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Thyroid hormone promotes differentiation of colon cancer stem cells

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ABSTRACT

Tumor formation and maintenance depend on a small fraction of cancer stem cells (CSCs) that can self-renew and generate a wide variety of differentiated cells. CSCs are resistant to chemotherapy and radiation, and can represent a reservoir of cancer cells that often cause relapse after treatment. Evidence suggests that CSCs also give rise to metastases. Thyroid hormone (TH) controls a variety of biological processes including the development and functioning of most adult tissues. Recent years has seen the emergence of an intimate link between TH and multiple steps of tumorigenesis. Thyroid hormone controls the balance between the proliferation and differentiation of CSCs, and may thus be a druggable anti-cancer agent. Here, we review current understanding of the effects of TH on colorectal CSCs, including the cross regulatory loops between TH and regulators of CSC stemness. Targeting TH in the tumor microenvironment may improve treatment strategies.

1. Introduction

1.1. Thyroid hormone, deiodinases and cancer

Thyroid hormone (TH) regulates a wide variety of cellular processes in vertebrates, including cellular proliferation, differentiation and apoptosis, by influencing the expression of different sets of genes (Gereben et al., 2008; Dentice and Salvatore, 2011). Most TH actions are initiated by the binding of T3 to its nuclear receptors in target cells (Yen, 2001; Mullur et al., 2014), which results in TH-dependent transcriptional activation or repression (Wu et al., 2001; Yen et al., 2006). Apart from this genomic action of TH, part of TH signal is also mediated via a non-genomic action involving binding of TRs with different cytosolic partners (Brent, 2012). The biological activity of TH is determined largely by the intracellular concentration of T3, which, in turn, depends on the deiodinases that catalyze the production (D1 and D2) or degradation (D3) of T3 (Visser, 2016). Indeed, despite the relatively constant TH plasma levels, TH signaling in individual tissues can significantly change consequent to local TH metabolism mediated by iodothyronine deiodinase (Dentice et al., 2013a). Several studies indicate that TH is closely linked to neoplastic transformation (Dentice et al., 2013b).

The expression of the deiodinases is often altered in cancer (Table 1). In fact, D1 expression was found to be lower in kidney cancer cells than in their normal counterparts (Pachucki et al., 2001), and significantly lower in lung cancer than in normal tissue (Wawrzynska et al., 2003). On the contrary, D1 expression and activity was found to be higher in breast cancer and in the breast cancer cell line MCF-7 than in controls (Macejova et al., 2001; Debski et al., 2007). A similar pattern occurs in thyroid cancer where, depending on the subtype and histological characteristics, D1 is expressed both in the tumor and in normal tissue (Schreck et al., 1994; de Souza Meyer et al., 2005). A very recent study demonstrated that loss of *Dio1* contributes to renal carcinogenesis, while induction of D1 expression inhibits proliferation and migration of renal cancer cells (Poplawski et al., 2017). D2 is over-expressed in most brain tumors, namely, astrocytomas, glioblastomas, gliosarcomas and oligodendrogliomas (Mori et al., 1993; Nauman et al., 2004), while down-regulated in pituitary tumors (Piekielko-Witkowska et al., 2013), and in papillary thyroid carcinoma (Arnaldi et al., 2005; Murakami et al., 2001). Notably, it is expressed in human osteoblast cells as well as in osteosarcoma cells (SaOS-2), suggesting that D2 is essential not only for osteoblast homeostasis but also for neoplastic transformation (Gouveia et al., 2005; Morimura et al., 2005). A recent study demonstrated that D2 is expressed in basal-cell carcinoma (BCC) in which D2 inactivation

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Table 1
Expression of deiodinases in different types of cancer.

