Biochimica et Biophysica Acta xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen

Review

Thyroid hormone receptors, cell growth and differentiation ☆

Angel Pascual, Ana Aranda *

Instituto de Investigaciones Biomédicas "Alberto Sols", Consejo Superior de Investigaciones Científicas and Universidad Autónoma de Madrid, Arturo Duperier 4, 28029 Madrid, Spain

ARTICLE INFO

Article history:
Received 19 December 2011
Received in revised form 1 March 2012
Accepted 20 March 2012
Available online xxxx

Keywords:
Thyroid hormone receptor
Gene expression
Tissue homeostasis
Progenitor/stem cell

ABSTRACT

Background: Tissue homeostasis depends on the balance between cell proliferation and differentiation. Thyroid hormones (THs), through binding to their nuclear receptors, can regulate the expression of many genes involved in cell cycle control and cellular differentiation. This can occur by direct transcriptional regulation or by modulation of the activity of different signaling pathways.
Scope of review: In this review we will summarize the role of the different receptor isoforms in growth and maturation of selected tissues and organs. We will focus on mammalian tissues, and therefore we will not address the fundamental role of the THs during amphibian metamorphosis.
Major conclusions: The actions of THs are highly pleiotropic, affecting many tissues at different developmental stages. As a consequence, their effects on proliferation and differentiation are highly heterogeneous depending on the cell type, the cellular context, and the developmental or transformation status. Both during development and in the adult, stem cells are essential for proper organ formation, maintenance and regeneration. Recent evidence suggests that some of the actions of the thyroid hormone receptors could be secondary to regulation of stem/progenitor cell function. Here we will also include the latest knowledge on the role of these receptors in proliferation and differentiation of embryonic and adult stem cells.
General significance: The thyroid hormone receptors are potent regulators of proliferation and differentiation of many cell types. This can explain the important role of the thyroid hormones and their receptors in key processes such as growth, development, tissue homeostasis or cancer. This article is part of a Special Issue entitled Thyroid hormone signalling.

© 2012 Elsevier B.V. All rights reserved.

1. Introduction

Although the thyroid gland predominantly secretes thyroxine (T4), triiodothyronine (T3) is the most active thyroid hormone (TH), since it has a higher affinity by the nuclear thyroid hormone receptors (TRs), which mediate most actions of these hormones [1]. THs are released by the thyroid gland to the circulation where they are carried bound to proteins such as thyroxin binding globulin, transthyretin or serum albumin. An important mechanism that regulates TH action is the expression on the cell membrane of transporter proteins that mediate their uptake. Although it was believed that these lipophylic hormones could enter the cell by a passive diffusion mechanism, in the last years it has been proved the existence of an ATP-dependent, saturable mechanism that transports THs into the target cell, involving the monocarboxylate transporters MCT8 and MCT10 and the organic anion transporter proteins (OATPs) [2].

Conversion of T4 to T3 in target tissues is catalyzed by selenoprotein enzymes called deiodinases. The type I and II deiodinases (DIO1 and DIO2), convert T4 to T3 in different tissues then increasing the levels of circulating T3 and increasing availability of the active hormone for the nuclear receptors in a tissue-specific manner. On the other hand, the inner ring DIO3 enzyme is responsible for hormone inactivation since it converts T4 and T3 to the inactive metabolites reverse T3 (rT3) or T2, respectively. Therefore, deiodinase expression and distribution play an important role on TH action *in vivo* by regulating the amount of hormone that reaches the nuclear receptor in specific cell types and at different times during development and adulthood [3].

Although it has been postulated the existence of rapid non-genomic mechanisms initiated at the cell membrane that could be involved in mediating the actions of the TH [4], the best known effects of these hormones on cellular proliferation and differentiation require the presence of TRs. TRs, the cellular counterparts of the retroviral v-*erb*A oncogene, are ligand-dependent transcription factors that belong to the superfamily of nuclear receptors [5]. TRs are encoded by two genes: TRα and TRβ, located on human chromosomes 17 and 3, respectively. Primary transcripts of these genes undergo alternative processing generating several protein isoforms, among which TRα1, TRβ1 and TRβ2 are the main hormone-binding isoforms.

