



Thyroid diseases and skin autoimmunity

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Abstract

The skin is the largest organ of the body, at the boundary with the outside environment. Primarily, it provides a physical and chemical barrier against external insults, but it can act also as immune organ because it contains a whole host of immune-competent cells of both the innate and the adaptive immune systems, which cooperate in eliminating invading pathogens following tissue injury. On the other hand, improper skin immune responses lead to autoimmune skin diseases (AISD), such as pemphigus, bullous pemphigoid, vitiligo, and alopecia. Although the interplay among genetic, epigenetic, and environmental factors has been shown to play a major role in AISD etiology and progression, the molecular mechanisms underlying disease development are far from being fully elucidated. In this context, epidemiological studies aimed at defining the association of different AISD with other autoimmune pathologies revealed possible shared molecular mechanism(s) responsible for disease progression. In particular, over the last decades, a number of reports have highlighted a significant association between thyroid diseases (TD), mainly autoimmune ones (AITD), and AISD. Here, we will recapitulate the epidemiology, clinical manifestations, and pathogenesis of the main AISD, and we will summarize the epidemiological evidence showing the associations with TD as well as possible molecular mechanism(s) underlying TD and AISD pathological manifestations.

Keywords Skin · Epidermis · Thyroid · Autoimmunity · Epidemiology · Pathophysiology

1 Thyroid diseases: a brief overview

Thyroid diseases (TD) are frequently encountered in clinical practice and occur more often among female patients [1]. In iodine-depleted areas, hypothyroidism and diffuse goiter, which can develop into nodular goiter, are commonly observed, while in iodine-sufficient areas, autoimmune TD (AITD), mainly chronic lymphocytic thyroiditis and Graves' disease, are the predominant types of TD [2–4]. Nodular TD is also very common among adults [5], so much that about half of the entire population is estimated to develop a thyroid nodule by the age of 60. Although the majority of thyroid nodules

are benign tumors, about 5% of them harbor a malignant lesion [5, 6].

1.1 Autoimmune thyroid diseases (AITD)

AITD represent the most frequent autoimmune disorders, with an expected prevalence of about 5% [3, 7]. As above mentioned, AITD include two main clinical entities: a) the chronic lymphocytic thyroiditis or Hashimoto thyroiditis, typically leading to hypothyroidism; b) Graves' disease or Basedow disease, characterized by hyperthyroidism [3, 4, 7]. Although both diseases occur with lymphocytic infiltration of the thyroid tissue, in Hashimoto thyroiditis self-reactive CD4+ T lymphocytes recruit B cells, typically producing anti-thyroglobulin (anti-Tg) and anti-thyroperoxidase (anti-TPO) antibodies, and CD8+ T lymphocytes which induce apoptosis of thyrocytes, progressively leading to gland fibrosis and hypothyroidism; by contrast, in Graves' disease activated CD4+ T cells induce B cells to secrete stimulating autoantibodies directed against the thyrotropin receptor (TRAb), causing unrestricted thyroid hormone synthesis and release [4]. Over the last decades, epidemiologic and genetic studies on AITD started to shed light on

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the molecular mechanisms causing the immune tolerance destruction responsible for disease progression. Currently, AITD is thought to be caused by a complex interaction between genetic and environmental factors [3, 8–10]. Regarding genetics, it has been shown that Hashimoto thyroiditis has the highest incidence in white people, and the lowest in black and in Asian/Pacific Islander individuals, while the opposite occurs for Graves' disease [8]. Gene polymorphisms determining increased individual susceptibility to AITD have been identified for either immune-regulatory genes (*i.e.* HLA-DR3, HLA-DR4, CD40, PTPN22, FOXP3) or thyroid-specific genes (*i.e.* thyroglobulin, TSHR) [3, 8, 9]. However, the observation that monozygotic twins do not show complete concordance for AITD strongly suggests that the genetic background might not be sufficient for the clinical onset of AITD [11]. Indeed, several environmental factors potentially capable of triggering AITD in genetically predisposed individuals have been recognized, including deficiency or excess of iodine, low level of vitamin D and selenium, medications (*i.e.* interferon-alpha and amiodarone), bacterial (*i.e.* *Yersinia enterocolitica*, *Borrelia burgdorferi*, *Helicobacter pylori*) and viral infections (*i.e.* hepatitis C virus), smoking, stress and pollutants (*i.e.* phthalates, bisphenol A, perfluorinated chemicals, polyaromatic hydrocarbons) [12–14].

