Thieme

Thyroid Peroxidase Revisited – What's New?

Authors
Marlena Godlewska[1], Damian Gawel[2], Ashley M. Buckle[3], J. Paul Banga[4]*

Affiliations
1 Department of Biochemistry and Molecular Biology, Centre of Postgraduate Medical Education, Warsaw, Poland
2 Department of Immunohematology, Centre of Postgraduate Medical Education, Warsaw, Poland
3 Department of Biochemistry and Molecular Biology, Biomedicine Discovery Institute, Monash University, Clayton, Australia
4 King's College London (Emeritus), London, UK

Key words
antibodies to thyroperoxidase, autoantibodies, autoimmunity, autoimmune thyroiditis, Graves' disease, Hashimoto's disease

received 18.08.2019
accepted 05.11.2019

Bibliography
DOI https://doi.org/10.1055/ a-1057-9469
Horm Metab Res 2019; 51: 765–769

ISSN 0018-5043

Correspondence
Marlena Godlewska
Department of Biochemistry and Molecular Biology,
Center of Postgraduate Medical Education,
Marymoncka 99/103
01–813 Warsaw
Poland
Tel.: +48/22/5693810, Fax: +48/22/5693712
marlena.godlewska@cmkp.edu.pl

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 dyshormonogenesis [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

* Professor Emeritus.

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 cytotoxity, 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 chronic 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.

References

[1] Czarnocka B, Eschler DC, Godlewska M et al. Thyroid autoantibodies: Thyroid peroxidase and thyroglobulin antibodies. In: Shoenfeld Y, Meroni PL, Gershwin ME, Eds. Autoantibodies. Third Edition ed. Oxford: Elsevier Inc; 2014: 365–373

[2] McLachlan SM, Rapoport B. Breaking tolerance to thyroid antigens: Changing concepts in thyroid autoimmunity. Endocr Rev 2014; 35: 59–105

[3] Rapoport B, McLachlan SM. Reflections on thyroid autoimmunity: A personal overview from the past into the future. Horm Metab Res 2018; 50: 840–852

[4] Williams DE, Le SN, Godlewska M et al. Thyroid peroxidase as an autoantigen in Hashimoto's disease: Structure, function, and antigenicity. Horm Metab Res 2018; 50: 908–921

[5] Mondal S, Raja K, Schweizer U et al. Chemistry and biology in the biosynthesis and action of thyroid hormones. Angew Chem Int Ed 2016; 55: 7606–7630

[6] Godlewska M, Banga PJ. Thyroid peroxidase as a dual active site enzyme: Focus on biosynthesis, hormonogenesis and thyroid disorders of autoimmunity and cancer. Biochimie 2019; 160: 34–45

[7] Targovnik HM, Citterio CE, Rivolta CM. Iodide handling disorders (NIS, TPO, TG, IYD). Best Pract Res Clin Endocrinol Metab 2017; 31: 195–212

[8] Persani L, Rurale G, de Filippis T et al. Genetics and management of congenital hypothyroidism. Best Pract Res Clin Endocrinol Metab 2018; 32: 387–396

[9] Begum MN, Islam MT, Hossain SR et al. Mutation spectrum in TPO Gene of Bangladeshi patients with thyroid dyshormonogenesis and analysis of the effects of different mutations on the structural features and functions of TPO protein through. Biomed Res Int 2019; 9218903

[10] Le SN, Porebski BT, McCoey J et al. Modelling of thyroid peroxidase reveals insights into its enzyme function and autoantigenicity. PLoS One 2015; 10: e0142615

[11] Godlewska M, Góra M, Buckle AM et al. A redundant role of human thyroid peroxidase propeptide for cellular, enzymatic, and immunological activity. Thyroid 2014; 24: 371–382

[12] Amouzegar A, Ghaemmaghami Z, Beigy M et al. Natural course of euthyroidism and clues for early diagnosis of thyroid dysfunction: Tehran thyroid study. Thyroid 2017; 27: 616–625

[13] Keyhanian M, Sarvghadi F, Mehran L et al. Long-Term variations of antithyroperoxidase antibodies and its clinical significance. Horm Metab Res 2019; 51: 347–352