Type I deiodinase			Type II deiodinase			Type III deiodinase		
Tumor	Expression	Ref.	Tumor	Expression	Ref.	Tumor	Expression	Ref.
Kidney cancer	Down	Pachuchi et al.,2001	Papillary thyroid carcinoma	Down	Arnaldi et al., 2005	Astrocytomas	Down	Nauman et al., 2004
Lung cancer	Down	Wawrzynska et al., 2003	Follicular thyroid carcinoma	Up	de Souza Meyer et al., 2005	Glioblastomas	Up	Nauman et al., 2004
Breast cancer	Up	Debski et al., 2007	Astrocytomas	Up	Nauman et al., 2004	Gliosarcomas	Up	Nauman et al., 2004
Papillary thyroid carcinoma	Down	de Souza Meyer et al., 2005	Glioblastomas	Up	Nauman et al., 2004	Oligodendromas	Up	Nauman et al., 2004
Follicular thyroid carcinoma	Up	de Souza Meyer et al., 2005	Gliosarcomas	Up	Nauman et al., 2004	Basal cell carcinomas	Up	Miro et al., 2017
			Oligodendrogliomas	Up	Mori et al., 1993	Colon carcinomas	Up	Dentice et al., 2012
			Basal-cell carcinoma	Up	Miro et al., 2017	Hemangiomas	Up	Dentice et al., 2013
			Pituitary tumors growth-hormone secreting adenoma	Down	Piekielko-Witkowska et al., 2013	Pituitary gland adenoma	Up	Dentice et al., 2013
			Osteosarcoma cells SaOS-2	Up	Gouveia et al., 2005			

accelerates cell cycle progression thereby enhancing the proportion of S-phase cells and cyclin D1 expression and reducing basal apoptosis (Miro et al., 2017).

The deiodinase that has been most frequently associated with mouse and human carcinogenesis is D3, which is in line with its definition as an oncofetal protein (Dentice, 2011). This observation suggests a link between deiodinase-mediated TH attenuation and tumorigenesis. Indeed, immortalized cell lines derived from BCCs, hemangiomas, hepatocarcinomas, breast cancer (MCF-7 cells), colon adenocarcinomas (Caco2, SW480, and HCT116 cells), thyroid cancer, endometrium cancer (ECC-1 cells), and neuroblastoma (SH-SY5Y cells) express elevated D3 levels (Huang et al., 2000; Kester et al., 2006; Dentice et al., 2009; Sibilio et al., 2012). D3 is also overexpressed in many human solid tumors, namely, vascular tumors, hepatic hemangiomas and colon carcinomas (Dentice et al., 2013b). Notably, D3 expression in colon cancer is significantly higher than in normal tissues but negatively correlated with the histologic grade of the lesions, which suggests that D3 could be an early marker of tumorigenesis.

Also TH receptor (TR) availability affects tumorigenesis as demonstrated by the finding that the v-erbA oncogene isolated from an avian retrovirus is a mutated form of the human TRα (Table 2), (Sap et al., 1986; Weinberger et al., 1986). Further evidence implicating TRs in cancer comes from studies showing that loss of heterozygosity is a frequent event in breast (Futreal et al., 1992), prostate (Gao et al., 1995) and gastrointestinal cancer (Huber-Gieseke et al., 1997). One of the most widely used mouse models created for studies of the role of TRs in cancer transformation, is the $Thrb^{PV/PV}$ mutant. This mouse has a single base insertion (cytosine) that leads to a frameshift in the C-terminal 14 amino acids of TRβ, and ends with the addition of 2 amino acids in the receptor's polypeptide chain (Kaneshige et al., 2000). These mice spontaneously develop follicular thyroid cancer (Lu et al., 2012) and mammary tumors (Guigon et al., 2011). Moreover, several TR mutations are frequent in hepatocellular carcinoma (Chen et al., 2008; Chan and Privalsky, 2009), thyroid cancer (Yen and Cheng, 2003) and renal clear cell carcinoma (Rosen and Privalsky, 2009).

1.2. Thyroid hormone and stem cells

Given TH's critical role as a regulator of the balance between cell proliferation and differentiation (Dentice et al., 2013a), it is not surprising that the self-renewal and specification of stem/progenitor cells are highly sensitive to TH action. The neural stem cell niche is regulated by TH and by the TRα1 receptor, which affect the decision of neural stem cells to self-renew and/or differentiate, so giving rise to different progenitor cells, i.e., neurons, oligodendrocytes, and astrocytes (Lopez-Juarez et al., 2012). Similarly, the dynamic control of the TH signal by deiodinases D2 and D3 is exploited by muscle stem cells to finely regulate amplification and differentiation during the linear progression of satellite cells (Dentice et al., 2014; Salvatore et al., 2014). Importantly, the differential expression of the deiodinases during myogenesis is epigenetically controlled through the combined action of a transcriptional machinery involving the DNA methyltransferase enzymes as well as muscle-specific transcriptional factors (Ambrosio et al., 2013). In the intestinal epithelium, the TRα1 receptor regulates the fate of precursor cells and crypt proliferation by interacting with the Wnt and Notch pathway (Kress et al., 2010; Sirakov et al., 2012, 2015). In particular, Sirakov et al. have demonstrated that the TH-TRα1 complex positively regulates the Notch signaling and the Notch downstream targets in mouse intestinal crypts, thus in turn resulting in altered proliferation/differentiation balance (Sirakov et al., 2015). Considering the intimate links between Notch

Table 2
Mutations of thyroid hormone receptors (TRs) in tumors.