2 Skin structure and epidermal autoimmune diseases

The skin represents the largest organ of the human body, accounting for approximately 15% of the body weight, and accomplishes dedicated functions crucial to human health. These include protection of the body against physical assaults (*i.e.* ultraviolet radiation, mechanical injury), microbial infections (*i.e.* bacteria, viruses, fungi) and chemical agents (*e.g.* irritants and allergens). In addition, the skin preserves the organism from excessive water loss and plays an important role in body thermoregulation [15]. The skin is also involved in the metabolism and elimination of xenobiotics, endogenous bioactive substances, lipids, and cholesterol; it is an important steroidogenic organ, capable of metabolizing various hormones from their precursors and to synthesize vitamin D, and it represents the main sensory organ for pressure, touch, and pain. Below we will briefly describe the main skin entities: epidermis, dermis, subcutaneous tissue and skin appendages.

2.1 Epidermis

The epidermis is the outermost layer of the skin. It is molded by three different cell populations: keratinocytes, the largely predominant epidermal cell type; melanocytes, which are melanin producing cells; Langerhans cells, namely dendritic

antigen presenting cells. In the epidermal structure, five overlapping layers can be identified, with keratinocytes changing their appearance from one layer to the superior as their differentiation proceeds. These include, from the innermost to the outermost layer:

- i. the basal or germinative layer, consisting of keratinocytes tightly bound by means of hemidesmosomes to the basement membrane located at the interface between dermis and epidermis. These cells undergo mitosis, and some daughter cells migrate and start to differentiate in the next outermost layer. Melanocytes are also present in this layer at a density of about 1000–2000 per square millimeter, representing about 5–10% of the basal layer cells [16].
- ii. the spinous layer, formed by keratinocytes connected to each other by desmosomes. The name “spinous” comes from the tufts of keratin filaments assembled into cables of intermediate filaments that anchor to desmosomes. Keratinocytes of the spinous layer start to produce lamellar bodies, secretory organelles enriched in polar lipids, glycosphingolipids, free sterols, phospholipids, and catabolic enzymes. The immunologically active Langerhans cells are located in this layer [17].
- iii. the granular layer, which marks the boundary between the inner metabolically active keratinocytes and the outermost layers consisting of dead cells. It is characterized by the presence of keratinocytes losing their nuclei and whose cytoplasm appears granular due to the accumulation of lamellar bodies. Lipids are released from the lamellar bodies into the extracellular space to form extracellular lamellar membranes between cells that block the movement of water and electrolytes.
- iv. the clear or translucent layer, present only in the skin of palms and soles, and consisting of two rows of flattened anucleated cells containing large amounts of keratins.
- v. the cornified layer, composed of 10 to 30 layers of polyhedral, anucleated corneocytes (final step of keratinocyte differentiation). Corneocytes are surrounded by a protein envelope, filled with water-retaining keratin proteins attached together through corneodesmosomes and surrounded by stacked layers of lipids in the extracellular space. The main barrier functions of the epidermis are due to this layer [15].

Corneocytes are lost by desquamation and replaced by new cells which start to differentiate from the basal layer as above described. The epidermal turnover time, *i.e.* the time taken to replace itself, is 47–48 days [18].

2.2 Dermis and hypodermis

Located below the epidermis, the dermis represents the bulk of the skin. It is a connective tissue usually divided in two

regions. The outermost zone, the papillary dermis, is characterized by the presence of ridges called papillae, responsible for the formation of individual fingerprints at the fingertips; the innermost zone of the dermis, called the reticular area, contains the vascular and lymphatic vessels and skin appendages (i.e. hair follicles, sweat and sebaceous glands). Dermal vasculature provides oxygen and nutrients also to the avascular epidermis. Fibroblasts represent the main cell type encountered in the dermis. They secrete collagen and elastin fibres, which confer to the skin the characteristic elasticity and strength, and glycosaminoglycans capable of retaining water [19, 20]. Cells of the immune system derived from the bone marrow may also populate the dermis; they include dendritic cells, macrophages, natural killer cells, mast cells and T lymphocytes [17]. Some of these (i.e. dendritic cells, macrophages and memory T cells) are considered skin-resident cells. Immune responses are initiated by resident populations and progress through the recruitment of additional circulating cells of both innate and adaptive immune systems to fight infections and aid the healing process [17]. The subcutaneous tissue, or hypodermis, consists essentially of adipose tissue, which besides functioning as energy store and providing heat isolation, offers protection to internal organs and bones against external skin pressure and injuries.

