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Review

Thyroid hormone receptors and cancer ☆

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ABSTRACT

Background: Thyroid hormone receptors (TRs) are ligand-dependent transcription factors that mediate the actions of the thyroid hormone (T3) in development, growth, and differentiation. The *THRA* and *THRB* genes encode several TR isoforms that express in a tissue- and development-dependent manner. In the past decades, a significant advance has been made in the understanding of TR actions in maintaining normal cellular functions. However, the roles of TRs in human cancer are less well understood. The reduced expression of TRs because of hypermethylation, or deletion of TR genes found in human cancers suggests that TRs could function as tumor suppressors. A close association of somatic mutations of TRs with human cancers further supports the notion that the loss of normal functions of TR could lead to uncontrolled growth and loss of cell differentiation.

Scope of review: In line with the findings from association studies in human cancers, mice deficient in total functional TRs (*Thra1*$^{-/-}$*Thrb*$^{-/-}$ mice) or with a targeted homozygous mutation of the *Thrb* gene (denoted PV; *Thrb*$^{PV/PV}$ mice) spontaneously develop metastatic thyroid carcinoma. This review will examine the evidence learned from these genetically engineered mice that provided strong evidence to support the critical role of TRs in human cancer.

Major conclusions: Loss of normal functions of TR by deletion or by mutations could contribute to cancer development, progression and metastasis.

General significance: Novel mechanistic insights are revealed in how aberrant TR activities lead to carcinogenesis. Mouse models of thyroid cancer provide opportunities to identify molecular targets as potential treatment modalities. This article is part of a Special Issue entitled Thyroid hormone signalling.

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1. Introduction

Molecular cloning of thyroid hormone receptor (TR) cDNA in 1986 ushered in an exciting era in the understanding of the structure, expression, functions, and transcription regulation of TRs [1,2]. Two human TR genes, *THRA* and *THRB*, located on different chromosomes, encode thyroid hormone (T3) binding TR isoforms (TRα1, β1, β2, and β3). Similar to other members of the nuclear receptor superfamily, these TR isoforms have an amino-terminal A/B domain, a central DNA-binding domain, and a carboxyl-terminal ligand-binding domain. These TR isoforms share extensive sequence homology in the DNA and ligand-binding domains, but differ in the length and amino acid sequence at the amino terminal A/B domain. Comparison of X-ray crystallographic structures of rat TRα and human TRβ ligand binding domains shows a close structural similarity [3,4]. However, there are subtype-dependent differences in the ligand-binding pocket that allow selective recognition of certain ligands [4].

The transcriptional activity of TRs is regulated by multiple mechanisms including the type of thyroid hormone response elements (TREs) located on the promoters of T3 target genes, the tissue- and development-dependent expression of TR isoforms, and a host of nuclear co-repressors and co-activators [5]. In the absence of T3, TRs recruit corepressor proteins, such as nuclear receptor co-repressor 1 (NCOR1) and silencing mediator of retinoid and thyroid hormone receptors (SMRT), and repress the transcription of target genes. In the presence of T3, TRs undergo a conformational change that results in the exchange of co-repressors for co-activators, such as p160/ steroid receptor co-activator-1 (SRC-1) family, to activate transcription of target genes. In addition to transcriptional stimulation, TRs also

Abbreviations: BM, basement membrane; ECM, extracellular membrane; EMT, epithelial mesenchymal transition; FAK, focal adhesion kinase; MAPK, mitogen-activated protein kinase; LOH, loss of heterozygosity; NCOR1, nuclear receptor co-repressor 1; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; PAX8, paired box gene 8; PIP2, phosphatidylinositol-4,5-biphosphate; PIP3, phosphatidylinositol-3,4,5-triphosphate; PI3K, phosphatidylinositol 3-kinase; PPARγ, peroxisome proliferator-activated receptor γ; PPRE, peroxisome proliferator responsive element; PPTG, pituitary tumor-transforming gene; PTEN, phosphatase and tensin homologue deleted from chromosome 10; RTH, resistance to thyroid hormone; RXRα, retinoid X receptor α; SH, Src homology; SKY, spectral karyotyping analysis; SMRT, silencing mediator of retinoid and thyroid hormone receptors; SRC, steroid receptor co-activator; TREs, thyroid hormone response elements; TRs, thyroid hormone nuclear receptors; T3, triiodothyronine; TSH, thyroid stimulating hormone

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repress gene expression in a T3-dependent manner by binding to negative TREs [5]. However, recent advances have expanded this T3-dependent corepressor–coactivator exchange model and shown that NCOR1 and SMRT play a role in determining T3-sensitivity in vivo, suggesting that corepressors can be recruited to TR in the presence of T3 [6–8].

