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Review

Thyroid hormones and the control of cell proliferation or cell differentiation: Paradox or duality?

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ABSTRACT

Amphibian metamorphosis perfectly illustrates a key paradox: thyroid hormones control diverse cellular processes depending on the tissue context. This point is also reinforced by a recent accumulation of evidence. For example, thyroid hormones and their nuclear receptor TRs have been described to function in different systems in synergy and/or in antagonism with other signaling pathways. This interaction helps explain their pleiotropic roles. This review summarizes the most important advances in this field, focusing in particular on the key action of thyroid hormones in controlling the balance between the processes of cell proliferation and cell differentiation in a few organs, with special attention paid to the intestine. We highlight similarities between the cellular and molecular events occurring during postnatal intestinal maturation at metamorphosis in amphibians, and comparable events observed at weaning in mice.

Contents

1. Introduction

1.1. Thyroid hormone production

Thyroid hormones (THs), L-thyroxine or T4 and 3,5,3′-L-triiodothyronine or T3, are essential for the development of several organs, including the central nervous system, skeleton, heart,

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intestine, skeletal muscle and sensory organs. Moreover, they also have important regulatory effects on oxygen consumption and metabolic rate (Oppenheimer et al., 1987). The follicular cells of the thyroid gland synthesize and secrete both hormones, but T4 is the most abundant. This process is under the control of circulating THs levels through the hypothalamus–pituitary–thyroid feedback regulatory loop (rev. in Fredric and Wondisford, 2004).

The intracellular concentration of T3 is dependent upon the uptake of T3 and T4, and their subsequent metabolism (Bianco and Kim, 2006). In fact, both hormones are actively transported across the cell membrane by specific transporter proteins, of which monocarboxylate transporter-8 is the best characterized (Dumitrescu et al., 2004; Friesema et al., 2004; rev. in Refetoff and Dumitrescu, 2007; Visser et al., 2007). Three iodothyronine deiodinase selenoenzymes (D1, D2 and D3) regulate TH activation and catabolism (Bianco and Kim, 2006). D1 and D2 catalyze the 5′-deiodination of T4 to its active metabolite T3. T3 is generated from the activity of D1, which is the main source of circulating T3. In contrast, D2 is the isoenzyme primarily responsible for local production of T3 in target cells. T3 derived from D2 activity in skeletal muscle may also contribute to circulating levels of T3. Conversely, D3 catalyzes the irreversible 5-deiodination of T4 and T3 to the inactive metabolites rT3 (3,5,5′-T3, or reverse T3) and 3,3′-T2, thereby protecting target cells from excess of THs, that can be deleterious especially during embryogenesis (Chassande, 2003). Thus, TH uptake and metabolism determine the levels of T3 availability into the cells.

1.2. The thyroid hormone nuclear receptors

The classical action of T3 is mediated via thyroid hormone nuclear receptors, the TRs, which belong to the nuclear hormone receptor superfamily of transcription factors (Laudet et al., 1992). From a molecular point of view, TRs heterodimerize with retinoid X receptors (RXRs) and bind to T3 response elements located within the genomic regions of target genes (Yen, 2001). In the absence of T3, TRs interact with co-repressor proteins to inhibit positively regulated target gene transcription. Following T3 binding, co-repressors are displaced and co-activator proteins are recruited to the ligand-bound TR complex, so as to facilitate T3-dependent activation of the target genes. Importantly, some genes, including Thyroid-Stimulating Hormone (TSH), are inhibited by T3, but the mechanism underlying T3-dependent repression of gene transcription is still poorly defined (Lazar, 2003).

TRs are encoded by the TRα and TRβ genes, which generate multiple isoforms by alternative promoter usage and alternative splicing (Fig. 1). The TRα locus encodes at least four different proteins (Fig. 1A), but only TRα1 is a true nuclear receptor. The other TRα isoforms, namely TRα2, TRΔα1 and TRΔα2 behave as antagonists of TRα1 (Koenig et al., 1989; Chassande et al., 1997; Plateroti et al., 2001). The TRβ locus encodes two receptors, TRβ1 and TRβ2 (Fig. 1B), which differ from each other by the length of their amino-termini (Flamant and Samarut, 2003). All these isoforms are conserved between mouse and human as suggested by direct observation or comparison of respective genomic sequences. The rat THRβ locus also encodes TRβ3 and TRΔβ3 isoforms (Fig. 1B) (Williams, 2000; Harvey et al., 2007). They can be translated separately or from a single transcript, which contains an internal TRΔβ3 translation start site (Williams, 2000). TRβ3 is a bona fide T3 nuclear receptor, while TRΔβ3 retains T3 binding ability but lacks the DNA-binding domain and exerts a cell- and TRE-specific inhibitory function on TRβ1, TRβ3 and TRα1 receptors (Harvey et al., 2007).