2.3 Main skin appendages

The main skin appendages include hair with the associated sebaceous glands and sweat glands. Hair has various functions, such as protection against external factors, thermoregulation and sensory perception. The pilosebaceous unit consists of the hair follicle with an attached sebaceous gland and arrector pili muscle. The attached sebaceous glands secrete a lipid-rich sebum into the hair follicular canal protecting the hair shaft and the skin with a hydrophobic barrier. The human hairs are built by the hair follicles, tube-like pockets of the epidermis that extend through the dermis and hypodermis. The hair is formed by the proliferation of cells in the region known as the bulb, at the follicle's base, where in the meanwhile melanin pigment is incorporated from neighbouring melanocytes. Human hair follicles go through cycles of activity which include three phases: the anagen represents the proliferation phase leading to the production of a new hair shaft, and which may last from few months (i.e. eyebrows) to several years (i.e. scalp); catagen, or transition phase, is the shortest one (may last only few weeks), and it is characterized by the arrest of proliferation and by the regression of the inferior part of the hair follicles; telogen, or resting phase, is the final stage of a hair's lifecycle in which the hair becomes fully keratinized [21].

Sweat glands are coiled tubes of epidermal origin, though they lie in the dermis. Their secretory cells surround a central space, or lumen, into which the secretion is extruded. There

are two distinct types of sweat glands: eccrine glands open by a duct directly onto the skin surface; apocrine glands usually develop in association with hair follicles and open into them.

3 Autoimmune skin diseases (AISD)

In 2006, McGonagle and McDermott proposed a new classification of the immunological diseases based on the improved comprehension of the genetic and molecular mechanisms involved [22]. This new classification was based on the distinction between autoinflammatory diseases, in which an aberrant activation of the innate immune system is predominant and responsible for host tissue injury, and autoimmune diseases, in which cells of the adaptive immune system give rise to the clinical expression of the disease [22]. In particular, McGonagle and McDermott stratified the immunological diseases in five groups or categories:

- i. rare monogenic autoimmune diseases
- ii. polygenic autoimmune diseases
- iii. mixed pattern diseases
- iv. polygenic autoinflammatory diseases
- v. rare monogenic autoinflammatory diseases.

The majority of AISD, including pemphigus, bullous pemphigoid, epidermolysis bullosa acquisita, dermatitis herpetiformis, alopecia areata, chronic spontaneous urticaria, and vitiligo belongs to the group of polygenic autoimmune diseases, while psoriasis is included either in the mixed pattern or in the polygenic autoinflammatory diseases [22–24]. It is worth to mention that some AISD (i.e. vitiligo and alopecia) may be present in the autoimmune polyglandular disease (APS) syndromes [25, 26]. APS are classified as:

- i. *APS I* or *APECED* (autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy), an autosomal recessive disorder occurring during childhood and caused by mutations of the *AIRE* (autoimmune regulator) gene [25]. It is characterized by at least two of the three most common clinical manifestations, which include chronic mucocutaneous candidiasis, hypoparathyroidism and Addison's disease [26, 27]. Other associated diseases include gonadal insufficiency, alopecia, vitiligo and chronic active hepatitis [26–28].
- ii. *APS II*, also known as Schmidt syndrome, characterized by the adult onset of Addison's disease associated with type 1 diabetes mellitus and/or AITD. It is the commonest APS, more frequently met in women than men [26–29]. Additional associated diseases include celiac disease, vitiligo, pernicious anemia, and alopecia. Gene polymorphisms identified in the APS II comprise the human leucocyte antigen (HLA)-DQ, HLA-DR and HLA-DP,

encoding the major histocompatibility complex (MHC) class II proteins [23–26]. Other non-HLA genes associated with APS II are the PTPN22, CTLA4, VNTR, and MICA5.1 [26–29].

