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甲状腺自身抗体对自身免疫性甲状腺疾病诊断作用的研究进展

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摘要　自身免疫性甲状腺疾病(autoimmune thyroid disease, AITD)是常见的甲状腺疾病, 发病率逐渐升高。AITD会引起甲状腺功能亢进或减退, 对患者的生活造成不可逆的长期影响。AITD包括桥本甲状腺炎(Hashimoto's thyroiditis, HT)和格雷夫斯病(Graves' disease, GD)。甲状腺自身抗体是AITD和非AITD的鉴别诊断指标, 可以提升疾病的诊断效能。该文综述了AITD、甲状腺自身抗体、甲状腺自身抗体与AITD的关系, 为AITD的诊断提供了新思路。

关键词　疾病诊断; 甲状腺自身抗体; 甲状腺自身抗体亚型; 自身免疫性甲状腺疾病

Research Progress of Thyroid Autoantibody Subtypes and Diagnosis of Autoimmune Thyroid Diseases

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Abstract　The AITD (autoimmune thyroid disease) is the common thyroid disease, with an increasing incidence. AITD can cause hyperthyroidism or hypothyroidism, which can have irreversible long-term effects on the patient's life. AITD includes HT (Hashimoto's thyroiditis) and GD (Graves' disease). Thyroid autoantibodies are the differential diagnostic index of AITD and non-AITD, and can improve the diagnostic efficiency of the disease. In this paper, AITD, thyroid autoantibodies, and the relationship between thyroid autoantibodies and AITD were reviewed, which provided new ideas for the diagnosis of AITD.

Keywords　disease diagnosis; thyroid autoantibodies; thyroid autoantibody subtype; autoimmune thyroid disease

1　自身免疫性甲状腺疾病(autoimmune thyroid disease, AITD)

AITD是一组由自身免疫紊乱导致的自身免疫性功能障碍的疾病[1-3], 主要包括格雷夫斯病(Graves' disease, GD)和桥本甲状腺炎(Hashimoto's thyroiditis, HT), 多发于女性[4-5], 部分患者累及眼部引发甲状腺相关性眼病, 少部分患者累及肾脏[6]、脑组织[7]等。AITD的病因是多因素的, 包括遗传、环境及其他自身免疫性疾病的影响[8]。遗传因素包括人类白细胞抗原DR、免疫调节基因(*CD40*、细胞毒性淋巴细胞相关蛋白4、*PTPN22*、*FOXP3*和*CD25*)和甲状腺特异性基因[甲状腺球蛋白抗体基因(thyroglobulin antibody, *TgAb*)和促甲状腺激素受体抗体基因(thyroid stimulating hormone receptor antibody, *TRAb*)]等[9]。环境因素包括感染、饮食因素(碘)、压力和妊娠等[10]。总的来说, AITD不仅影响甲状腺本身, 而且会累及其他免疫系统, 需要综合确定治疗方案。

1.1　格雷夫斯病

GD是一种AITD, 主要特征是甲状腺激素分泌过多, 引起甲状腺功能亢进[11]。患者体内产生的促

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甲状腺刺激性抗体会模拟促甲状腺激素的作用，持续刺激甲状腺产生过多的甲状腺激素，刺激甲状腺肿大，导致甲状腺功能亢进[12]。GD在女性中的发病率明显高于男性，这可能是因为女性的激素水平受年龄的增长、妊娠等原因的影响[13]。目前，治疗GD的方法主要包括^{131}I[14]、抗甲状腺药物和手术等治疗[15-16]。^{131}I的治疗通过破坏甲状腺组织，减少甲状腺激素的产生。抗甲状腺药物的治疗主要通过抑制甲状腺激素合成、减少甲状腺激素释放以及影响免疫调节作用等方法，将甲状腺激素水平维持在正常范围内。手术治疗通过切除甲状腺减少甲状腺激素的合成与分泌。总的来说，GD治疗的主要目标是控制甲状腺激素的过度产生和减轻甲亢症状。