TRα			TRβ		
Tumor	Mutation	Ref.	Tumor	Mutation	Ref.
Breast cancer	LOH	Gao et al., 1995	Breast cancers	LOH	Huber-Gieseke et al., 1997
TSHoma	H435Y; TRβ2 aberrant alternative - splicing	Rosen and Privalsky, 2009	Small cell lung cancers	LOH	Huber-Gieseke et al., 1997
Hepatocellular carcinoma	K74E; K74R; M150T; E159K; A264V	Chan and Privalsky, 2009	Gastrointestinal cancer	LOH	Huber-Gieseke et al., 1997
Non-functioning pituitary adenomas	S45I; L370N; S377L	Rosen and Privalsky, 2009	Hepatocellular carcinoma	M32I;C207R; T368N; S43L; C446R; M313I; K113N; T329P	Chan and Privalsky, 2009
Papillary thyroid carcinoma	T80I; L109P; E213D; S305P; K337R; G57E; K29T; C97Xa; Y352C; S183N; H184Q; Q187Xa; R228H; E245V; K288E; S183N; H184Q; R228H; M369V; S183N; H184Q; R228H; S271I	Rosen and Privalsky, 2009	Papillary thyroid carcinoma	M32V; E34G; P141L; A318D; F451I; N76D; S81L; I135V; Q136H; R201Xa F403L; C446R; K91R; K289M; Q235X; M379T; D427G; K411E; Q205L; K103R; M32T; L373P; K411E; H435R; S99R	Rosen and Privalsky, 2009
Renal clear cell carcinoma	S183N; H184Q; R228H; K288E; I116N; M388I; I116N; A225T; M388I	Rosen and Privalsky, 2009	Renal clear cell carcinoma	S99R; W219L; F451I; Y321H; F451S; Q252R; A387P; F417L;; K155E; K411E; D1-26; S380F	Rosen and Privalsky, 2009

and Wnt pathway and the control of stemness, these findings raised the intriguing possibility that TH might be involved in the control of CSC behavior, and that the TH signal might be a critical component of the CSC compartment.

This Review focuses on the evolving concept that the TH signal plays a role in CSC biology. Particular emphasis is placed on recent studies showing how the plastic control of TH by D2 and D3 drastically affects the differentiation of CSCs thereby influencing their sensitivity to conventional therapies (Graphical Abstract). The finding that TH reduces the tumorigenesis of some cancer types by acting not only on the tumor mass, but also on CSCs has reinforced the concept that TH may be a tool with which to manipulate the cancer stem cell pool in tumors.

2. Two established D3-dependent tumors: BCC and colon cancer

D3 has been consistently found in many hyperproliferative conditions as well as in cancer cells and tumors (Dentice et al., 2013b; Dentice, 2011). A functional link has been demonstrated between D3 expression, TH attenuation and tumorigenesis in two examples of epithelial tumorigenesis (BCC and colon cancer) (Dentice et al., 2007, 2012). Basal cell carcinoma is the most frequently diagnosed human cancer and accounts for approximately 80% of all non-melanoma skin cancers. In BCC-derived cells and in BCC solid tumors, D3 is under the control of the Shh-Gli2 cascade (Dentice, 2011). By directly inducing D3 in keratinocytes, Shh causes a hypothyroid state at intracellular level that increases the proliferative rate. D3 expression in BCC cells determines a proliferative advantage for the tumor and, conversely, D3-depletion attenuates tumorigenesis and enhances the apoptotic process. Moreover, T3 treatment or D3-depletion reduces tumor growth by promoting Gli degradation and Shh pathway inhibition (Luongo et al., 2014). Additionally, it was recently demonstrated that D3 is also controlled by the cancer-associated microRNA-21 in BCC and that a reciprocal regulation between TH action and miR21 is essential for BCC formation (Di Girolamo et al., 2016).

