Cancer Letters 419 (2018) 175–186

Contents lists available at ScienceDirect

Cancer Letters

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

Mini-review

Thyroid hormone in the regulation of hepatocellular carcinoma and its microenvironment

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ARTICLE INFO

Article history:
Received 9 November 2017
Received in revised form
14 January 2018
Accepted 18 January 2018

Keywords:
Thyroid hormone
Liver cancer
Tumor microenvironment
Liver fibrogenesis

ABSTRACT

Hepatocellular carcinoma (HCC) commonly arises from a liver damaged by extensive inflammation and fibrosis. Various factors including cytokines, morphogens, and growth factors are involved in the crosstalk between HCC cells and the stromal microenvironment. Increasing our understanding of how stromal components interact with HCC and the signaling pathways involved could help identify new therapeutic and/or chemopreventive targets. It has become increasingly clear that the cross-talk between tumor cells and host stroma plays a key role in modulating tumor growth. Emerging reports suggest a relationship between HCC and thyroid hormone signaling (dysfunction), raising the possibility that perturbed thyroid hormone (TH) regulation influences the cancer microenvironment and cancer phenotype. This review provides an overview of the role of thyroid hormone and its related pathways in HCC and, specifically, its role in regulating the tumor microenvironment.

1. Introduction

Liver cancer is the sixth most common cancer worldwide, with more than 782,500 new cases diagnosed in 2012 [1]. Although the incidence of hepatocellular carcinoma (HCC), the primary form of liver cancer, varies according to gender, etiology, age, and geographic region, it typically develops in a microenvironment that is characterized by pro-inflammatory, pro-angiogenic, and pro-fibrotic milieus. Liver fibrosis is a repair response to chronic injury that is recognized as the underlying pathogenic driver of carcinogenesis. Therefore, factors stimulating liver fibrosis may be potential therapeutic targets to limit tumor progression.

Several reports suggest that extrahepatic factors are key regulators of liver repair [2–5]. Dysregulation of thyroid hormone (TH) homeostasis and downstream signaling pathways have been shown to influence liver fibrogenesis, and accumulating data suggest that aberrant expression or mutations of the thyroid hormone receptor (TR) are associated with the development of human neoplasia. However, the association between TH and cancer remains controversial, with some investigators reporting that

Abbreviations: ALT, alanine amino transferase; BBC, basal cell carcinoma; CCL4, carbontetrachloride; CD, choline-deficient; CDK2, cyclin-dependent kinase; CSC, cancer stem cell; DKK, dickkopf Wnt signaling inhibitor 4; DEN, diethylnitrosamine; DIO1-3, iodothyronine deiodinases; ECM, extracellular matrix; GSTP, glutathione S-transferase-positive; HCC, hepatocellular carcinoma; HFD, high-fat diet; HSC, hepatic stellate cells; LPR5/6, low-density lipoprotein receptor-related protein; MF, myofibroblasts; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NCoR, nuclear receptor corepressor; PKA, protein kinase A; SMRT, silencing mediator for retinoid or thyroid-hormone receptors; RXR, retinoid X receptor; SBE, smad binding element; SRC, steroid receptor coactivator; Shh, sonic hedgehog; SMAD, mothers against decapentaplegic; STMN1, stathmin; rT3, reverse T3; T3, triiodothyronine; T4, thyroxine; TGF-β, transforming growth factor beta; TH, thyroid hormone; TR, thyroid hormone receptor; TRE, thyroid hormone response element.

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https://doi.org/10.1016/j.canlet.2018.01.055
0304-3835/

hyperthyroidism promotes either cancer development or progression [6–8], whereas others have reported a tumor suppressive role of TH [9].

The mitogenic effects of triiodothyronine (T3) have been extensively studied *in vivo* [10–13]. However, the effectiveness on normal hepatocytes *in vitro* has not been definitively established. As this criterion has not been met, it remains controversial whether T3 should be considered as a direct mitogen in the liver [10,14]. Nonetheless, T3 is well known for ameliorating liver regeneration after partial hepatectomy in rodent models [15–19]. In accordance with these findings, TH can be an important determinant of the regeneration process.

In contrast, T3 seems to have different effects on liver cancer cell growth as it inhibits liver cancer cell growth *in vitro* [20,21]. Moreover, clinical findings support the hypothesis of a procarcinogenic effect of hypothyroidism, as case-control studies demonstrated an independent positive association between hypothyroidism and HCC development [22,23].

Recent studies show that the tumor microenvironment plays an important role in regulating tumor growth and shaping tumor response to therapy (reviewed in Ref. [24]). The liver tumor microenvironment consists of multiple cell types and the extracellular matrix (ECM). Activated hepatic stellate cells (HSC) or myofibroblasts (MF) are the major cell types responsible for the secretion of collagen, laminin, and elastin that constitute the ECM. Other stromal cell types include bone marrow-derived fibrocytes, resident portal fibroblasts, liver progenitor cells, as well as resident and recruited immune cells which secrete cytokines and chemokines that modulate inflammatory and fibrogenic responses [25,26].