[14] Du Puy R, Poortvliet RKE, Snel M et al. Associations of elevated anti-TPO antibodies with thyroid function, survival, functioning and depressive symptoms in the oldest old: The Leiden 85-plus study. Thyroid 2019; 29: 1201–1208

[15] Legakis I, Adamopoulos D, Stamatiou I et al. Divergent patterns of thyrotropin and other thyroidal parameters in relationship with the sex of healthy neonates and infants less than two years old: A longitudinal study. Thyroid 2019; 29: 920–927

[16] Amouzegar A, Bakhtiyari M, Mansournia MA et al. Sex- and age-specific reference values and cutoff points for TPOAb: Tehran thyroid study. Thyroid 2016; 26: 458–465

[17] Bromińska B, Bromiński G, Owecki M et al. Anti-thyroidal peroxidase antibodies are associated with thyrotropin levels in hypothyroid patients and in euthyroid individuals. Ann Agric Environ Med 2017; 24: 431–434

[18] Tozzoli R, Villalta D, Bizzaro N. Challenges in the standardization of autoantibody testing: A comprehensive review. Clin Rev Allergy Immunol 2017; 53: 68–77

[19] Tozzoli R, D'Aurizio F, Ferrari A et al. The upper reference limit for thyroid peroxidase autoantibodies is method-dependent: A collaborative study with biomedical industries. Clin Chim Acta 2016; 452: 61–65

[20] Li W, Fan G, Chen L et al. A new type of natural bispecific antibody with potential protective effect in Hashimoto thyroiditis. J Clin Endocrinol Metab 2014; 99: E1602–E1609

[21] Medici M, Porcu E, Pistis G et al. Identification of novel genetic Loci associated with thyroid peroxidase antibodies and clinical thyroid disease. PLoS Genet 2014; 10: e1004123

[22] Kuś A, Szymański K, Peeters RP et al. The association of thyroid peroxidase antibody risk loci with susceptibility to and phenotype of Graves' disease. Clin Endocrinol (Oxf) 2015; 83: 556–562

[23] Schultheiss UT, Teumer A, Medici M et al. A genetic risk score for thyroid peroxidase antibodies associates with clinical thyroid disease in community-based populations. J Clin Endocrinol Metab 2015; 100: E799–E807

[24] Brčić L, Barić A, Gračan S et al. Association of established thyroid peroxidase autoantibody (TPOAb) genetic variants with Hashimoto's thyroiditis. Autoimmunity 2016; 49: 480–485

[25] Barić A, Brčić L, Gračan S et al. Association of established hypothyroidism-associated genetic variants with Hashimoto's thyroiditis. J Endocrinol Invest 2017; 40: 1061–1067

[26] Kuś A, Szymański K, Jurecka-Lubieniecka B et al. Gender-dependent and age-of-onset-specific association of the rs11675434 single-nucleotide polymorphism near TPO with susceptibility to Graves' ophthalmopathy. J Hum Genet 2017; 62: 373–377

[27] Tomari S, Watanabe M, Inoue N et al. The polymorphisms in the thyroid peroxidase gene were associated with the development of autoimmune thyroid disease and the serum levels of anti-thyroid peroxidase antibody. Endocr J 2017; 64: 1025–1032

[28] Godlewska M, Czarnocka B, Gora M. Localization of key amino acid residues in the dominant conformational epitopes on thyroid peroxidase recognized by mouse monoclonal antibodies. Autoimmunity 2012; 45: 476–484

[29] Mikoś H, Mikoś M, Obara-Moszyńska M et al. The role of the immune system and cytokines involved in the pathogenesis of autoimmune thyroid disease (AITD). Endokrynol Pol 2014; 65: 150–155

[30] Ruggeri RM, Vicchio TM, Cristani M et al. Oxidative stress and advanced glycation end products in Hashimoto's thyroiditis. Thyroid 2016; 26: 504–511

[31] Habza-Kowalska E, Kaczor AA, Żuk J. Thyroid peroxidase activity is inhibited by phenolic compounds-impact of interaction. Molecules. 2019; 24: pii E2766. doi:10.3390/molecules24152766