1.2 桥本甲状腺炎

HT是一种常见的AITD，又称慢性淋巴细胞性甲状腺炎，HT患者一般有甲状腺功能减退、甲状腺肿大和TPOAb的产生等症状[17-18]。HT患者经历的从甲状腺功能正常到甲状腺功能亢进(甲亢)最后发展成甲状腺功能减退(甲减)，是甲状腺细胞的损伤和甲状腺碘储存的丢失过程，是一个不可逆的过程。因此，对HT的提早发现、治疗对疾病的进展至关重要。从甲状腺功能正常到甲状腺功能亢进再到甲状腺功能减退的过程的治疗方案[4,19]需要根据病情的变化，及时调整。HT患者在甲状腺功能正常期一般没有症状，无需用药，只需定期检测甲状腺功能、抗体水平。而HT患者在甲亢期是暂时性的，一般不需要药物治疗，只需定期检测甲状腺功能和抗体水平，甲亢症状明显的HT患者可以小剂量、短期口服抗甲状腺药物。HT患者在甲减期的主要治疗方式是甲状腺激素替代治疗，用于恢复和维持足够的T4激素水平，改善甲减症状[20]。

2 甲状腺自身抗体

甲状腺自身抗体是一种针对甲状腺某些成分的免疫球蛋白[21]，由于自身免疫紊乱而产生。它们是由免疫系统错误地攻击自身甲状腺组织产生的，主要分为两大类，针对甲状腺细胞表面的抗体和针对甲状腺细胞内容物的抗体，即TRAb和TgAb、甲状腺过氧化物酶抗体(thyroid peroxidase antibody, TPOAb)，其会影响甲状腺激素的合成和分泌，参与甲状腺功能调节、免疫反应等过程，是AITD诊断的重要标志物。

2.1 促甲状腺激素受体抗体

TRAb是一种针对促甲状腺激素受体(thyroid stimulating hormone receptor, TSHR)的自身抗体[22]，与GD的发病密切相关[11]，作用在TSHR胞外区域的不同位点，是诊断GD的重要指标[23]。TRAb可以分为刺激性抗体(thyrotropin receptor stimulating antibody, TSAb)、抑制性抗体(thyroid stimulating hormone receptor blocking antibody, TBAb)和中和性抗体三种亚型[24]。在生理状态下，血液中的促甲状腺激素(thyroid stimulating hormone, TSH)与甲状腺滤泡上皮细胞表面的TSHR结合，释放甲状腺素(图1)[25]。但是当疾病存在的时候，TSAb就会和TSHR结合，从而释放更多的甲状腺素导致甲亢的发生(图1)；TBAb和TSHR结合，抑制甲状腺素的分泌，导致甲减的发生[26]。TRAb对于甲状腺疾病的诊断和治疗决策有重要参考价值[27]。例如，TRAb可以作为GD患者的一线筛查方法[28]，对无明显甲状腺肿大的轻微甲亢和其他原因引起的甲亢的鉴别具有临床指导价值[29]。但是，现在对TSAb和TBAb的检测方法仍有局限以及TSAb和TBAb的生物功能仍没有详尽的介绍，现有的检测方法都是对TRAb的检测。因此TRAb的水平变化主要应用于GD的诊断、评估治疗效果，且TRAb是甲状腺功能的生物标志物。

2.2 甲状腺球蛋白抗体

TgAb是AITD的一个重要检测指标，TgAb的存在通常表示免疫系统错误地攻击了甲状腺，导致甲状腺功能受损。正常情况下甲状腺球蛋白(thyroglobulin, Tg)储存于甲状腺滤泡腔中，但是在病理状态下，甲状腺滤泡破坏引起Tg分泌或溢漏到血液中，诱发产生TgAb[30]。TgAb与Tg结合后，通过激活自然杀伤细胞攻击靶细胞及催化Tg水解，导致甲状腺细胞破坏，此类现象常见于AITD中[31]，例如桥本甲状腺炎(HT)[32]。TgAb的浓度越高，淋巴细胞的浸润程度越大，甲状腺滤泡的破坏程度越严重[33]。高滴度的TgAb与Tg结合，激活自然杀伤细胞，引起甲状腺细胞破坏，是甲状腺功能减退的危险因素[34]。总之，TgAb在AITD的诊断、治疗和监测中扮演着重要角色。

2.3 甲状腺过氧化物酶抗体(TPOAb)

