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's action on progenitor/stem cell biology: New challenge for a classic hormone? ☆

Maria Sirakov [b], Seham Skah [a], Julien Nadjar [a], Michelina Plateroti [a,*]

[a] Centre de Génétique et de Physiologie Moléculaire et Cellulaire, Université Claude Bernard Lyon 1, France
[b] Institut de Biologie et de Médecine Moléculaires, Université Libre de Bruxelles, Belgium

ARTICLE INFO

Article history:
Received 31 March 2012
Received in revised form 1 July 2012
Accepted 29 July 2012
Available online xxxx

Keywords:
Intestine
Retina
Thyroid hormone
Thyroid hormone receptor TR
Stem cells

ABSTRACT

Background: Thyroid hormones are involved in developmental and homeostatic processes in several tissues. Their action results in different outcomes depending on the developmental stage, tissue and/or cellular context. Interestingly, their pleiotropic roles are conserved across vertebrates. It is largely documented that thyroid hormones act via nuclear receptors, the TRs, which are transcription factors and whose activity can be modulated by the local availability of the hormone T3. In the "classical view", the T3-induced physiological response depends on the expression of specific TR isoforms and the iodothyronine deiodinase selenoenzymes that control the local level of T3, thus TR activity.
Scope of the Review: Recent data have clearly established that the functionality of TRs is coordinated and integrated with other signaling pathways, specifically at the level of stem/progenitor cell populations. Here, we summarize these data and propose a new and intriguing role for thyroid hormones in two selected examples.
Major Conclusions: In the intestinal epithelium and the retina, TRα1 and TRβ2 are expressed at the level of the precursors where they induce cell proliferation and differentiation, respectively. Moreover, these different functions result from the integration of the hormone signal with other intrinsic pathways, which play a fundamental role in progenitor/stem cell physiology.
General Significance: Taken together, the interaction of TRs with other signaling pathways, specifically in stem/progenitor cells, is a new concept that may have biological relevance in therapeutic approaches aimed to target stem cells such as tissue engineering and cancer. This article is part of a Special Issue entitled Thyroid hormone signaling.

1. Introduction

1.1. General aspects and function

Thyroid hormones (THs) regulate cellular metabolic activity as well as cell proliferation, apoptosis, and differentiation. Their "pleiotropic nature" has been evident since their characterization at the beginning of the 20th century as major players during amphibian metamorphosis. Three types of changes take place during this process: complete involution of some organs, remodeling of other organs, and *de novo* development of new organs. At the cellular level, these changes are caused by a combination of apoptosis and cell proliferation, and the entire process is strictly controlled by THs [1].

The synthesis of THs is regulated through the hypothalamus–pituitary–thyroid axis [2,3]. The follicular cells of the thyroid gland synthesize and secrete L-thyroxine (T4) and 3, 3′, 5-L-triiodothyronine (T3). This process is under the control of circulating TH levels through negative feedback loops of this axis [2,3]. In most vertebrates, the predominant hormone produced by the thyroid gland is T4, and this hormone is transported by blood to peripheral organs. Although T3 and T4 can act via non-genomic mechanisms [4], T3 is considered the active form of TH because it can bind to the thyroid hormone nuclear receptor TRs. The TRs, TRα and TRβ, are transcription factors encoded by the THRA and THRB genes that, in humans, are located on chromosomes 17 and 3, respectively. Alternative splicing and the use of different promoters result in the synthesis of a number of receptor isoforms including TRα1, TRβ1 and TRβ2 [4,5]. These isoforms show a specific pattern of expression in different tissues [6,7]. In addition to their expression level, TR activity in a given tissue is correlated with local T3 availability, which depends on the presence of specific deiodinase selenoenzymes. These enzymes are able to locally modify the T3 and T4 hormones [8–10]. Specifically, deiodinase 2 (Dio2) converts the T4 to the active form T3 through the removal of an iodine atom. On the contrary, deiodinase 3 (Dio3) removes an iodine atom converting T4 and T3

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

* Corresponding author at: Centre de Génétique et de Physiologie Moléculaire et Cellulaire, Université Lyon 1. 16 Rue Raphael Dubois, 69622 Villeurbanne, France. Tel.: +33 472431595; fax: +33 4 72432685.
E-mail address: michelina.plateroti@univ-lyon1.fr (M. Plateroti).

0304-4165/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbagen.2012.07.014

into the inactive reverse triiodothyronine (rT3) or diiodothyronine (T2), respectively. These inactive products do not bind TRs. Finally, deiodinase 1 (Dio1) can have both activating and inactivating activities.

From a molecular point of view, TRs can act as both transcriptional activators and repressors [11]. They heterodimerize with retinoid X receptors (RXRs) and bind to thyroid hormone response elements (TREs) that are located within the regulatory regions of target genes. In the absence of T3, TRs can interact with co-repressor proteins to inhibit positively regulated target genes. In the classical model, co-repressors are displaced after T3 binding to the receptor, and co-activator proteins are recruited to the ligand-bound TR complex, allowing T3-dependent activation of target genes [5]. Other mechanisms of TR action have been described. For example, both TRβ1 and TRα1 can interact with β-catenin [12,13], the intracellular mediator of the Wnt pathway [14], to form a complex in thyrocytes and in the intestinal epithelium, respectively. Interestingly, the action of TH *via* TRs on the Wnt pathway results in opposite outcomes: TRα1 activates and TRβ1 blocks the Wnt pathway [12,13]. It remains unclear whether this opposite effect is due to the intrinsically different properties of TRα and TRβ or is due to the different cellular context in which their interaction with β-catenin occurs.

