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Review

The thyroid hormones and their nuclear receptors in the gut: From developmental biology to cancer☆

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ABSTRACT

The thyroid hormones control the development and the homeostasis of several organs in vertebrates. Their actions depend, for the most part, on nuclear receptors, the TRs, which are transcription factors whose activity is modulated by the hormone T3. The gastrointestinal tract is a well characterized target of thyroid hormones and TRs, as extensively described in the literature. In fact, its remodeling in amphibians during thyroid hormone-dependent metamorphosis is well characterized at the cellular and the molecular levels. However, whereas a great attention has been paid to the nervous system and to cardiac development and physiology, the function of thyroid hormones and TRs in the mammalian gastrointestinal tract has been, until recently, underestimated. Several studies have described an important conservation of this hormonal signal during intestinal development and have suggested that it may play a role in stem cell physiology in both amphibians and mammals. These findings show the importance of the thyroid hormones and TRs, whose homologous actions are maintained across species. In the present review, we summarize the most recent data on this issue, starting from work that has been conducted on amphibian metamorphosis to results on postnatal development, homeostasis, and tumorigenesis in mammals. This article is part of a Special Issue entitled: Translating nuclear receptors from health to disease.

1. The thyroid hormones and the nuclear receptors

1.1. Thyroid hormone synthesis and metabolism

The synthesis of thyroid hormones (THs) is regulated through the hypothalamus–pituitary–thyroid axis [1] (Fig. 1). The follicular cells of the thyroid gland synthesize and secrete L-thyroxine, or T4, and 3,5,3′-L-triiodothyronine, or T3. This process is under the control of the circulating TH levels through negative feedback loops of this axis [1]. In most vertebrates, the predominant hormone produced by the thyroid gland is T4. This hormone is transported by the blood to the peripheral organs, where it is deiodinated by types I and II T4-5′-deiodinases. The loss of one iodine atom allows the synthesis of T3, which is considered the active hormone because of its binding to the nuclear receptor TR [2]. The liver and the kidney are the principal organs responsible for T4 deiodination and the synthesis of T3, which accounts for up to two-thirds of T3 production and release into the blood. However, most of the organs and tissues are also efficient in producing T3, as discussed below [3].

The intracellular concentration of T3 is dependent upon the uptake of T3 and T4 and their subsequent metabolism [4]. Both of these hormones are actively transported across the cell membrane by specific transporter proteins, of which, monocarboxylate transporter-8 and organic anion-transporting polypeptide-1c are the best characterized [5–8]. Three iodothyronine deiodinase selenoenzymes (D1, D2, and D3) regulate TH activation and catabolism [4]. As mentioned previously, D1 and D2 catalyze the 5′-deiodination of T4 to its active metabolite T3. In particular, the action of D1 provides the main source of circulating T3, whereas D2 is the isoenzyme that is primarily responsible for the local production of T3 in the target cells. T3 that is derived from D2 activity in the skeletal muscle may also contribute to the circulating levels of T3. Conversely, D3 catalyzes the irreversible 5-deiodination of T4 and T3 to their inactive metabolites rT3 (3,5,5′-T3, or reverse T3) and 3,3′-T2 and protects the target cells from an excess of THs. Altogether, these mechanisms that are related to TH uptake and metabolism determine the levels of T3 availability in cells [4].

1.2. The thyroid hormone nuclear receptors

The thyroid hormone receptors (TRs) are transcription factors that belong to the nuclear receptor superfamily [9]. The main characteristic of the TRs is the presence of a DNA- and a hormone-binding domain, known as DBD and HBD, respectively (Fig. 2). The amino-acid sequence of these domains is highly conserved across species [10].

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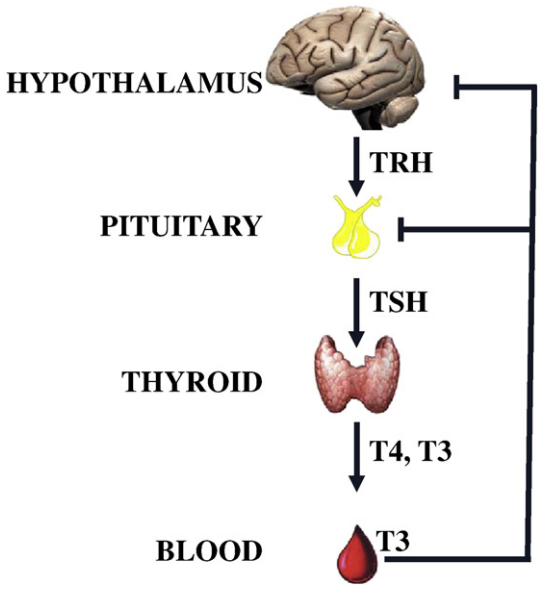

Fig. 1. Regulation of thyroid hormone synthesis. The picture shows the complex hypothalamus–pituitary–thyroid regulatory loop. TSH stimulates TH synthesis in the thyroid. Increased levels of circulating TH repress TRH and TSH expression, maintaining unaltered levels of circulating hormones.

The DBD contains two zinc finger structures [3,11]. The HBD allows for hormone-binding and for interaction with co-regulators [10]. Activating function 1 and activating function 2, which are located at the amino-terminal and carboxy-terminal ends, respectively, are responsible for the hormone-independent or hormone-dependent transactivation properties of the receptors [12]. The amino-terminal end also contains a sequence for nuclear localization (NLS) [13].