TPOAb是一种针对自身免疫的抗体，是针对甲状腺过氧化物酶(thyroid peroxidase, TPO)产生

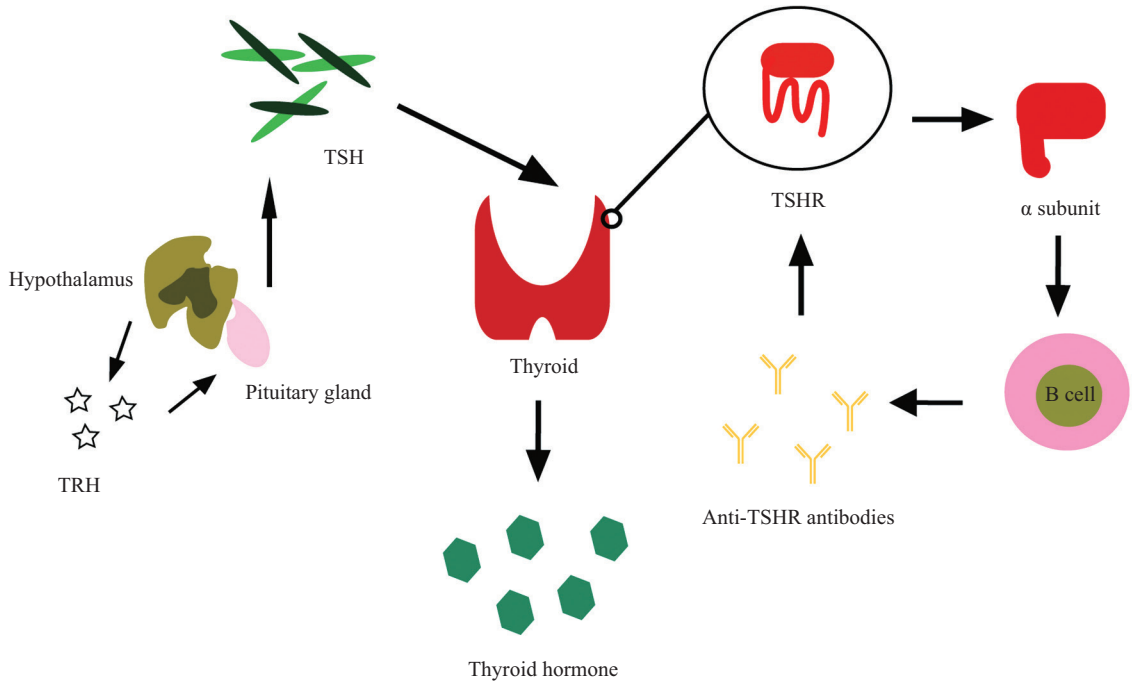

图1中, 下丘脑分泌的促甲状腺激素释放激素(TRH)刺激脑垂体分泌TSH, TSH作用于甲状腺细胞上的TSHR释放甲状腺激素。但是疾病发生时, TSHR上的α亚基跟β亚基分离成为抗原, 被免疫系统识别并产生自身抗体TRAb, TRAb作用于TSHR, 刺激甲状腺激素的生成。

In Fig.1, TRH (thyrotropin-releasing hormone) secreted by the hypothalamus stimulates the pituitary gland to secrete TSH, which acts on the TSHR on the thyroid cells to release thyroid hormone. However, when disease occurs, the alpha subunit on TSHR separates from the beta subunit to become an antigen, which is recognized by the immune system and produces the TRAb autoantibody, which acts on TSHR and stimulates the production of thyroid hormone.

图1 TRAb的生成过程(根据参考文献[25]修改)

Fig.1 TRAb generation process (modified according to reference [25])

的。TPOAb的产生通常是由于免疫系统错误地识别TPO为外来物质, 激活补体系统, 导致甲状腺滤泡上皮细胞的破坏, 从而产生针对TPO的自身免疫反应[35]。这种自身免疫反应可能引起甲状腺滤泡细胞的破坏, 进而影响甲状腺激素的合成和分泌, 从而引起AITD。在亚临床或早期HT患者中, TPOAb的存在可能预示着未来发展为临床甲减的风险, 而TPOAb的滴度变化可以作为疾病活动性的指标。TPOAb水平的下降可能表明治疗效果良好, 持续升高的TPOAb水平则可能提示疾病复发或持续活动[36]。因此, TPOAb有助于早期发现和诊断HT, 以及进一步预测病情[37]。