- iii. *APS III*, characterized by the presence of AITD associated with other autoimmune diseases (excluding Addison's disease and hypoparathyroidism). Depending on these associations, APS III is sub-grouped in 4 classes: IIIA, IIIB, IIIC, and IIID [24]. In the APS IIIC, AITD associated with vitiligo, alopecia, myasthenia gravis, multiple sclerosis, and stiff-man syndrome [29, 30].
- iv. *APS IV*, characterized by the association of two or more organ-specific autoimmune diseases not included in the other APS categories [27, 29].

Below, the epidemiology and pathogenesis of the major AISD will be briefly overviewed, as well their association with TD.

3.1 Bullous pemphigoid disease

The bullous pemphigoid (BP) is a rare blistering autoimmune disease usually affecting elderly people, but it may also occur during infancy and childhood [23, 31, 32]. The BP include also as a pregnancy-specific dermatosis called pemphigoid gestationis (PG) or gestational pemphigoid, which may evolve to BP in severe cases [33]. The BP annual incidence has been reported to vary from 1.2 to 4.3/100.000 persons [31]. The disease, besides causing a poor quality of life, is characterized by a significant mortality rate, ranging from 12% to 40% during the first year from the diagnosis [34, 35]. The blisters or bullae arise at the interface between dermis and epidermis [31, 32]. The affected subjects develop IgG autoantibodies against two different components of the hemidesmosomes, the multiprotein complexes responsible for the maintenance of the dermal-epidermal adhesion. In particular, the autoantibodies target the proteins dystonin, also known as BP180 antigen (BPAg1, Bullous Pemphigoid Antigen 1), and/or the type XVII collagen, also known as BP230 antigen (BPAg2, Bullous Pemphigoid Antigen 2) [23, 31, 32]. Binding of these autoantibodies in the skin elicits complement activation, mast cell degranulation and accumulation of inflammatory cells, including eosinophils, mast cells, and neutrophils. The release of proteases from these inflammatory cells is thought to induce the cleavage of the basement membrane and blister formation. In this context, it is worth to mention that mutations in either the BPAg1 or the BPAg2 gene may cause epidermolysis bullosa, an autosomal inherited disorder [36, 37]. In BP patients the presence of CD4+ T-cells secreting both Th1 and Th2 cytokines has been documented [38]. The HLA-DQB1*0301 allele has been shown to associate with different clinical variants of BP, while several environmental triggers, including trauma, burns, radiotherapy, ultraviolet radiation,

and drugs have been identified [31, 39–41]. In women affected by gestational pemphigoid the associations with the HLA-B8, HLA-DR3 and HLA-DR4 have been demonstrated [33, 42].

BP has been also described in association with different autoimmune disorders, among which rheumatoid arthritis, autoimmune thrombocytopenia, dermatomyositis, systemic lupus erythematosus, alopecia, vitiligo, and AITD [31, 42]. Regarding AITD, both Hashimoto thyroiditis and Graves' disease have been found to occasionally associate with BP in some case reports [43–45]. A recent work analyzed the prevalence of anti-TPO antibodies in a case study with 23 patients affected by BP, 25 patients with pemphigus and 46 control subjects [46]. The results showed a higher prevalence of anti-TPO antibodies in BP, but not in pemphigus patients, compared to the control group [47]. Moreover, women affected by gestational pemphigoid showed a higher prevalence of other autoimmune diseases, including Hashimoto thyroiditis and Graves' disease [42]. Altogether, these lines of evidence warrant further clinical investigations on larger case studies to definitively establish the presence of a relationship between AITD and BP.

3.2 Epidermolysis bullosa acquisita

The epidermolysis bullosa acquisita (EBA) is a rare autoimmune skin disease characterized by the production of IgA and IgG autoantibodies directed against collagen VII (C7), the main component of the fibrils that anchor the basement membrane to dermis [47–49]. As a result, these patients are typically affected by blisters, erosions, scars, milia, and nail loss, features that are reminiscent of the genetic dystrophic epidermolysis bullosa, caused by mutations in the gene encoding for C7 [47–49]. The disease, however, may have different clinical presentations which, in addition to the classical hallmarks, may encompass BP-like phenotype, cicatricial Pemphigoid-like phenotype, Brunsting-Perry pemphigoid-like and linear IgA bullous dermatosis-like phenotype. As a consequence, EBA diagnosis is often difficult due to clinical features overlapping with other blistering skin diseases [49]. A genetic factor associated with EBA is the HLA-DR2 [42].

