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Thyrotropin receptor, still much to be learned from the patients

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In the absence of crystal available for the full-length thyrotropin receptor, knowledge of its structure and functioning has benefitted from the identification and characterization of mutations in patients with various thyroid dysfunctions. The characterization of activating mutations has contributed to the elaboration of a model involving the extracellular domain of the receptor as an inverse tethered agonist which, upon binding of the ligand, relieves the transmembrane domain from an inhibiting interaction and activates it. The models derived from comparisons with other receptors, enriched with the information provided by the study of mutations, have proven useful for the design of small-molecule agonists and antagonists that may be used in the future to treat thyroid dysfunctions. In this review, extrathyroidal expression of the thyrotropin receptor is described, the role of which is still poorly defined.

The thyrotropin receptor (TSHR), a key actor in the regulation of the thyroid function [1], and is a member of G Protein-coupled receptor superfamily, also known as the seven transmembrane domain receptors. Together with the follitropin receptor (FSHR) and the luteinizing hormone receptor (LHR), it

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constitutes the subgroup of glycoprotein hormone receptors, owing to their related ligands and structure homologies. They all have large extracellular domains (ectodomain) linked to the transmembrane domain by a hinge region [1–5]. The ectodomain is the ligand binding domain as shown by swapping experiments, and the transmembrane or serpentine domain is the signal transduction domain, which couples to the downstream effectors, mainly the G-Proteins ([1,5–7]). The ectodomain is also the binding site of thyroid stimulating antibodies responsible for the hyperthyroidism in Graves' disease.

Structure of the TSHR

The ectodomain harbors several leucin-reach repeats, a feature that has helped to modelize its tridimensional structure based on other leucine-reach repeats, such as the porcine ribonuclease inhibitor. A horseshoe shape was proposed with parallel beta strands linked by alpha helixes, which delineate the binding surface for the ligand [8]. This model was later confirmed when a crystal of the ectodomain was obtained with a thyroid-stimulating antibody first [9], then a thyroid-blocking antibody [10] bound and, when the ectodomain of the follitropin receptor was crystallized, with FSH bound [11,12].

Because of the common structural features shared by the three related receptors, results and models obtained for one receptor can be used to refine and complete the model of the others [13,14]. However, TSHR differs from FSHR and LHR in the hinge region, which is longer in the TSHR. In addition, the TSHR hinge region is cleaved at the plasma membrane [15,16]. The N-terminally located ligand binding domain remains linked to c-terminal part of the hinge region by disulfide bridges. Some shedding of the ectodomain occurs, either through reduction of the disulfide bridges [17] or through further cleavage of the cysteines engaged in these bridges. The exact site of cleavage is still unknown as well as the protease(s) responsible for it. Several groups have endeavored to demonstrate that the cleavage and shedding do occur *in vivo* in thyroid cells, are not technical artefacts, and may have a physiological role. A large and precise review on this has recently been published [15]; however, the physiological role of this phenomenon, which relies on an evolutionary conserved structure exclusive to the thyrotropin receptor, if any, is unknown at present, except for an involvement in the appearance of autoimmunity [15].

The hinge region was later proven to be important for the activation of the receptor, according to data obtained from mutations found in patients and from targeted mutagenesis and modelization. This will be discussed later. In addition to the site of cleavage leading to shedding, the hinge region is also a site for glycosylation and more peculiarly for sulfatation of a conserved tyrosine. This has been shown to be important for activation by TSH, as well as for the FSHR and LHR and their respective ligands, although with some differences among receptors. Interestingly, the sulfatation was dispensible for the binding of thyroid stimulating antibodies [18,19]. Although this region is known to be important, current models or crystals of the ectodomain do not include it, possibly because the tridimensional configuration is less organized and dependent on interaction with both the leucine-reach repeats region and the transmembrane domain [7].

The transmembrane or serpentine domain was modelized owing to the growing number of GPCRs available and to the data obtained with activating or inactivating mutations found in patients with genetic hyperthyroidism or hypothyroidism, respectively. The global organization does not differ much from other GPCRs, with seven transmembrane helixes bound by three extracellular loops and three intracellular loops. As already stated, the expanding information drawn from the study of different GPCR, including an increase in the number of crystallized GPCRs, has helped to refine the models proposed for TSHR [7]. Nevertheless, some unusual features have led to the modification of the common models proposed for GPCRs. Although the serpentine domain of GPCRs is usually described as a bundle of seven alpha helixes, it is known that the prolines present in some of the domains introduce a disruption, a kink, in the structure of the corresponding helixes, with some secondary changes in the contacts and bonds between the different domains. The thyrotropin receptor misses one of these proline in the fifth transmembrane helix, which implies that the available models have to be adapted as it was confirmed by mutagenesis [20] and by crystals of other receptors also devoid of the corresponding proline [7].

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