TRs share a common structure with other nuclear receptors, displaying a modular structure with several regions: an N-terminal region (A/B), a conserved DNA binding domain (DBD) or region C composed of two zinc fingers responsible for DNA binding, a hinge region D that links the DBD with the ligand binding domain (LBD), and

☆ This article is part of a Special Issue entitled Thyroid hormone signalling.

* Corresponding author at: Instituto de Investigaciones Biomédicas, Arturo Duperier 4, 28029 madrid, Spain. Tel.: +34 915854453; fax: +34 915854401.
E-mail address: aaranda@iib.uam.es (A. Aranda).

0304-4165/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbagen.2012.03.012

an E region containing the LBD and the residues responsible for receptor dimerization. Transcriptional regulation by the nuclear receptors is mediated by two autonomous activation functions (AFs): a constitutive N-terminal AF-1 in the A/B region and a ligand-dependent AF-2 located in the receptor C-terminus [5]. TRs normally regulate gene expression by binding, preferentially as heterodimers with the retinoid X receptors (RXRs), to short DNA sequences (thyroid hormone response elements or TREs) located in regulatory regions of target genes [6].

The actions of the nuclear receptors on transcription are mediated by the recruitment of coregulators: coactivators and corepressors. Unliganded TRs can act as strong constitutive repressors when bound to TREs in some positively regulated genes, since they associate with corepressors such as NCoR (nuclear receptor corepressor) or SMRT (silencing mediator of retinoic and thyroid receptor). These corepressors serve as platforms for the formation of repressor complexes that contain histone deacetylases. This creates a closed chromatin conformation for transcriptional machinery leading to transcriptional repression [7]. Ligand binding induces a conformational change in the receptor that causes corepressors release and recruitment of multiple coactivator complexes in a sequential manner. Some coactivators are chromatin remodeling factors or possess histone modifying activity such as acetylation or arginine methylation, whereas others interact with the basic transcriptional machinery and can recruit the RNA Polymerase II to the target promoter. Recruitment of coactivators causes chromatin decompactation and transcriptional stimulation.

The receptors can also repress gene expression in a ligand-dependent manner. In some cases this regulation involves binding to negative TREs. In the case of negatively regulated genes the role of corepressors and coactivators has not yet been totally defined, but it has been suggested that they could act in a mirror manner with respect to T3 positively-regulated genes. The nuclear receptors can also regulate the expression of genes that do not contain a hormone response element by positive or negative interference with the activity of other transcription factors or signaling pathways, a mechanism referred to as transcriptional crosstalk [5]. In this case, the receptors do not bind directly to the DNA recognition motifs for those transcription factors, but can be tethered to these elements of the target promoter via protein-to-protein interactions. Thus, we have shown that TRs can antagonize AP-1 [8,9], cyclic AMP (cAMP) response element-binding protein (CREB) [10,11], or NF-κB-mediated transcription [12,13] without binding to these motifs. Functional crosstalk between nuclear receptors and these transcription factors has been reported for various classes of receptors [14] and has been shown to be crucial for regulation of many cellular functions [15,16]. Fig. 1 illustrates the main aspects of thyroid hormone actions on cells.

2. Role of thyroid hormones and thyroid hormones' receptors in tissue homeostasis

2.1. Gastrointestinal tract

2.1.1. Liver

In several organs of the gastrointestinal tract including liver, intestine and pancreas, the THs stimulate cell proliferation. The TH has been long recognized as a potent hepatomitogen that can cause liver hyperplasia [17]. Liver expresses both TRα and TRβ. In adult liver TRβ is the predominant form, and gene profiling of livers from TRβ KO mice identified a large number of differentially regulated genes, revealing a clear predominance of TRβ over TRα in adult liver function [18,19]. However, TRα is predominant in the hepatocyte precursor, the stellate cells, and this isoform could play a critical role in hepatocyte maturation during the perinatal period [20].