[32] Liu Y, Liu S, Mao J et al. Serum trace elements profile in Graves' disease patients with or without orbitopathy in northeast China. Biomed Res Int 2018; 3029379

[33] Wang W, Mao J, Zhao J et al. Decreased thyroid peroxidase antibody titer in response to selenium supplementation in autoimmune thyroiditis and the influence of a SEPP Gene polymorphism: A prospective, multicenter study in China. Thyroid 2018 Epub 2018/11/06 doi:10.1089/thy.2017.0230

[34] McLachlan SM, Aliesky H, Banuelos B. Variable effects of dietary selenium in mice that spontaneously develop a spectrum of thyroid autoantibodies. Endocrinology 2017; 158: 3754–3764

[35] Shan Z, Chen L, Lian X et al. Iodine status and prevalence of thyroid disorders after introduction of mandatory universal salt iodization for 16 years in China: A cross-sectional study in 10 cities. Thyroid 2016; 26: 1125–1130

[36] Bliddal S, Boas M, Hilsted L et al. Increase in thyroglobulin antibody and thyroid peroxidase antibody levels, but not preterm birth-rate, in pregnant Danish women upon iodine fortification. Eur J Endocrinol 2017; 176: 603–612

[37] Borowiec A, Labochka D, Milczarek M et al. Graves' disease in children in the two decades following implementation of an iodine prophylaxis programme. Cent Eur J Immunol 2018; 43: 399–404

[38] Rayman MP. Multiple nutritional factors and thyroid disease, with particular reference to autoimmune thyroid disease. Proc Nutr Soc 2019; 78: 34–44

[39] Ajjan RA, Weetman AP. The pathogenesis of Hashimoto's thyroiditis: Further developments in our understanding. Horm Metab Res 2015; 47: 702–710

[40] Diana T, Brown RS, Bossowski A et al. Clinical relevance of thyroid-stimulating autoantibodies in pediatric Graves' disease-a multicenter study. J Clin Endocrinol Metab 2014; 99: 1648–1655

[41] Lee JH, Park SH, Koh DG et al. Thyroid peroxidase antibody positivity and triiodothyronine levels are associated with pediatric Graves' ophthalmopathy. World J Pediatr 2014; 10: 155–159

[42] Jarusaitiene D, Verkauskiene R, Jasinskas V et al. Predictive factors of development of Graves' ophthalmopathy for patients with Juvenile Graves' Disease. Int J Endocrinol 2016; 8129497

[43] Lantz M, Planck T, Asman P et al. Increased TRAb and/or low anti-TPO titers at diagnosis of graves' disease are associated with an increased risk of developing ophthalmopathy after onset. Exp Clin Endocrinol Diabetes 2014; 122: 113–117

[44] Turck N, Eperon S, De Los Angeles Gracia M et al. Thyroid-associated orbitopathy and biomarkers: Where we are and what we can hope for the future. Dis Markers 2018; 7010196

[45] Chan S, Boelaert K. Optimal management of hypothyroidism, hypothyroxinaemia and euthyroid TPO antibody positivity preconception and in pregnancy. Clin Endocrinol (Oxf) 2015; 82: 313–326

[46] Vissenberg R, Manders VD, Mastenbroek S et al. Pathophysiological aspects of thyroid hormone disorders/thyroid peroxidase autoantibodies and reproduction. Hum Reprod Update 2015; 21: 378–387

[47] Yehuda M, Wang CH, Pak Y et al. Parity and risk of thyroid autoimmunity based on the NHANES (2001-2002, 2007-2008, 2009-2010, and 2011-2012). J Clin Endocrinol Metab 2017; 102: 3437–3442

[48] Bliddal S, Feldt-Rasmussen U, Rasmussen Å et al. Thyroid peroxidase antibodies and prospective live birth – A cohort study of women with recurrent pregnancy loss. Thyroid 2019; 29: 1465–1474

[49] Alexander EK, Pearce EN, Brent GA et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 2017; 27: 315–389

[50] Derakhshan A, Korevaar TIM, Taylor PN et al. The Association of maternal thyroid autoimmunity during pregnancy with child IQ. J Clin Endocrinol Metab 2018; 103: 3729–3736