Although rarely, EBA has been shown to associate with other systemic diseases [49, 50]. The strongest association is found with inflammatory bowel disease (IBD) (mainly Crohn's disease). In fact, about 68% of patients affected by IBD have circulating autoantibodies against C7, and Crohn's disease has been recognized in approximately 30% of EBA patients [51, 52]. It has been speculated that the expression of C7 in both colon and skin leads to a cross-reaction to the same antigen in different tissues. Otherwise, in EBA patients C7 could harbor the 'primary' epitope of a spreading phenomenon towards IBD autoimmunity [49]. An EBA association

with thyroiditis has also been described, but this finding is still preliminary because it was obtained from few patients [49].

3.3 Linear IgA dermatosis

Linear IgA dermatosis (LAD) is a rare subepidermal autoimmune blistering disease characterized by linear deposition of IgA along the basement membrane [39]. LAD is classified either as idiopathic or drug-induced [42, 53]. Different autoantigens of the basement membrane have been implicated, including the BP180, C7 and $\alpha 3$ subunit of laminin-332 [54, 55]. The best characterized antigen is a 97-kd protein though to represent a portion of the extracellular domain of the bullous pemphigoid antigen BPAG2, isolated from human epidermis and capable of binding IgA obtained from sera of patients with LAD [56]. The pathogenesis of LAD has not been completely elucidated. In one study, 5 out of 9 LAD patients carried the haplotype HLA-A1, B8, DR3 suggesting the presence of a genetic susceptibility to the disease [57]. In the drug-induced LAD, it has been hypothesized that drugs cause disruption of self-tolerance by a hapten-mediated process or by structural modifications of the basement membrane proteins, and that environmental triggers (*i.e.* infections) may act as co-factors [58, 59]. Vancomycin is the drug most commonly associated with the induction of LAD [42].

About 5% of LAD patients shows concomitant malignancies, with Hodgkin disease, non-Hodgkin's lymphoma and chronic lymphocytic leukemia being the more common [42]. In two case reports LAD was also found to arise together with more than one pathology, among which Hashimoto thyroiditis [60, 61]. The significance of such association remains, however, uncertain.

3.4 Dermatitis herpetiformis

Dermatitis herpetiformis (DH) is an autoimmune itchy skin blistering disease characterized by IgA deposits in perilesional skin. It is strongly associated with the celiac disease (CD), of which it is considered a cutaneous manifestation [23, 42]. CD, also known as gluten sensitive enteropathy (GSE), DH and gluten-induced neuropathies (GIN) are grouped together as gluten-induced autoimmune diseases (GIAD). In agreement, DH and CD have been theorized to share common genetic and immunopathological mechanisms [62]. In fact, both CD and DH have a 95% incidence of the haplotype HLA-DQ2, and small bowel villous atrophy, typical of CD, is encountered in about 70% of DH patients [42, 63]. Epidermal transglutaminase (TG3) is the autoantigen for IgA deposited in the skin, while tissue transglutaminase (TG2) is the autoantigen for IgA accumulating in the small bowel mucosa [63].

Several studies showed that DH associates with additional autoimmune diseases such as AITD, mainly Hashimoto thyroiditis [42, 64–66]. In particular, the percentage of DH

patients positive for anti-TPO autoantibodies found in several studies ranges from 18 to 48% [66].

3.5 Pemphigus

The pemphigus disease includes a group of rare skin and mucous membrane autoimmune blistering diseases characterized by the presence of intraepidermal bullae: the pemphigus vulgaris, the pemphigus foliaceus, the pemphigus erythematous, the pemphigus vegetans, the paraneoplastic pemphigus, the drug-induced pemphigus and the IgA pemphigus [23]. The disease shows an annual incidence comprised between 0.1–0.5/100.000 persons [20]. Depending on bullae localization, it can be also classified as suprabasal, subcorneal or intragranular pemphigus. IgG1 and IgG4 autoantibodies directed against the desmosome desmoglein 1 (Dsg1) and Dsg3 proteins, as well as other desmosome proteins, are held responsible for the pathogenesis of the disease, causing keratinocyte detachment and acantholysis [67, 68]. Genetic factors associated with pemphigus susceptibility involve different HLA class II genes identified in diverse populations analyzed: HLA-DRB1*0402 in Ashkenazi Jews; HLA-DQB1*0503 in non-Jewish population; HLA-DRB1*1404 in the Indo-Asian population; HLA-DRB1*0102 in the Brazilian population [23, 69–71]. Non-HLA genes involved in pemphigus vulgaris, identified by genome-wide association studies (GWAS), include ALCAM, LINGO2, ARPP-21, PATAG, GPD1L and TCF4, while IL4/13 is associated with pemphigus foliaceus [70]. Environmental triggers related to pemphigus are drugs (*i.e.* penicillamine, captopril, and rifampicin), pesticides, gardening materials, metal vapor, sunlight (UVB), viral infection (Herpes), and diet (*i.e.* garlic, onion and leek) [71].