3 甲状腺自身抗体对自身免疫性甲状腺疾病诊断的研究进展

临床上通过甲状腺功能测试、甲状腺抗体(TRAb、TgAb、TPOAb)检测、甲状腺超声检查来诊断AITD。对于GD来说, 患者体内产生的TRAb与血清中的TSH竞争与TSHR的结合, 促进甲状腺素的分泌, 引起甲状腺功能亢进。因此, TRAb阳性是GD的显著特征, 此外血清促甲状腺激素水平降低, 游离甲状腺激素或总甲状腺激素水平增加也是GD的典型症状[28,38-40]。诊断GD需要综合临床症状、甲状腺抗体测试和甲状腺超声等结果。此外, TRAb作为GD的特异性指标, GD患者通常表现出高水平的TRAb, TRAb水平随着治疗的进行会显著降低, 该指标的变化可以辅助临床评估治疗效果和疾病缓解情况[41], 如高水平TRAb或TRAb水平持续升高提示疾病未缓解或疾病复发[42]。而对于HT来说, 患者体内产生针对甲状腺抗原的自身抗体, 包括TPOAb和TgAb。TPOAb、TgAb攻击甲状腺组织, 引起甲状腺细胞的破坏、淋巴细胞的浸润变化、甲状腺滤泡的破坏, 导致甲状腺激素分泌减少, 最终表现为甲状腺功能减退[43]。对于HT的诊断则需要综合考虑病史、实验室检查和影像学检查结果[44], 如典型的临床症状[甲状腺肿大、眼部症状和甲减相关症状(乏力、畏寒等)]以及甲状腺功能测试、甲状腺抗体测试和甲状腺超声检查[45]等。其中TgAb和TPOAb阳

性为HT的典型特征之一[17,34]。TPOAb和TgAb在HT患者中的水平显著高于健康人[34], 可以显著提高HT的诊断效能, 且TPOAb、TgAb水平在HT的不同阶段中也存在差异[46]。大量研究表明, TRAb、TgAb、TPOAb在GD、HT患者中的水平显著高于健康对照组。其中, TgAb、TPOAb在HT中的阳性率都高于90%[47-48], TRAb在GD中的阳性率则高达95%[49], 因此甲状腺自身抗体可应用于自身免疫性甲状腺疾病的诊断[50](甲状腺抗体对AITD发生发展机制的研究进展见表1)。

近年来研究表明, GD和HT之间可能存在转换现象[51-54]。HT患者包括三个阶段, 初期时甲状腺功能正常, 中期时为甲亢期, 晚期时为甲减期。在一项对HT患者的研究中, 发现有部分患者在随访期间发展成了GD[51]。这些患者在HT期间, 平均TSH水平较高, 需要接受左甲状腺素治疗。而在转换为GD后, 这些患者的血清促甲状腺激素、游离四碘甲状腺原氨酸、游离三碘甲状腺原氨酸和促甲状腺激素阻断型抗体水平发生了显著变化。这一现象表明, 尽管GD和HT通常被视为两种不同的疾病, 但它们之间可能存在一定的连续性, 会存在合并GD和HT的阶段。

有研究者发现, GD患者中存在的TSAb和TBAb, 这两种抗体可以分别导致甲亢和甲减, 而TSAb和TBAb可共存于患者血清中, 并在机体内可潜在转化, 甲状腺功能状态由占优势抗体决定, 因此机体是甲亢还是甲减由优势抗体决定[55]。此外, 还有研究发现, 在HT患者中也存在TSAb和TBAb, 但只有一半是甲状腺功能减退症状, 可能是由于TSAb的作用抵消了TBAb的作用[56]。在同组的另一项研究中, 700名HT患者均患有甲状腺眼病, 并且研究人员在患者体内中均检测到TSAb, 但是66.7%的患者却表现为甲状腺功能减退, 这可能是基于细胞介导的细胞毒性引起炎症所致[57]。

总之, GD和HT在组织学上没有明显差异, 都会有甲状腺肥大、增生性的滤泡等表现[17,31,58], 医务工作者仅结合激素水平、影像学报告等结果仍难以对两种疾病的转换进行诊断[53]。而在GD和HT患者中则均存在TRAb、TgAb、TPOAb[59], 通过对这三种抗体的检测, 也无法准确鉴别两种疾病。此外GD、HT的转换现象, 也增加了正确诊断两种疾病的难度。然而AITD在治疗上存在显著差异, 所以对AITD的提早发现及正确诊断对预测疾病的进展、尽早干预和治疗疾病至关重要。