Colorectal cancer (CRC) is one of the most common and lethal tumors worldwide. Given the high regenerative and proliferative nature of the intestinal epithelium, it is not surprising that the intestinal system provides enormous opportunities for the accumulation of genetic mutations (Markowitz and Bertagnolli, 2009; Lampropoulos et al., 2012). In fact, the tumorigenesis of CRC is a multi-step process in which over 90% of cancers originate from activating mutations in the Wnt pathway (Beck and Blanpain, 2013). In colon cancer stem cells (CR-CSCs) dual D2-D3 expression is tightly regulated by the Wnt/β-catenin pathway (Dentice et al., 2012). Specifically, the TH-activating D2 enzyme is downregulated by β-catenin, whereas D3 is a direct target of β-catenin that binds to the D3 promoter and activates D3 transcription. The result of this dual regulation is a potent reduction of intracellular T3 induced by the Wnt pathway in the formation of colon cancer. Alterations of this mechanism perturb tumorigenesis as demonstrated by the finding that D3-depletion and T3 treatment increase E-cadherin expression, and reduce nuclear translocation of β-catenin, thereby resulting in cell differentiation and reduced cellular proliferation. Collectively, these two examples of epithelial tumorigenesis indicate that multiple oncogenic signals concur to reduce the TH environment in the tumor context.

Notably, regulation of intracellular T3 concentrations can now be added to the list of extrinsic factors that could be exploited to therapeutically modulate, in a locally restricted fashion, the action of TH in TH-sensitive tumors.

3. Colon cancer stem cells

The cell of origin of colorectal cancer is unknown, but various models have been proposed to explain the growth and heterogeneity of the tumor. According to the CSC theory, the first mutation occurs in a colonic stem cell. Throughout their life, CSCs continue to accumulate oncogenic mutations and start to divide symmetrically and asymmetrically thus giving rise to other CSCs and progenitors (Boman and Huang, 2008). Based on the spontaneous lineage progression of intestinal stem cells toward the crypt-villus axis, two alternative models, namely, "top-down" and "bottom-up", have been proposed for the histogenesis of CRC. According to the top-down model, the more differentiated (luminal) cells re-acquire stem cell-like properties and produce aberrant crypt foci where tumors develop. Conversely, the bottom-up hypothesis suggests that stem cells at the base of the crypt base amplify and migrate upwards, thus constituting tumor-initiating cells (Zeuner et al., 2014; Basu et al., 2016). In both models, Wnt/β-catenin signaling is considered a master inducer of colon CSC biogenesis, which is in agreement with the concept that nearly 90% of colon cancers have mutations in the same signaling pathway (Boman and Huang, 2008). Indeed, Dow and colleagues demonstrated that suppression of antigen-presenting cells (APC) results in the development of colon cancer in mice, while re-expression of APC in these tumors down-grow the tumorigenic lesions, even in mice harboring oncogenic *Kras* and *p53* mutations (Dow et al., 2015).

Various specific markers for the CSC phenotype have been identified. Colon CSCs (CR-CSCs) were originally identified in primary tumors through their expression of CD133 (O'Brien et al., 2007; Ricci-Vitiani et al., 2007). CD133 expression was observed not only in tumor cells, but also in normal colon albeit at a low level. These results suggest a relation between normal and CSCs.

A second well-established CR-CSC marker is Lgr5, which is a target gene of Wnt signaling (Barker et al., 2007). Lgr5-positive cells act as tumor-initiating cells that lead to adenoma formation (Barker et al., 2009). Moreover, high Lgr5-expressing CRC cells (Lgr5-Hi) had a greater propensity to expand clonally, while Lgr5 suppression resulted in the loss of their ability to form colonies (Kemper et al., 2012). Other CR-CSC markers are Ascl2 and Sox9 (Munoz et al., 2012), which are also a Wnt target thereby highlighting the requirement for sustained Wnt signaling for the maintenance of the stem cell population in colon cancer.

In the last decade, CR-CSCs have been successfully isolated by FACS sorting from colon cancers by specific surface epitopes, i.e., CD44, CD166, CD133 and ESA (epithelial-specific antigen, also known as "EpCAM") surface markers (Todaro et al., 2014; Dalerba et al., 2007). These cells represent a dynamic population highly sensitive to genetic, epigenetic, and micro-environmental factors (Kreso and Dick, 2014). Consequently, changes in the cell niche can drastically affect their stemness and resistance to cancer therapy.

