Always on the Move

A static model of thyroid hormone receptor function is revised.

Thyroid hormone (TH) is a primary endocrine regulator of human metabolism and homeostasis. Acting through three forms of its receptor (ThR), TH regulates target gene expression in nearly every cell in the body, modulating many fundamental processes. According to the decade's-old "bimodal switch model," ThRs bind stably to chromatin at cognate recognition elements and serve as a scaffold for supercomplexes of cofactors, which activate or repress transcription. In the absence of TH, these scaffolds attract repressive cofactors; upon activation by TH, repressive factors are displaced, new activating cofactors are recruited, and target genes are induced.

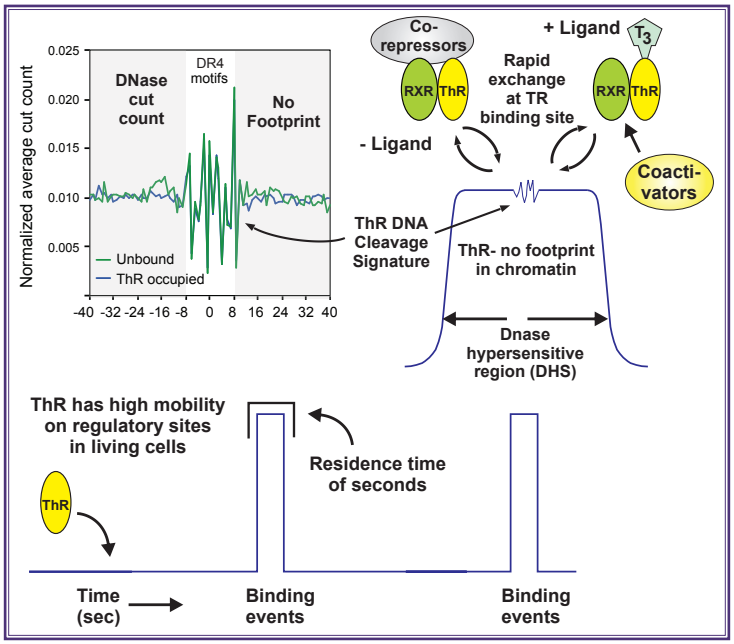
Researchers led by Sheue-yann Cheng, Ph.D., Senior Investigator in CCR's Laboratory of Molecular Biology, and Gordon Hager, Ph.D., Chief of CCR's Laboratory of Receptor Biology and Gene Expression, with assistance from Paul Meltzer, M.D., Ph.D., Chief of CCR's Genetics Branch, recently challenged this view of ThR action in the mouse liver. Their findings were published in *Nature Communications*.

Combining genome-wide ChIP-seq analysis for receptor binding with DNase-seq data to monitor open and closed chromatin states, the researchers observed many *de novo* genome-binding events for the receptor. That is, rather than existing as a stable, chromatin-bound repressive factor, the receptor often moved actively to thyroid response elements (TREs) in a hormone-dependent fashion. Furthermore, the receptor often created localized open chromatin structures at the binding sites.

The researchers also monitored the stability of bound ThR. A bound factor should protect its binding site within hypersensitive regions of the DNA from degradation by DNase, resulting in a predictable footprint. None of the ThR-binding sites, either activating or repressing, showed any evidence of a corresponding footprint. ThR-binding sites were universally marked by specific cleavage signatures, which correspond precisely to the ThR DNA–binding motifs. These signatures represent non-random cleavages due to primary DNA structure.

The combined results support an altered view of ThR function, in which, the receptor exchanges rapidly and continuously with response elements in chromatin. In the absence of a ligand, the receptor recruits corepressors to binding elements, but these complexes are not statically bound to chromatin. Upon activation by the hormone, the receptor recruits coactivators, thus inducing target genes, but the receptor continues to exchange rapidly with binding elements. For steroid receptors, this mode of action has recently been termed dynamic-assisted loading.

"The nuclear receptors as a class appear to behave as highly mobile factors with the ability to initiate the chromatin transitions necessary for cofactor recruitment and enhancer action," said Cheng. "The genomic action of the thyroid hormone now appears more in alignment with well-developed models for steroid receptor action and gives us a clearer understanding of the molecular mechanisms through which this important hormone operates."



(Figure: SY. Cheng and G. Hager, CCR)

Revised model of ThR function stresses dynamic interchange of factors on DNA.

To learn more about Dr. Cheng's research, please visit her CCR website at http://1.usa.gov/1PWpj0y.

To learn more about Dr. Hager's research, please visit his CCR website at http://1.usa.gov/1WjAEgc.