

Thyroid Peroxidase Revisited – What’s New?

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ABSTRACT

Thyroid peroxidase (TPO) is an enzyme that participates in thyroid hormone biosynthesis. TPO is also a major autoantigen in autoimmune thyroid diseases (AITD). In this review, we summarize the latest developments in the field of TPO research. We present the current understanding of immunodominant serologic determinants, frequency of TPO-specific autoantibodies in the population, as well as genetic and environmental factors contributing to their development. Moreover, we report recent progress in the clinical utilities of TPO autoantibody testing, including thyroid dysfunctions and extra-thyroidal disorders.

Introduction

Autoimmune thyroid diseases (AITD) range from the hyperthyroidism of Graves’ disease (GD) to destructive Hashimoto’s thyroiditis (HT), which leads to hypothyroidism. Most patients with AITD are positive for autoantibodies directed against thyroid peroxidase (TPO) and usually also for thyroglobulin (Tg). Autoantibodies against TPO (TPOAbs) and TPO-specific T cells play important roles in the autoimmune destruction of thyrocytes [1–4]. TPO is also the key enzyme involved in the generation of thyroid hormones in the apical surface of thyroid epithelial cells [5, 6]. In this short commentary, we present an update on TPO, with latest findings reported over the past 5 years.

TPO gene and protein

Human thyroid peroxidase is encoded by *TPO* gene located on chromosome 2p25 and its expression is regulated by multiple factors [6]. Inactivating mutations in *TPO* gene lead to congenital hypothyroidism resulting from thyroid dysmorphogenesis [7–9]. *TPO* mRNA composed of 17 exons is most abundant in human thyrocytes and encodes the 933-amino acid TPO-1 protein. Due to alternative splicing, multiple transcripts without at least one exon are also generated [6]. TPO-1 is a dimeric glycoprotein with covalently linked heme, where the large N-terminal extracellular region (ectodomain) projects into the follicular lumen. The protein also has a short transmembrane domain and intracellular C-terminal region. The TPO ectodomain shows areas with homology to other proteins: myeloperoxidase (MPO-like domain; residues 142–738), complement control protein (CCP-like domain; residues 739–795), and

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epidermal growth factor (EGF-like domain; residues 796–846) [4, 6, 10]. Presently, the full tertiary structure of TPO remains unknown, however, high sequence identity to proteins of known structure has provided some insights into the three-dimensional organization of TPO by homology modeling approaches [11]. Recently, a model of full-length, membrane-bound dimeric TPO has been generated [4, 10]. Molecular models were used extensively to predict the structure of epitopes recognized by TPO-specific autoantibodies, but a complete understanding eagerly awaits high resolution structure determination.

Characteristics of TPOAbs

Almost all HT patients and nearly 75% of individuals with diagnosed GD have detectable TPOAbs [1]. These autoantibodies are also frequently present in euthyroid subjects, particularly women, even within the normal range for thyrotropin (TSH). TPOAbs level is one of the predictive factors for conversion from euthyroidism to thyroid dysfunction [12]. Recently published data on 10-year observation of TPOAbs variations in a population-based prospective study in Iran showed an increasing trend in TPOAbs levels over time accompanied by the rise in hypothyroidism incidence [13]. Another recent Dutch population-based prospective cohort study in the elderly (aged 85 and older) also confirmed an increased risk of subclinical and overt hypothyroidism in individuals with elevated TPOAbs [14]. Moreover, TPOAbs-positivity in oldest old community is associated with higher TSH level and a decreased 10-year mortality risk [14]. Legakis et al. have shown that in the first months of life, the variability of TPOAbs titers in neonates and infants is higher in boys than in girls [15]. The cut-off between TPOAb-positive and negative sera continue to be debated [16–18]. TPOAbs values may differ significantly between different immunoassays due to TPO antigen preparations (native or recombinant antigen purified preparations) used to coat solid phase ELISA plates [19]. TPOAbs in patient's sera are polyclonal and belong predominantly to the IgG class. They usually have high affinity for TPO and preferentially bind to conformationally intact protein [1]. Interestingly, a recently identified type of natural bispecific antibody against TPO and Tg may play a protective role in the pathogenesis of HT [20]. Extensive studies conducted by various groups on genetic loci associated with the presence of TPOAbs revealed their localization, for example, in the *HLA* region and inside or near genes encoding TPO, TSH receptor (TSHR), and Tg [21–27].

Epitope organization of TPO

Human TPOAbs recognize discontinuous determinants on TPO called immunodominant region A (IDR-A) and B (IDR-B) [1, 4, 6]. Numerous studies have restricted IDR-A and -B to MPO-like domain and to a lesser extent the CCP-like domain [10]. A number of contact residues that constitute IDR-A and IDR-B have been identified: 225, 353–363, 377–386, 597–604, 611–618, 620, 624, 627, 630, 646, 707, 713–720, and 766–775 [6, 28]. Spatial arrangement of epitopes in the context of oligomeric state, domain architecture and positioning in the membrane suggests that interaction of TPO with autoantibodies may require significant changes in the overall tertiary structure of the antigen [4, 10]. The distribution of IDR-A and -B-specific TPOAbs is similar in HT and GD patients, where the TPO epitope pattern is inherited in families and stable over time [6].