4. TH and colon cancer stem cells

One of the most exciting recent findings about TH in tumorigenesis is that, not only do TH and deiodinases affect the proliferation and differentiation of CR-CRCs but that the control of TH in the tumor microenvironment profoundly affects CSC behavior (Catalano et al., 2016). Analysis of D2 and D3 expression in different cell populations of human CR-CSCs demonstrated that D2 and D3 are dynamically expressed by quiescent-versus-differentiated CR-CSCs. In particular, D3 is potently expressed in undifferentiated CR-CSCs, in which the Wnt pathway is very active. Conversely, D2 is up-regulated in CR-CSCs in parallel with differentiation, which suggests that TH might contribute to stem cell differentiation. Indeed, TH treatment induces a differentiation program of quiescent CR-CSCs similar to the differentiation effects of serum. As concern the TRs expression, both TRα and TRβ are expressed in human CR-CSCs (Catalano et al., 2016). Although D3 did not exert transforming ability *per se* in normal colon cells, D3 expression is required for tumor formation and maintenance as demonstrated by the drastically attenuated clonogenic capacity and tumorigenesis of D3-depleted colon cancer stem cells (Catalano et al., 2016). Interestingly, the effects of TH and its metabolism are quite different in CSCs compared to what observed for the adult quiescent stem cells. For instance, in the intestine epithelium, by positively regulating Notch signaling, TH and its receptor TRα increases the proliferation of progenitor cells of the crypt (Sirakov et al., 2015). Conversely, TH signal amplification induces CSCs differentiation (Catalano et al., 2016). These discrepancies might be due to the different traits that distinguish CSCs from adult stem cells. For example, while adult stem cells are quiescent, mitotically dormant cells, the CSCs for their tumorigenic nature, are more prone to the proliferation.

Identification of the differentiative ability of TH on CR-CSCs raised the question "can TH treatment affect the sensitivity of these cells to conventional chemotherapy". Notably, pre-treatment of CR-CSCs with TH increased cell death induced by the chemotherapeutic agents oxaliplatin and 5-fluorouracil (Catalano et al., 2016). Nearly all the pro-differentiative effects of TH on CR-CSCs were promoted by regulation of two signaling pathways involved in the control of stemness and differentiation of intestinal stem cells, namely the Wnt and BMP pathways. The molecular mechanisms by which TH influences CR-CSC stemness and differentiation involve the Wnt and BMP pathways. Indeed, TH treatment enhances BMP expression in human CR-CSCs and attenuates the effect of the Wnt pathway and of a large cohort of Wnt pathway target genes (Catalano et al., 2016).

Taken together, these data indicate that by inducing differentiation, growth reduction, and chemosensitization of CR-CSCs, the endocrine signal of TH promotes CSC-depletion in colon cancerogenesis (Graphical Abstract). The exciting consequences of this process might be that the combined action of intracellular T3 and chemotherapy may strengthen colorectal cancer treatment and open new avenues for the use of tissue-specific regulation of deiodinases for treating cancer.

5. Conclusions

The discovery that cancer is driven by CSCs has attracted a great deal of attention particularly in view of the potential for the treatment of solid malignancies. Conventional therapies induce tumor regression, but fail to effectively target CSCs, leading to increased risk of relapse. Therefore, in order to prevent tumor recurrence it is important to develop drugs that can specifically target and eliminate CSCs (graphical abstract). Despite advances in therapeutic strategies, CRCs remain the third leading cause of cancer-related deaths worldwide, and one of the major reasons for failing therapies is that treatment strategies were designed to reduce the mass of the tumor. Colorectal cancer stem cells have been successfully isolated from human colon carcinomas using stem cell markers. These cells accounted for approximately 2.5% of tumor cells; they can induce xenograft tumors in immunocompromised mice and can also reconstitute the tumor containing differentiated cells and the original heterogeneity.

The recently introduced concept that TH and its regulating enzymes D2 and D3 are dynamically regulated in different subpopulations of CR-CSCs according to their stem-like versus differentiated shape has suggested that the control of intracellular TH availability might be a tool with which to affect the stemness and amplification potential of these cells. As illustrated in graphical abstract, thyroid hormone not only induces the differentiation of

CR-CSCs, but also attenuates symmetric cancer cell division and sensitizes these cells to conventional anti-cancer treatments, thereby overcoming drug resistance. Thyroid hormone controls the most important pathways involved in the regulation of CR-CSCs: the WNT, BMP and Notch pathways (Sirakov et al., 2015; Catalano et al., 2016). By regulating multiple oncogenic pathways, TH might represent a critical hub that can influence the CSC compartment and eliminate symmetric cancer populations.

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