TRα and TRβ genes are widely expressed within different organs and tissues. TRα1 and TRα2 are expressed almost ubiquitously, whereas the TRΔα transcripts are found mostly in the small intestinal epithelium, lung, brain and early embryo. TRβ1 is also widely

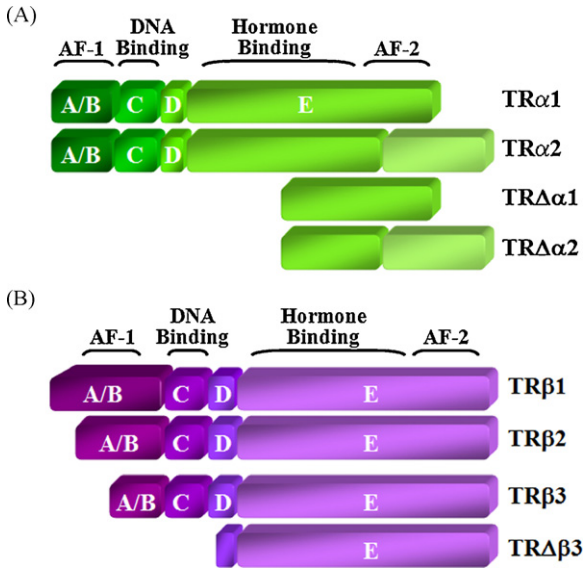

Fig. 1. Schematic representation of the various isoforms encoded by TRα (A) or TRβ (B) genes. These are generated by alternative splicing or use of different promoters. The pictures show the different domains involved in TR function. These include DNA-binding and hormone-binding domains specifically present in TRα1, TRβ1, TRβ2 and TRβ3 proteins, which are bona fide T3 nuclear receptors. 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), as well as dimerization domains (located in C and E). AF-1 and AF-2 domains are important for transcriptional activation.

expressed and it represents the most abundant TR isoform in the liver. TRβ2 expression is restricted to the pituitary, hypothalamic TRH neurons, the developing inner ear and retina (Flamant and Samarut, 2003). The TRβ3 isoform has been described in rat liver, kidney and lung and the TRΔβ3 in rat skeletal muscle, heart, spleen and brain (Williams, 2000).

1.3. Membrane and cytoplasm-mediated effects of THs

Besides the classically characterized TR-mediated functions, THs also exert rapid non-genomic actions that are initiated at the cell membrane. Data from Davis's laboratory has shown that the integrin αvβ3 is a specific membrane receptor for THs, and this binding leads to activation of the mitogen-activated protein kinase (MAPK) intracellular cascade (Lin et al., 1999; rev. in Davis et al., 2008). TH-dependent MAPK activation subsequently results in a series of complex responses that occur at the cell membrane, including modulation of the membrane potential by regulation of ion channels, activation of the Na+/K+ exchanger and Ca2+-ATPase, or regulation of actin cytoskeletal components anchored at the cell membrane (Klein and Ojamaa, 2001). Moreover, TH-activated MAPK can rapidly translocate to the nucleus and induce serine phosphorylation of TRs, thereby resulting in the induction of angiogenesis or tumor cell proliferation (Davis et al., 2000). Nuclear targets for phosphorylated TRs include the transcription factors p53, STAT1a and STAT3 (Lin et al., 1999). T3 also exerts TRα-dependent actions to regulate mitochondrial gene expression and metabolic function (Wrutniak-Cabello et al., 2000).

TRα and TRβ have been shown to form a cytoplasmic complex with the p85 subunit of phosphatidylinositol 3-kinase (PI3K) and induce nuclear translocation of the protein kinase B/Akt (Cao et al., 2005; Hiroi et al., 2006). Studies in TRβPV knock-in mice, which harbor a mutation in the TRβ gene responsible for the syndrome of Resistance to Thyroid Hormones (RTH, Refetoff, 2003), showed that these mice spontaneously develop thyroid cancer and distant metastasis. This is likely due to TR-PI3K interaction and the