[51] Seror J, Amand G, Guibourdenche J et al. Anti-TPO antibodies diffusion through the placental barrier during pregnancy. PLoS One 2014; 9: e84647

[52] Korevaar TI, Steegers EA, Pop VJ et al. Thyroid autoimmunity impairs the thyroidal response to human chorionic gonadotropin: Two population-based prospective cohort studies. J Clin Endocrinol Metab 2017; 102: 69–77

[53] Hou Y, Liu A, Li J et al. Different thyroidal responses to human chorionic gonadotropin under different thyroid peroxidase antibody and/or thyroglobulin antibody positivity conditions during the first half of pregnancy. Thyroid 2019; 29: 577–585

[54] Zhang Y, Zhang C, Yang X et al. Association of maternal thyroid function and thyroidal response to human chorionic gonadotropin with early fetal growth. Thyroid 2019; 29: 586–594

[55] Garin MC, Arnold AM, Lee JS et al. Subclinical hypothyroidism, weight change, and body composition in the elderly: The cardiovascular health study. J Clin Endocrinol Metab 2014; 99: 1220–1226

[56] Liu J, Duan Y, Fu J et al. Association between thyroid hormones, thyroid antibodies, and cardiometabolic factors in non-obese individuals with normal thyroid function. Front Endocrinol (Lausanne) 2018; 9: 130

[57] Ehlers M, Schott M. Hashimoto's thyroiditis and papillary thyroid cancer: Are they immunologically linked? Trends Endocrinol Metab 2014; 25: 656–664

[58] Nagayama Y. Thyroid autoimmunity and thyroid cancer – the pathogenic connection: A 2018 update. Horm Metab Res 2018; 50: 922–931

[59] Muller I, Barrett-Lee PJ. The antigenic link between thyroid autoimmunity and breast cancer. Semin Cancer Biol 2019; pii: S1044-579X(19)30043-4 doi:10.1016/j.semcancer.2019.05.013. [Epub ahead of print]

[60] Wu X, Lun Y, Jiang H et al. Coexistence of thyroglobulin antibodies and thyroid peroxidase antibodies correlates with elevated thyroid-stimulating hormone level and advanced tumor stage of papillary thyroid cancer. Endocrine 2014; 46: 554–560

[61] Zhao H, Li H, Huang T. High urinary iodine, thyroid autoantibodies, and thyroid-stimulating hormone for papillary thyroid cancer risk. Biol Trace Elem Res 2018; 184: 317–324

[62] Selek A, Cetinarslan B, Tarkun I et al. Thyroid autoimmunity: Is really associated with papillary thyroid carcinoma? Eur Arch Otorhinolaryngol 2017; 274: 1677–1681

[63] Muller I, Kilburn LS, Taylor PN et al. TPOAb and thyroid function are not associated with breast cancer outcome: Evidence from a large-scale study using data from the Taxotere as Adjuvant Chemotherapy Trial (TACT, CRUK01/001). Eur. Thyroid J 2017; 6: 197–207

[64] Muller I, Giani C, Zhang L et al. Does thyroid peroxidase provide an antigenic link between thyroid autoimmunity and breast cancer? Int J Cancer 2014; 134: 1706–1714

[65] Godlewska M, Arczewska KD, Rudzińska M et al. Thyroid peroxidase (TPO) expressed in thyroid and breast tissues shows similar antigenic properties. PLoS One 2017; 12: e0179066

[66] Godlewska M, Krasuska W, Czarnocka B. Biochemical properties of thyroid peroxidase (TPO) expressed in human breast and mammary-derived cell lines. PLoS One 2018; 13: e0193624

[67] Witkowska-Sędek E, Borowiec A, Kucharska A et al. Thyroid autoimmunity in girls with turner syndrome. Adv Exp Med Biol 2017; 1022: 71–76

[68] Zwaveling-Soonawala N, Witteveen ME, Marchal JP et al. Early thyroxine treatment in Down syndrome and thyroid function later in life. Eur J Endocrinol 2017; 176: 505–513

[69] Bliddal S, Nielsen CH, Feldt-Rasmussen U. Recent advances in understanding autoimmune thyroid disease: The tallest tree in the forest of polyautoimmunity. F1000Res 2017; 6: 1776