Thus, the overall biological effect of THs in a given tissue depends on a number of factors: the amount of bioavailable hormone [8,9], the levels of different TR isoforms expressed [15], their post-transcriptional modifications [16,17], the heterodimerization partner retinoid X receptors (RXRs) [18,19], the interaction with co-repressors and co-activators [5,20–24], and the structure of TREs [11]. Finally, some genes, including thyroid-stimulating hormone (TSH), are inhibited by T3-liganded TR; however, the mechanism of the transcriptional repression by TRs is still poorly defined [25].

2. Tissue-resident adult stem cells: Focus on the intestine and retina

The maintenance and repair of adult tissues relies on small populations of resident stem cells [26]. Stem cells are defined by two fundamental properties. First, they have the ability to self-renew such that every time they divide, they give rise to a cell with an identical stem cell program. Second, they are multipotent because they have the ability to generate all the types of differentiated cells in the tissue [26]. Only a few stem cells within a tissue are necessary to maintain homeostasis under physiological conditions [27–29]. Generally speaking, the stem cells are mostly dormant, have a low metabolic rate, have low growth factor requirement and live a long life. Stem cells rarely enter the cell cycle, but when they do in response to cellular loss or damage, they exhibit a tremendous potential to regenerate the entire tissue [26]. These properties represent a protective mechanism against the accumulation of mutations that can possibly occur during cell divisions [30,31]. Furthermore, the stem cells possess an arsenal of defense mechanisms against chemical and toxic insults and a strong response system against DNA damage compared to their early progeny [30,31]. Finally, stem cells live in a defined environment called the "stem cell niche", which is composed of other cells and of a specific molecular environment. The niche is an absolute requirement for stem cell physiology [32].

From here on, we will use the term "stem cell" to refer to potential or established self-renewing, multipotent cells. The term "progenitor" will be used to designate their "more engaged" progeny. Finally, "precursor cell" will be used as a generic term to encompass both stem and progenitor cells.

An increasing body of literature suggests that THs and TRs participate in somatic stem/progenitor cell physiology. Indeed, observations indicate that the TH signal can be received and integrated within the stem/progenitor cell environment where it may play a primary role [33–36].

Here, we decided to focus on two examples of the activity of TH on stem/progenitor cells. First, the somatic stem cells of the intestinal epithelium that are now well characterized, as it is their functional niche across the vertebrates [28,37]. On the contrary, retinal stem cells and their niche are still poorly defined in mammals; however, in lower vertebrates, a clear niche has been characterized, but bona fide stem cell markers have not yet been described [38]. Nevertheless, in both examples, the function of TH and TRs in precursor's cells is well established along with that of key signaling pathways. As second step, we discuss data functionally linking TH in particular to the Wnt pathway and to stem/progenitor cell physiology in the intestine. We will extend these concepts to the retina, in which TH predominantly regulate progenitor's cell fate.

2.1. The intestinal epithelium stem cells

The mammalian intestinal epithelium is segregated into two functionally distinct compartments: the proliferative compartment, the crypts of Lieberkun, and the differentiated compartment, the villi (small intestine) or the flat epithelial surface (the colon) [39]. The intestinal epithelium is known to be a highly dynamic tissue with a rapid and perpetual renewal every 3–5 days in the mouse. The whole process includes continuous proliferation, migration, differentiation and apoptosis along the crypt–villus or crypt–surface axis [39]. Such remarkable renewal is fueled by the somatic intestinal stem cells (ISCs) located at the bottom of the crypts [28], which are cells of primary importance within the epithelium.

The adult ISCs are multipotent cells characterized by a very long self-renewal capability, and they give rise to highly proliferating progenitors called transit-amplifying (TA) cells, which differentiate while migrating upward [39]. At the tip of the axis, the cells die by apoptosis and are exfoliated into the lumen. Altogether, these highly coordinated processes primarily depend on the activity of the stem cells. Recent advances have led to defining these stem cell characteristics, and we summarize these data. The current view of the intestinal crypt cell hierarchy is illustrated in Fig. 1.

The study of ISCs started in the 1970s and remains an active field of research. In fact, the identification of specific markers had a late start, and their characterization has only recently begun. The early unitarian theory, proposed by Cheng and Leblond in 1974, states that all epithelial cell lineages of the intestine are monoclonal populations derived from a single stem cell [40]. They defined the crypt base columnar (CBC) cells as ISCs based on morphological criteria and because of their position at the bottom of the crypts between the Paneth cells. Moreover, labeling retention experiments with [3H]-thymidine and a concomitant pulse of bromodeoxyuridine showed that ISCs are almost quiescent (steady state) and that they are located just above the Paneth cells at the +4 position, counting from the crypt base [41]. This result was in agreement with the concept of "dormant" somatic stem cells.

This model was further supported by another approach showing that the +4 crypt cells appear to be extremely sensitive to radiation, which is considered to be a protective mechanism that prevents stem cells from accumulating and propagating DNA damage to their progeny [42]. However, this study did not describe or reveal the multipotency of the +4 cells. In 1999, Bjerknes and Cheng reported for the first time the presence of ISCs that are capable of generating all the intestinal cytotypes [43]. Indeed, chemical mutagenesis was used to genetically and randomly mark the intestinal epithelial cells by somatic mutation. If the mutation is acquired by ICSs, their progeny will inherit it. Then, by following the inheritance pattern of specific mutations, they demonstrated that the intestinal crypts contain a population of somatic multipotent stem cells that are located between the +1 and +4 positions from the bottom of the crypts [43].

Further characterization of ISCs required the definition of markers to enable the isolation of homogeneous populations for detailed characterization. The identification of markers led to important advances

Please cite this article as: M. Sirakov, et al., Thyroid hormone's action on progenitor/stem cell biology: New challenge for a classic hormone? Biochim. Biophys. Acta (2012), http://dx.doi.org/10.1016/j.bbagen.2012.07.014