In this review, we will discuss the potential impact of TH on liver cancer biology and its effects on the tumor microenvironment. We will attempt to reconcile the apparent discrepant reports of TH-induced effects on cancer cells and will discuss how TH and related pathways modulate cancer cell proliferation, invasion, and metastasis.

2. Molecular basis of TH action

T3 and L-thyroxine, T4 are the two major thyroid hormones being critical for tissue and organ development, cellular growth, differentiation and (lipid-)metabolism [27]. The primary circulating thyroid hormone, T4 (the prohormone), is deiodinated within cells by iodothyronine deiodinases type I and type II (Dio1, Dio2) to become biologically active T3. In contrast, deiodinase type III (Dio3) reduces intracellular thyroid activity by degrading T4 and T2 into the "inactive" metabolites reverse T3 (rT3) and T2, respectively [28].

On entering the nucleus, the gene-regulating activity of T3 is mediated by binding to specific DNA sequences, known as thyroid hormone response elements (TREs), located on the promoter regions of thyroid hormone target genes (Fig. 1). The two major thyroid receptor isoforms, thyroid hormone receptor α and β (TRα and TRβ), have tissue-specific distribution. While TRβ mediates the metabolic actions of T3 and is the known major receptor isoform expressed in the liver (hepatocytes), TRα is expressed predominantly in the heart, skeletal muscle, and adipose tissues, and specifically mediates adaptive thermogenesis. Transporter molecules such as MCT8 or OATP1 transport T4 and T3 into the cell. Unbound TR may heterodimerize with retinoid X receptor (RXR), which then binds to a TRE and to a corepressor complex. These corepressors include nuclear receptor co-receptor 1 (NCoR1) and silencing mediator for retinoid or thyroid-hormone receptors (SMRT), which may act to repress positively regulated genes and activate negatively regulated genes [27] (Fig. 1). T3-binding to the ligand-binding domain results in the movement of the carboxy-terminal helix 12, disruption of corepressor binding, and promotion of coactivator binding (among others, these include: steroid receptor coactivator 1 (SRC1), SRC2, and p300/CBP) which then leads to recruitment of polymerase III and initiation of positively regulated gene transcription [28].

3. Linking thyroid hormone and its receptors to chronic liver disease

TH is a major regulator of lipid metabolism [29–32]. By binding the cognate TRs, TH regulates cholesterol and carbohydrate metabolism through direct actions on gene expression. TH also modulates hepatic insulin sensitivity, which is important for the suppression of hepatic gluconeogenesis **(reviewed in** Ref. [27]).

Among individuals with non-alcoholic fatty liver disease

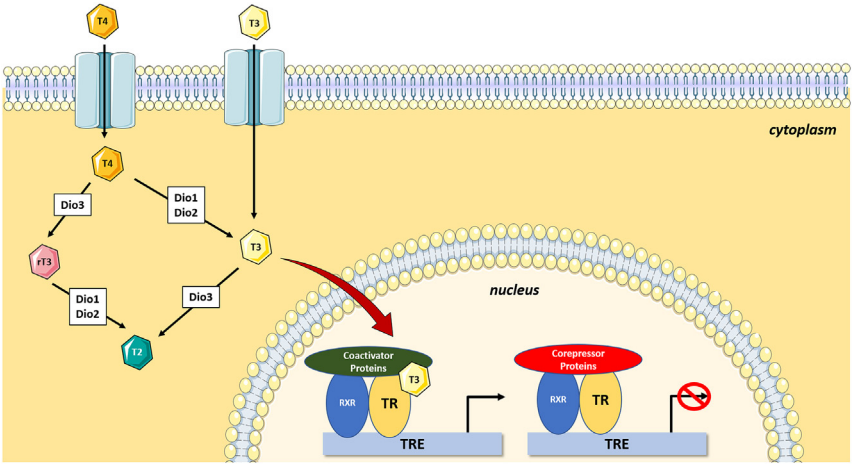

Fig. 1. Nuclear action of Thyroid Hormone. Thyroid hormone (TH) and TH-signaling are critical for tissue and organ development, growth, differentiation, and metabolism (including lipid and cholesterol handling). The main circulating thyroid hormone T4 (the prohormone) is deiodinated within cells by deiodinases (DIO1, 2) to become the biologically-active T3. Deiodination can also lead to biologically inactive forms like T2 or rT3. On entering the nucleus, T3 binds to nuclear thyroid hormone receptors (TRs), which are transcription factors and usually form a heterodimer with the retinoid X Receptor (RXR). Those are bound to positive or negative thyroid hormone response elements (TREs) located in the regulatory region of target genes. In the unliganded state, TRs interact with one of the several corepressor proteins, while during the liganded state, a coactivator complex is present.