The TRs bind specific DNA sequences named thyroid hormone response elements (TREs), which are generally located within the genomic non-coding regions of the target genes. The canonical TRE consensus is a tandem of AGGT(C/A) sequences in direct repetition that are separated by four base pairs, named the direct repeat 4 (DR4) [14]. However, the TREs that are present in the promoters of the target genes often differ from the consensus sequences in terms of their arrangements as palindromes or inverted palindromes or in the number of nucleotides that separate the tandem sequences [15]. The existence of this variety of TREs may help explain the different modalities of transcriptional modulation by TRs (*i.e.*, activation *vs.* repression) [14].

The characteristics summarized in this paragraph refer to the TRs in mammals, but their peculiarities are conserved in the phyla and genera for which they have been described. In fact, genome-wide analyses have revealed that TRs are not unique to chordates because orthologous genes are present in platyhelminths and molluscs. Until now, no TR orthologs had been identified in Porifera or Cnidaria. A detailed analysis of the gene structure and the function of the TRs in invertebrates is reported by Wu et al. [16]. The authors presented an interesting overview of TR functionality (*in silico* and *in vitro*) but gave very little information about their expression patterns. TRs have also been described in the cephalochordate amphioxus [17] and in non-mammalian vertebrate species, such as salamanders [18], crocodiles [19], gold fish [20], salmon [21], and amphibians [22,23].

Due to tetraploidy, there are four TR genes in Xenopus: two TRα genes and two TRβ genes. Alternative splicing of the TRβ transcripts gives rise to two different isoforms for each TRβ gene [24]. Two genes in mammals encode for the T3 nuclear receptors: TRα and TRβ [14]. Each gene generates different proteins using different promoters and/or alternative splicing (Fig. 2, [2,14]). The TRα locus codes for four isoforms (Fig. 2A), but only TRα1 can bind both T3 and DNA [14,25]. TRα1 and TRα2 result from the alternative splicing of a primary transcript [26]. TRΔα1 and TRΔα2 result from the alternative splicing of a secondary transcript, starting from an internal promoter that is located in the intron 7 [27]. Previous studies have shown that TRα2, TRΔα1, and TRΔα2 behave as antagonists of TRα1 on its target genes through a mechanism that has not yet been characterized [26–28]. TRα1 and TRα2 have a widespread, ubiquitous expression, whereas the short TRΔα1 and TRΔα2 isoforms display restricted expression patterns [29]. The TRβ locus codes for four isoforms (Fig. 2B), including three receptors, TRβ1, TRβ2, and TRβ3, that result from three different transcription start sites [29,30]. The TRΔβ3 form does not contain the DNA-binding domain and behaves as an inhibitor of the three TRβ and TRα1 receptors [30,31]. It is worth noting, however, that TRβ3 and TRΔβ3 have only been described in the rat genome [31]. TRβ1 displays a ubiquitous expression and is the main TR isoform that is expressed in the liver. The expression of TRβ2 is restricted to the pituitary gland, the TRH neurons of the hypothalamus, the developing retina, and the inner ear. TRβ3 is present in the liver, the kidneys, and the lungs, and TRΔβ3 is present in the skeletal muscles, the heart, the spleen, and the brain [29,31].

From a molecular point of view, TRs heterodimerize with retinoid X receptors (RXRs) and bind to T3 response elements that are located within the genomic regions of target genes. In the absence of T3, TRs interact with co-repressor proteins to inhibit positively regulated target genes. Following T3 binding, co-repressors are displaced and co-activator proteins are recruited to the ligand-bound TR complex to facilitate T3-dependent activation of the target genes. Importantly, some genes, including thyroid-stimulating hormone (TSH), are inhibited by T3-liganded TR; however, the mechanism that underlies the T3-dependent repression of gene transcription is still poorly understood [2].

2. Intestinal physiology

For many years, the intestine has been described as an organ target of TH action [32]. The first evidence for a role of these hormones as key regulators of gastrointestinal development came from observations of the amphibian metamorphosis at the beginning of the 20th century. In fact, metamorphosis is strictly and exclusively controlled by TH, and during this process, the gastrointestinal tract undergoes a dramatic remodeling, which includes a first phase of apoptosis and,

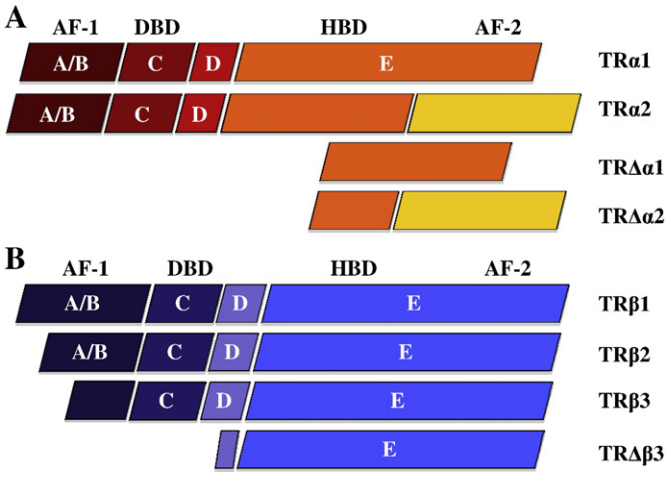

Fig. 2. Representation of the various isoforms encoded by TRα (A) or TRβ (B) genes. The pictures show the different domains involved in TR function. These include the DBD and HBD that are specifically present in the TRα1, TRβ1, TRβ2, and TRβ3 proteins, *bona fide* T3 nuclear receptors (bold). TRα2 and the truncated TRΔ isoforms lack each or both domains. Other functional regions of the TRs include cofactor-binding domains (located in A/B, D, and E) and dimerization domains (located in C and E). AF-1 and AF-2 domains are important for transcriptional activation.