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MOLECULAR BASIS OF THYROID HORMONE ACTION

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INTRODUCTION

3,3',5-triiodothyronine (T3), the active thyroid hormone (TH) metabolite of thyroxine (T4), affects the differentiation, growth, and cellular metabolism of virtually all tissues (1-3). TH exerts its major effects at the genomic level, although it also may have activities at nongenomic sites such as the plasma membrane, cytoplasm, and mitochondrion. A general schema for TH effects on gene transcription is shown in Fig. 1.

Figure 1. General model for genomic effects of thyroid hormone in the cell.
Circulating free TH enters the cell by either passive diffusion or other poorly understood transport mechanisms. Additionally, the more biologically active form of TH, T3, may be converted from circulating serum T4 in some tissues by iodothyronine 5'-deiodinases. TH then enters the nucleus where it binds to nuclear thyroid hormone receptors (TRs) with high affinity and specificity (Kds in the nanomolar range). TRs are ligand-regulated transcription factors that are intimately associated with chromatin, and heterodimerize with another member of the nuclear receptor superfamily, retinoid X receptors (RXRs) and other co-factors involved in ligand-regulated transcription. These, in turn, are bound to target DNAs known as TH-response elements (TREs) which are commonly located in the promoter regions of target genes. Formation of liganded TR/DNA complexes leads to activation of positively-regulated target genes, and results in increases in mRNA and protein. TH also can negatively-regulate target genes. During the past 15 years, much progress has been made in understanding the molecular mechanisms involved in TH regulation of gene transcription, and highlights are summarized below.

**THYROID HORMONE RECEPTORS**

The TR isoforms, TRα and TRβ, were first identified and cloned in 1986 by the Vennstrom and Evans laboratories (4, 5). These landmark studies ushered in the molecular era for our understanding of TRs and TH action. TRs are the cellular homologs of v-erbA, a viral oncogene product involved in chick erythroblastosis. TRs also are members of the nuclear hormone receptor (NR) superfamily that include the steroid, vitamin D, retinoic acid, peroxisomal proliferator, and "orphan" (unknown ligand and/or DNA target) receptors (1, 6). TRs act as ligand-regulatable transcription factors that bind both TH as well as TREs located in the promoters of target genes. They have a central DNA-binding domain (DBD) that contains two “zinc finger” motifs and a carboxy-terminal ligand-binding domain (LBD) (Figure 2). The hinge region between these two domains contains a lysine-rich sequence that is important for nuclear localization of the receptor (1-3). Recent X-ray crystallographic studies of the liganded rat TRα-1 LBD show that TH is buried in a hydrophobic "pocket" lined by discontinuous stretches of amino acids with additional hydrophobic interfaces likely contributing to heterodimerization with TR’s heterodimer partner, RXR (7). The LBD is comprised of twelve amphipathic helices with specific helices providing the contact surfaces for protein-protein interactions with co-activators and co-repressors (helices 3,5,6,12 and 3,4,5,6, respectively) (2). Ligand-binding causes major conformational changes in the TR LBD, particularly in helix 12, that affect TR interaction with co-activators and co-repressors, respectively. Recently, it has been shown that TRs shuttle continuously between the cytoplasm and nucleus, and ligand-induces reorganization of