4 甲状腺自身抗体亚型与自身免疫性甲状腺疾病诊断

甲状腺自身抗体属于免疫球蛋白(immunoglobulin, IgG), 参与补体激活系统、抗体依赖性细胞介导的细胞毒性(antibody-dependent cell-mediated cytotoxicity, ADCC)、抗体依赖性细胞介导的吞噬作用(antibody-dependent cell-mediated phagocytosis, ADCP)等[60]。根据重链结构区别分为四个亚型(IgG1、IgG2、IgG3、IgG4), 每个亚型具有的生物学特征不同, 使得它们在不同的免疫反应和疾病状态下扮演着不同的角色[61]。IgG1、IgG3介导ADCC和补体依赖的细胞毒性作用(complement-dependent cytotoxicity, CDC)的能力强, 在炎症过程中起主要作用; IgG2、IgG4介导ADCC的能力弱, 而在免疫调节和耐受中起作用[62]。在HT、GD患者中同时存在TgAb、TPOAb[34], TgAb和TPOAb在这两种疾病中起到的作用不同, 其亚型分布及含量对于这两种疾病的转换也存在不同的影响[63], 可以通过研究甲状腺自身抗体的亚型转换预测AITD的临床转归(甲状腺自身抗体亚型研究进展见表1)。AITD自身抗体亚型主导类别不同提示自身免疫性甲状腺疾病的进展不同。FOROUHI等[64]研究发现, AITD患者中TgAb的亚型主要为IgG1、IgG4。进一步研究发现TgAb IgG3亚型在HT患者中的阳性率高达70%[65], 这是由于HT是一种炎症反应, IgG3介导ADCC和CDC的能力强[66-67], 在炎症过程中起主要作用, 使得甲状腺细胞被破坏, 释放大量甲状腺激素, 加重炎症, 因此TgAb IgG3亚型为HT患者中的主要亚型[34]可以提示发生HT的风险高。与此不同的是, IgG2、IgG4的致炎能力虽然较弱, 但在减少炎症反应中仍起到一定的作用。相关研究发现TgAb IgG2在HT中占主导地位[68-69], 同时LI等[70]发现TgAb IgG2升高提示甲状腺功能减退。然而CATURECLI等[68]发现TgAb IgG4是GD中的主要亚型, YUAN等[65]提出TgAb IgG2、IgG4亚型, TPOAb IgG2亚型水平高提示发生GD的风险高。这可能是由于IgG2通过激活补体系统参与炎症和病原体清除反应, 来维持免疫系统的平衡, 但个体差异、感染疾病状态不同导致其在人体内发挥的作用不同[71]。

表1 甲状腺自身抗体及其亚型

Table 1 Thyroid autoantibodies and their subtypes

抗体 Antibodies	研究进展 Research progress	参考文献 References
Thyroid autoantibody		
TRAb	TRAb is a diagnostic index of GD, and the positive rate of GD is as high as 95%. Both TSAb and TBAb exist in GD patients, which can be potentially transformed in the body, and the thyroid function status is determined by the dominant antibody	[49]
TgAb	TgAb is a diagnostic index of HT, and the positive rate in HT is as high as 90%	[47-48]
TPOAb	TPOAb is a diagnostic indicator of HT, and the positive rate in HT is as high as 90%	[47-48]
Thyroid autoantibody subtype		
IgG1	IgG1 has a strong ability to mediate ADCC and CDC, and plays a major role in the inflammatory process	[67]
	TgAb IgG1 is the main subtype in AITD	[64]
	After ^{131}I treatment, the content of TgAb IgG1 in GD increases	[73]
IgG2	IgG2 has a weak ability to mediate ADCC, but plays a role in immune regulation and tolerance	[67]
	Positive TPOAb IgG2 indicates the risk of hypothyroidism in hepatitis C patients	[75]
	High TPOAb IgG2 levels suggest a higher risk of hypothyroidism	[70,74]
	TgAb IgG2 and TPOAb IgG2 indicate high risk of GD occurrence	[65]
	TgAb IgG2 is dominant in HT	[68]
IgG3	IgG3 has a strong ability to mediate ADCC and CDC, and plays a major role in the inflammatory process	[67]
	The TgAb IgG3 subtype indicates a high risk of HT	[34]
	After ^{131}I treatment, the content of TgAb IgG3 in GD increases	[73]
IgG4	IgG4 has a weak ability to mediate ADCC, but plays a role in immune regulation and tolerance	[67]
	Positive IgG4 in HT patients suggests a higher risk of developing papillary thyroid cancer	[76]
	TgAb IgG4 is the main subtype in AITD	[64]
	TgAb IgG4 is the main subtype of GD, suggesting a high risk of GD occurrence	[65]
	TRAb is a diagnostic index of GD, and the positive rate of GD is as high as 95%. Both TSAb and TBAb exist in patient with GD, which can be potentially transformed in the body, and the thyroid function status is determined by the dominant antibody	[74]