Pemphigus has been described to associate with a number of other autoimmune disorders, including AITD [42, 72–74]. Several studies reported a significantly higher prevalence of anti-TPO autoantibodies in pemphigus patients, compared to the control groups [73, 75, 76]. On the other hand, two independent studies failed to document any increase of anti-TPO autoantibodies serum level in pemphigus patients [46, 77–79]. Thus, also for the pemphigus further clinical investigations on larger case studies are needed to prove its association with AITD.

3.6 Vitiligo

Vitiligo is a chronic autoimmune skin disorder clinically characterized by the progressive loss of melanocytes causing the appearance of well-circumscribed milky cutaneous macules [80]. Histologically, lesional skin shows dermal inflammation, with complete or nearly complete loss of melanocytes at the basal layer (81–84). Based on clinical manifestations, vitiligo has been classified into three major forms: segmental vitiligo (SV), non-segmental vitiligo (NSV), and mixed vitiligo (MV),

defined as the combination of initial SV followed by the occurrence of bilateral NSV patches several months later [80, 81]. Its prevalence has been estimated to be 0.5–1% of the world's population and, owing to its disfiguring effects, it likely has detrimental effects on patient's quality of life and mental health [84–87]. By means of candidate gene association studies, genome-wide linkage studies and genome-wide association studies (GWAS), about 36 genes possibly causing individual susceptibility to vitiligo have been identified [88]. Of them, 90% encodes immunoregulatory proteins implicated in both innate and adaptive immune responses, including the HLA-A*02:01 and HLA-DRB1*04, and about 10% encodes melanocyte-specific proteins, such as tyrosinase [70, 71, 87–92]. Different factors have been linked to the onset of the disease in genetically predisposed individuals, among which cutaneous trauma (Koebner phenomenon), pregnancy, sunburn, exposure to phenolic chemicals and major psychological stress [71, 80, 91, 93]. Patients affected by vitiligo show the presence of autoantibodies directed against TYR (tyrosinase), MCHR1 (melanin-concentrating hormone receptor-1), MART1 (melanoma antigen recognized by T cells-1), gp100 and TH (tyrosine hydroxylase) [23, 92]. The same autoantigens are held responsible for CD8+ T cells activation causing melanocyte apoptosis [23, 92].

The epidemiological evidence demonstrated the association of vitiligo with several other autoimmune diseases [80]. In particular, as above mentioned, vitiligo is present within the APS I, APS II and APS IIIC. In addition, vitiligo is more frequently diagnosed in family members of patients affected by autoimmune diseases, such as IBD, psoriasis, rheumatoid arthritis, type 1 diabetes, systemic lupus erythematosus, pernicious anemia and AITD [81, 94–104]. AITD is the most frequent autoimmune disorder associated with vitiligo [96, 98, 103–108]. In a recent meta-analysis, it was shown that patients affected by vitiligo had a prevalence of AITD of 14.3% and a positivity to thyroid-specific antibodies (*i.e.* anti-TPO, anti-Tg, and TRAb) of 20.8% [109]. In addition, anti-thyroid hormone antibodies (**THAb**) have been detected in 97.5% of vitiligo patients, which suggest for them a possible pathogenetic role [110]. *Vice versa*, the prevalence of vitiligo has been shown to fluctuate between 2.7% to 7% among AITD patients [101, 102, 111, 112]. From these findings, it emerges that the screening of vitiligo patients for thyroid diseases and thyroid autoantibodies could reveal undiagnosed TD or ameliorate the risk assessment of their future onset. Interestingly, in a recent report it has been also demonstrated that about 50% of patients affected by APS III had thyroid hormone antibodies [113].

