The Thyroid-Stimulating Hormone Receptor: Impact of Thyroid-Stimulating Hormone and Thyroid-Stimulating Hormone Receptor Antibodies on Multimerization, Cleavage, and Signaling

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KEYWORDS

• TSH receptor • Multimerization • Oligomerization
• Signaling • TSHR antibodies • Autoimmune thyroid disease

The thyroid-stimulating hormone receptor (TSHR) (**Fig. 1**) is a G-protein coupled receptor anchored to the surface of thyroid epithelial cells (or thyrocytes). The hormone TSH, synthesized by anterior pituitary thyrotrope cells, binds to the TSHR and regulates thyroid growth and development, as well as thyroid hormone synthesis and release.[1] The TSHR is also the major autoantigen in Graves' disease and is the target of antigen-specific T cells and autoantibodies that either stimulate the gland, leading to hyperthyroidism, or block endogenous TSH leading to hypothyroidism.[1] The transmission of these extracellular signals following the binding of TSH or

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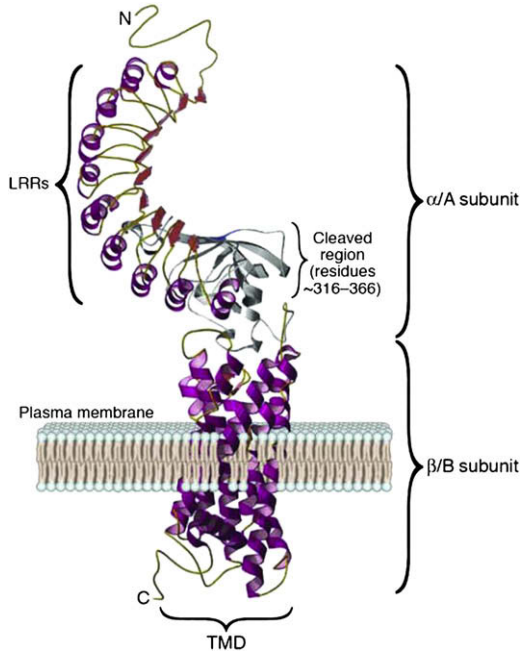

Fig. 1. Structure of TSH receptor. This model of the TSHR shows the seven transmembrane domains (TMDs) as spirals embedded within the lipid bilayer of the plasma membrane. The short cytoplasmic tail and the TMDs together make up the β/B subunit of the receptor. The unique 50aa long cleaved region (residues 316–366 aa) is as indicated. The nine leucine rich repeats (LRRs) each consisting of 20–24 aa, are depicted as spirals (α and β pleated sheets) on the ectodomain of the receptor and make up the major portion of the α/A subunit. The LRRs have a characteristic horseshoe shape with a concave inner surface. C, C- terminus; N, N-terminus. (*Adapted from* Davies TF, Ando T, Lin RY, Tomer Y, Latif R. Thyrotropin receptor-associated diseases: from adenomata to Graves disease. J Clin Invest 2005;115:1972–83; with permission.)

autoantibodies to the large extracellular domain of the TSHR is orchestrated via G proteins coupled to transmembrane loops of the TSHR in the inner leaflet of the plasma membrane resulting in activation of a myriad of signaling pathways. This, in turn, leads to proliferation and survival of the thyrocyte. Our understanding of this complex signaling and regulation has broadened in the past decade following better insights into TSHR structure-function and the dynamic changes of the TSHR on the cell surface. This article provides an update on the posttranslational changes in the TSHR, their impact on structure-function, and emphasizes the role of TSHR antibodies (TSHR-Abs) and the insights they have provided.

THE THYROID-STIMULATING HORMONE RECEPTOR IN DEVELOPMENT, HEALTH, AND DISEASE

The Thyroid-Stimulating Hormone Receptor in Thyroid Maturation

Since the cloning of the TSHR in 1989[2–4] the gross structure of the TSHR and its function in regulating thyroid cell signaling and proliferation have been exhaustively studied in both primary thyroid cells and TSHR transfected cell culture models. There are several comprehensive reviews on this topic.[5] Further, studies of the role of the TSHR in thyroid development and differentiation have revealed that TSH and the TSHR have pivotal roles in regulating the size and function of the thyroid gland but are not required for early thyroid