此外, 有研究认为IgG亚型水平随着疾病的进展由IgG3、IgG1、IgG2、IgG4依次转换[72]。LATROFA等[73]研究发现, 经过^{131}I治疗后, GD中TgAb IgG1、IgG3含量上升, 可能是增加了补体激活系统, 加快了炎症反应的清除。HT患者经历从甲亢期到亚临床甲减期再到甲减期, 亚型也随之变化。正如XIE等[74]在研究不同甲状腺功能状态的HT患者血清中TPOAb IgG亚类的分布时发现, HT甲减期处于HT发展的末期, 而HT甲减期患者血清中IgG2、IgG4的阳性率高于HT甲亢期患者, 因此, 他们提出, TPOAb IgG2、IgG4水平高提示HT初期患者发展为HT甲减的风险高[74]。总之, 由于GD、HT患者同时存在TgAb和TPOAb, 无法通过这两种甲状腺自身抗体区分两种AITD, 但这两种甲状腺自身抗体亚型含量在两种AITD中的差异可能为临床鉴别诊断和治疗两种AITD提供方向。

5 总结与展望

GD和HT是两种常见的AITD, 它们在病理生理学、临床表现和治疗上存在显著差异。临床上这两种疾病之间的转换以及症状重叠现象, 给这两种疾病的诊断和治疗带来了不确定性。目前, 针对这两种疾病仍没有较高诊断效能的生物标志物, 临床上对于这两种疾病的诊断, 更多的是依靠长期监测甲状腺功能、甲状腺抗体、甲状腺超声, 或者通过病理穿刺, 综合考虑患者的临床表现来确诊。多项研

究发现，AITD自身抗体亚型在AITD中起到的生物学作用不同，IgG1、IgG3在疾病的炎症反应中起主导作用，这与疾病的急性期相关，而IgG2、IgG4在免疫调节和耐受中起作用，与疾病的慢性期相关[77]。这种差异可能预示着疾病的进展。如AITD自身抗体亚型从IgG1主导转变为IgG4主导则表明疾病从急性期进入稳定期。此外AITD自身抗体亚型在AITD的进程中的水平变化呈现特定顺序，依次为IgG3、IgG1、IgG2、IgG4的顺序变化[72]，这种动态变化可能有助于预测疾病的复发风险。如GD患者在接受^{131}I治疗后TgAb IgG1、IgG3含量增加，HT患者在不同发展期的主导亚型含量不同。因此检测自身抗体亚型水平的变化，可以对GD和HT的相互转换、进展起到更好的预测和监测作用。

此外，相关研究发现，甲状腺自身抗体亚型水平的差异对预测其他疾病进展也具有提示意义，如YU等[76]研究发现，HT患者的IgG4阳性状态是病情进展为乳头状甲状腺癌的一个危险因素。SHAO等[75]研究发现，TPOAb IgG2的存在会引起C型肝炎患者甲状腺功能减退。总的来说，甲状腺自身抗体亚型的具体致病机制复杂，涉及多种免疫细胞和分子，具体作用因个体差异以及感染或疾病的状态差异而有所不同[78]，因此，进一步深入研究甲状腺自身抗体亚型转换的免疫学机制和亚型转换在AITD发病中的作用十分重要。目前对于甲状腺自身抗体亚型分布的相关研究有限，未来可以在更大的样本量和更广泛的研究中进一步验证甲状腺自身抗体亚型对AITD的诊断、治疗的指示作用，为AITD的早期诊断及治疗提供新的方向。

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