α-ketoglutarate underlie a variety of essential metabolic reactions and are used by chromatin modifiers in the establishment of epigenetic signatures [151].

Chromatin remodeling is a requirement for the transcription of genes associated with anuran metamorphosis. Intestinal SCs are generally characterized by having open chromatin that allows them to change quickly from self-renewal to differentiation. In amphibians, the presence of different co-activators, which act as histone modifiers, remodel the chromatin in the presence of THs and allow the transcription of TR-responsive genes [152]. Many data on TR-mediated chromatin remodeling came from observations on TRβ and its interactions with various protein complexes. The SWI/SNF chromatin remodeling complex, for example, which is associated with NCOR, a well-known TR co-repressor [31], has been shown to be required for TRβ-mediated gene repression in human thyroid epithelial cell lines [153]. In these same cells, the recruitment of the SWI/SNF complex in T3-activated genes is dependent on interactions between TRβ and the p300/CBP coactivator complex [153], with T3 increasing the chromatin accessibility in proximal rather than in distal binding sites [153]. Furthermore, steroid receptor coactivators (SRCs) and p300/CBP function synergistically to stimulate TRβ-dependent transcription [154]. SRC facilitates the recruitment of p300/CBP to T3-regulated promoters via histone acetylation [154], allowing the recruitment of SWI/SNF and Mediator complexes [155]. It is important to underline that the TRs involved in these chromatin modifications may play a critical role in cellular reprogramming. As discussed earlier, TRα1 is expressed in the intestinal crypts in mammals, whereas TRβ1 is expressed in the villi. This specific expression pattern suggests that, as in amphibians, each TR is associated with a distinct profile of epigenetic regulation in the various epithelial cells [156].

Large-scale studies showed that regulation of gene expression by TRs is not only due to the binding of TREs but also to chromatin remodeling in regions close to TREs [138]. This changed the prevailing view that the transition from a repressed to an activated state might not simply work through a switch from co-repressor to co-activator interaction with pre-occupied TRs [138]. In addition, co-activators and chromatin remodelers may also be recruited through ligand-dependent TR occupancy of chromatin, a mechanism already observed for other nuclear hormone receptors [138]. Most T3-activated genes associate with hormone-facilitated TR recruitment to chromatin [138]. For example, some TH target genes fall under epigenomic regulation, which modifies their transcription [152, 156, 157]. Interestingly, sirtuin-mediated epigenetic modifications may regulate the metabolic state of various adult SCs, including intestinal SCs as well as the cells participating in the niche [rev. in 158]. SIRT1 is a NAD-dependent deacetylase that removes acetyl groups from proteins like histones inducing

NAD+/SIRT1-mediated gene repression [157]. The NAD^+/NADH ratio is important for SIRT1 activity and reflects the metabolic status of the cells. Indeed, SIRT1 has been connected to the beneficial effects of calorie restriction in mice. Physiological adaptation to starvation results in higher SIRT1 activity in liver and brown adipose tissue parallel to decreased TH serum levels, to achieve energy conservation [159]. SIRT1 was also found to cooperate with PGC-1α to enhance the response to T3 in the liver, but it also stimulated TRβ1 activity independently of PGC-1α [160]. This last effect depends on the interaction between SIRT1 and TRβ1, promoting T3-dependent TRβ1 deacetylation and increasing ubiquitin-mediated TRβ1 turnover [160]. Surprisingly, only a subset of TRβ1 target genes, including glucose 6 phosphatase, were strongly inhibited by SIRT1 knockdown in the liver [160], suggesting a complex SIRT1-dependent and independent function of TRβ1. The hormone T2 can also activate SIRT1 and induce PGC-1α deacetylation, resulting in the activation of genes required for FAO [2]. Thus, it can be speculated that SIRT1 might cooperate with PGC-1α and stimulate TRα1 to modulate the metabolic status of the intestinal SCs and their niche cells.

Altogether, THs and TRs can increase the pool of regulated target genes by controlling metabolic fluxes and chromatin remodeling. This, in turn, may affect the metabolic activities of different cell types in both the normal intestine and in tumors. Last, but not least, TH/TR-dependent alterations in the metabolic status influence cell identity (i.e., stem vs non-stem) and behavior (*i.e.*, normal vs tumor).

Conclusions

In this review, we have highlighted the importance of TH-dependent signaling on intestinal SC physiology, including a direct action on SCs as well as in the SC niche. In addition, since alteration of TH signaling can lead to tumor development, we also discussed new insights into CSC biology and human CRCs.

The *THRA* gene is frequently upregulated in CRC patients [63], in particular in molecular subtypes linked to high metabolic features and elevated Wnt signaling [63]. These results are clearly of high clinical relevance and raise the question of the overall impact of an altered TH/TRα1 axis in CRC biology from tumor initiation to progression and metastasis.

Author contributions MVG and MP shared the responsibility to write the paper.

Funding MP lab is supported by the FRM (Equipes FRM 2018, DEQ20181039598), by the Inca (PLBIO19-289) and by the Ligue Contre le Cancer, Département Grand Est (01X.2020 and 01AE.2021). MVG received support from the FRM.

Data availability Not applicable.

Declarations

Conflict of interests The authors have no competing interests.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent to publish Not applicable.

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