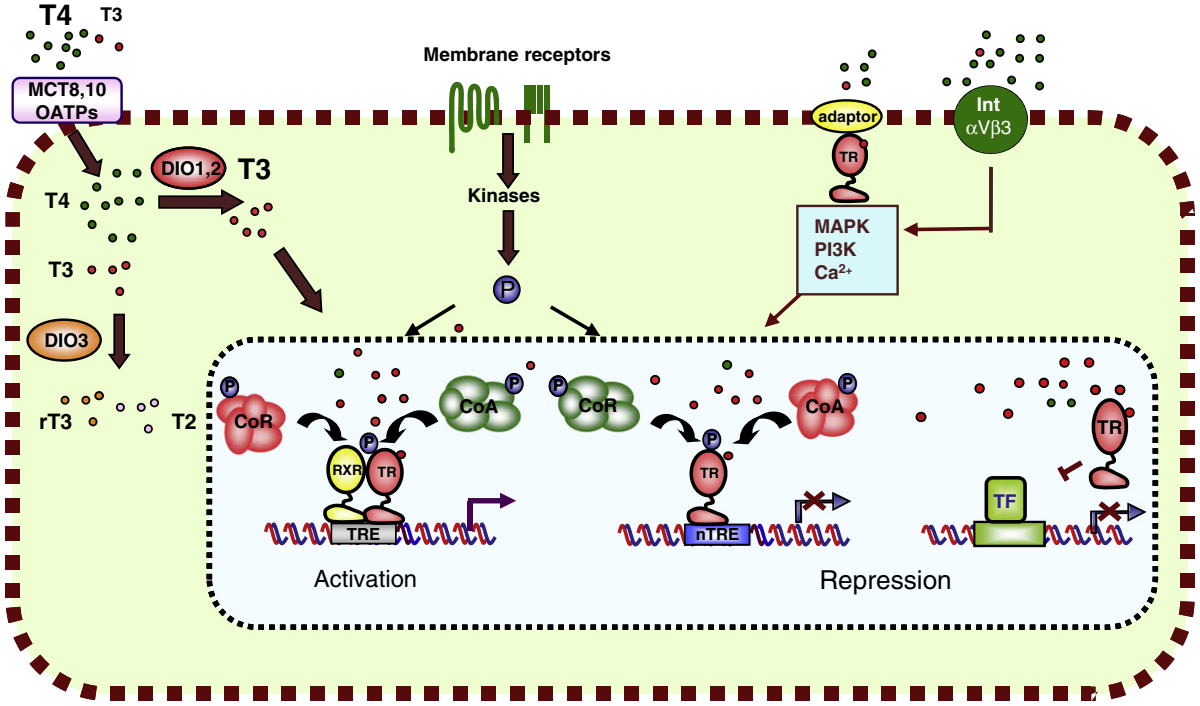

Fig. 1. Mechanism of action of the thyroid hormone receptors. Thyroxine (T4) and triiodothyronine (T3) enter the cell through transporter proteins such as MCT8 and 10 or OATPs. Inside the cells, deiodinases (DIO1,2) convert T4, the major form of thyroid hormone in the blood, to the more active form T3. DIO3 produces rT3 and T2 from T4 and T3, respectively. T3 binds to nuclear thyroid hormone receptors (TRs) that activate transcription by binding, generally as heterodimers with the retinoid X receptor (RXR), to thyroid hormone response elements (TREs) located in regulatory regions of target genes. Activity is regulated by an exchange of corepressor (CoR) and coactivator (CoA) complexes. Negative TREs (nTRE) can mediate ligand-dependent transcriptional repression, although in this case the role of coactivators and corepressors is not well defined. TRs can also regulate the activity of genes that do not contain a TRE through "cross-talk" with other transcription factors (TF) that stimulate target gene expression. Both receptors and coregulators are targets for phosphorylation (P) by signal transduction pathways stimulated by hormones and growth factors. Binding of T3 to a subpopulation of receptors located outside the nuclei can also cause rapid "non-genomic" effects through interaction with adaptor proteins, leading to stimulation of signaling pathways. T4 can also bind to putative membrane receptors such as integrin αVβ3 inducing mitogen activated protein kinase (MAPK) activity.

Please cite this article as: A. Pascual, A. Aranda, Thyroid hormone receptors, cell growth and differentiation, Biochim. Biophys. Acta (2012), doi:10.1016/j.bbagen.2012.03.012

Download English Version:

https://daneshyari.com/en/article/10800604

Download Persian Version:

https://daneshyari.com/article/10800604

Daneshyari.com