In spite of significant progress in understanding the molecular mechanisms by which TR functions in maintaining normal physiological T3-mediated homeostasis, the roles of TR in human cancers are less well understood. Early evidence to suggest that mutated TR could be involved in carcinogenesis came from the discovery that TRα1 is the cellular counterpart of the retroviral v-ERBA involved in

Table 1
Somatic mutations of thyroid hormone receptor genes in human cancers.

Type of cancer	Gene	Mutation	Impaired activity			Dominant negative activity	Reference
			T3 binding	DNA binding	Transcription		
Hepatocellular carcinoma	*THRB*	234G insertion	ND	ND	ND	ND	[22]
		D211N	No	No	ND	ND	
		R153L	No	No	ND	ND	
		R194G	ND	ND	ND	ND	
		M27I, C102R, T363N	Yes	Yes	ND	ND	
		K258E	No	No	ND	ND	
		S38L, C441R	ND	ND	ND	ND	
		M308I	Yes	No	ND	ND	
		H400Y, F434N	Yes	No	ND	ND	
		K108N, T324P	Yes	No	ND	ND	
		S38P, I54T, P273S, P273L, E306G	Yes	No	ND	ND	
		K23E, I187V	Yes	Yes	ND	ND	
	THRA	A225G, T227N	ND	ND	ND	ND	
		A225G, D246N, G350K	Yes	No	ND	ND	
		S40T, K136R, L251P, V390A	Yes	No	ND	ND	
		K74E, A264V	Yes	Yes	ND	ND	
		K74R, M150T, E159K	Yes	No	ND	ND	
		N179I	ND	ND	ND	ND	
		S38Q, Q108K, F112L, I299V	Yes	Yes	ND	ND	
		C110Y, C254A	Yes	Yes	ND	ND	
		G24E, M256V, E343A, P269L	Yes	No	ND	ND	
Renal cell carcinoma	*THRB*	S99R, W129L, F451I	Yes	No	ND	Yes	[24]
		Y321H	Yes	No	ND	No	
		F451S	Yes	No	ND	No	
		Q252R, A387P, F417L	Yes	No	ND	No	
		K155E, K411E	No	Yes	ND	No	
		Δ1–26, S380F	Yes	No	ND	No	
		E299K, H412R, L456S	Yes	No	ND	No	
	THRA	S183N, H184Q, R228H, K288E	Yes	Yes	ND	No	
		I116N, M388I	Yes	Yes	ND	No	
		I116N, A225T, M388I	Yes	Yes	ND	No	
Breast cancer	*THRB*	Deletion (123–242)	ND	ND	ND	ND	[25]
		Deletion (319–366)	ND	ND	ND	ND	
		Truncated at 167	ND	ND	ND	ND	
		Deletion (166–402)	ND	ND	ND	ND	
		Deletion (181–382)	ND	ND	ND	ND	
Pituitary tumor	*THRB*	R438H	Yes	No	ND	ND	[26,27]
		H450Y	Yes	No	ND	ND	
Thyroid cancer	*THRB*	V109A, I431T	ND	ND	Yes	Yes	[28]
		R185K, T273A, L456S	ND	ND	Yes	Yes	
		M32V	ND	ND	No	No	
		E34G, P141L	ND	ND	Yes	Yes	
		A318D, F451I	ND	ND	Yes	Yes	
		N76D, S81L, I135V, Q136H, R201X	ND	ND	Yes	Yes	
		F403L, C446R	ND	ND	Yes	Yes	
		K91R, K289M	ND	ND	Yes	Yes	
		Q235X, M379T, D427G	ND	ND	Yes	Yes	
		K411E	ND	ND	Yes	Yes	
		Q205L	ND	ND	Yes	Yes	
		K103R	ND	ND	Yes	Yes	
		M32T, L373P	ND	ND	Yes	Yes	
		K411E, H435R	ND	ND	Yes	No	
		S99R	ND	ND	Yes	Yes	
	THRA	T80I, L109P	ND	ND	Yes	Yes	
		E213D	ND	ND	Yes	Yes	
		S305P, K337R	ND	ND	Yes	Yes	
		G57E	ND	ND	Yes	Yes	
		K29T, C97X	ND	ND	Yes	No	
		Y352C	ND	ND	Yes	Yes	
		S183N, H184Q, Q187X, R228H, E245V, K288E	ND	ND	Yes	Yes	
		S183N, H184Q, R228H, M369V	ND	ND	Yes	Yes	
		S183N, H184Q, R228H	ND	ND	Yes	Yes	
		S271I	ND	ND	Yes	Yes	

ND. Not determined.