Role of TPO and TPOAbs in thyroid dysfunctions

A high incidence of TPOAbs in AITD patients' sera justified numerous attempts to understand their role in thyroid pathology. It is postulated that TPOAbs can damage thyrocytes by antibody-dependent cell cytotoxicity, activation of complement cascade, and cell damage [29]. TPOAbs-positivity has been recently found to be a main risk factor for developing oxidative stress in euthyroid individuals with HT [30]. On the other hand, dietary phenolic antioxidants can interact with TPO leading to its enzymatic activity inhibition [31]. The putative factors contributing to the breaking in the self-tolerance to TPO and other thyroid antigens have been summarized [2]. Since then, Liu et al. has reported that serum TPOAbs titers are negatively correlated with serum selenium concentrations in GD patients [32]. More recently, Wang et al. published results of a randomized, placebo-controlled study, in which selenium supplementation decreased TPOAbs titers in serum positive patients with autoimmune thyroiditis [33]. Individual patients exhibited different decreases in TPOAbs levels that may be associated with genetic background [33]. Animal model studies confirmed that low dietary selenium potentiates the development of TPOAbs and TgAbs in female mice; on the other hand, the authors did not observe any reduction in thyroid antibodies titers due to higher dietary selenium administration [34]. Numerous studies have also shown that the prevalence of TPOAb-positivity in individuals is correlated with increased dietary iodine intake [35–38].

Clinical utility of TPOAbs testing

As mentioned above, TPOAbs are a useful marker in AITD diagnosis (especially in hypothyroid patients), whereas in euthyroid patients TPOAbs positivity may increase the risk of future thyroid disorders [1, 39]. In recent years, new findings regarding the connection between TPOAbs and Graves' orbitopathy (GO) development in children have been revealed. Some studies did not find a significant correlation between them [40], whereas others show a positive association [41, 42]. In addition, studies on TPOAbs as risk factors of GO development in adult individuals with GD can provide conflicting data [43, 44]. Recently, much interest has been attracted to the role of thyroid autoimmunity in fertility [45–47]. TPOAb positivity, even in euthyroid women, may have a connection with subfertility and increased rates of pregnancy complications, including preterm delivery and miscarriage [48]. Therefore, the monitoring of TPOAbs indices is recommended for thyroid screening during pregnancy in the latest guidelines [49]. A recent prospective birth cohort study reported that TPOAbs-positivity during early pregnancy is associated with lower child IQ in Dutch, but not in the United Kingdom population [50]. Iodine status (lower in the latter) may be one of the reasons for these differences [50]. TPOAbs are able to cross the human placenta and their titers in cord blood at the moment of birth are similar to third-trimester maternal concentrations [51]. Nevertheless this passage is likely not associated with fetal thyroid dysfunction [49]. The phenomenon of TPOAbs- and TgAbs-attenuated thyroidal response to human chorionic gonadotropin (hCG) during the first half of pregnancy has been recently reported [52, 53]. In particular, it is known that serum hCG, due to its high homology to TSH, can bind the TSH receptor on thyrocytes and stimulate secretion of thyroid hormones [54]. Detection of TPOAbs during pregnancy can predict the development of post-

partum thyroiditis [49]. Increased interest has been focused on the association between thyroid function and metabolic disorders in euthyroid individuals [55, 56]. For example, Liu et al. have recently shown that TPOAbs level is associated with cardiometabolic risk factors in non-obese euthyroid individuals [56]. Another widely discussed issue is the connection between thyroid antibodies and cancer [57–59]. Some authors reported positive association between anti-thyroid autoantibodies (TgAbs and/or TPOAbs) titers and papillary thyroid cancer (PTC) risk and severity [60, 61], however, others question the role of thyroid autoimmunity in thyroid cancer [62]. The large majority of studies reported higher frequency of thyroid antibodies, especially TPOAbs, in breast cancer patients in comparison with healthy controls [59]. Several reports showed a more favorable outcome of breast cancer in TPOAbs-positive patients than in TPO-negative patients, nevertheless the protective role of TPO-driven autoimmunity continues to be debated [59, 63]. One hypothesis suggested shared antigen(s) between thyroid and breast tissues, which trigger immune reaction in thyroid autoimmunity and breast cancer. Recent findings showing TPO expression in tumoral breast and adjacent breast peri-tumoral tissues supported this assumption [64, 65]. Biochemical properties of thyroid and breast TPO are similar, with only some differences [66]. Importantly, breast TPO was effectively recognized by a broad panel of conformation-sensitive mAbs and human autoantibodies from AITD patients [65, 66]. Patients with non-thyroid autoimmune disorders (e. g., type 1 diabetes) or congenital disorders (e. g., Down's and Turner's syndromes) predispose individuals to TPOAbs development [1, 67–69].

Conclusions

Despite significant progress in TPO research, there are still many questions left unanswered. An atomic resolution structure of TPO remains elusive, and thus a detailed molecular understanding of its antigenicity. Moreover, the mechanism of breaking self-tolerance to TPO as well as the role of TPO antibody-positivity in various pathologies (e. g., breast and thyroid cancer) remain to be fully elucidated.

Conflict of Interest

The authors declare that they have no conflict of interest.

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