3.7 Chronic urticaria

Urticaria is a skin disorder characterized by the formation of itchy wheals, which can be classified as: a) acute urticaria when

there is a single manifestation of the disease lasting for no more than 6 weeks; b) chronic urticaria (CU) when disease activity is maintained for more than 6 weeks; c) episodic urticaria when disease activity is intermittent or recurrent [114, 115]. Chronic urticaria affects 0.5–1% of individuals, which experience a significant reduction of life quality [115]. In approximately 45% of CU patients an autoimmune pathogenesis can be documented, while the remaining 55% present with an idiopathic CU [114]. The autoimmune group of patients displays a more severe phenotype, characterized by the presence of IgG directed against either the α subunit of the IgE receptor (Fc ϵ RI) or the IgE itself [114]. Wheals generate following vasodilation, increased blood flow and vascular permeability resulting from mast cell activation and histamine release, along with other inflammatory mediators held responsible for the formation of itchy erythematous lesions [114, 115]. Urticaria wheals originate in the papillary dermis, and they may appear along with angioedema involving the deeper reticular dermis and subcutaneous tissue. Urticaria and angioedema co-exist in about 40% of CU patients, while about 50% have urticaria alone. The remaining 10% of patients have only angioedema [114, 115]. The HLA-DRB1*04 and its related allele DQB1*0302 have been linked to CU [116]. Several etiologic factors are thought to contribute to CU onset in genetically predisposed individuals, such as pseudo-allergens, actual allergens, *Helicobacter pylori* infection, other infections/infestations, autoimmunity/autoreactivity and AITD [117–119].

A number of autoimmune diseases were reported to have a higher prevalence among CU patients compared to the general population, including diabetes, rheumatoid arthritis, psoriasis, celiac disease, vitiligo, pernicious anemia and AITD [120]. As for AITD, there is no clinical or experimental evidence demonstrating a direct connection between the presence of serum anti-thyroid antibodies and CU pathogenesis [121]. However, several epidemiological data suggest an association between CU and AITD, with hypothyroidism and Hashimoto thyroiditis more frequently encountered than hyperthyroidism and Graves' disease [122–126]. The majority of studies documented an increased rate of thyroid dysfunctions (hypothyroidism and/or hyperthyroidism) and thyroid autoantibodies (anti-TPO and/or anti-Tg and TRAb) positivity in patients with CU [121]. *Vice versa*, a higher prevalence of urticaria was found in AITD patients [112, 124, 127]. Of interest are also the observations showing that CU symptoms may ameliorate in response to treatments for thyroid disease (*i.e.* levothyroxine for Hashimoto thyroiditis patients or anti-thyroid drugs for Graves' disease) [125]. In view of these observations, routine screening of CU patients for signs and symptoms of AITD would be worthwhile.

3.8 Alopecia areata

Alopecia areata (AA) is an autoimmune disease characterized by round or oval patches of non-scarring hair loss. The

complete loss of scalp is defined as alopecia totalis, while the complete loss of body hair is defined alopecia universalis. Lastly, ophiasis is a form of AA branded by the loss of head hair with a wave shape [128, 129]. The reported prevalence of AA is about 0.1% to 0.2%, and it is estimated to affect 6 to 7 million people in the United States [128]. The exact pathogenesis of the disease remains to be elucidated, but it is assumed that AA is an organ-specific autoimmune disease mediated by CD4+ and CD8+ T cells, which are typically found in the inflammatory infiltrate around the bulb of anagen hair follicles [130, 131]. These autoreactive immune cells are tough to attack specific epitopes of keratinocytes and melanocytes in the hair follicle [132]. In addition, since the latter is an immune privileged site, disease progression may be facilitated by the unjustified expression of HLA class I genes that lead to the loss of the immune privilege status [133]. As seen for other AISD, genetic and environmental factors appear to contribute to the disease pathogenesis [69, 130, 132]. Both HLA class I and II alleles were found to be associated with AA, with the HLA-DQ3, HLA-DQ7, HLA-DR4, HLA-DR5, and HLA-DPW4 alleles more frequently involved [133]. In addition, a number of further genes, mainly immunoregulatory, have been demonstrated to associate with AA, including CTLA4, ULBP3 and 6IL2/21, IL2RA and others [70, 132]. Clinical and experimental findings indicate that environmental insults (i.e. emotional/physical stressors, hormones and infections) significantly contribute to the autoimmunity process in AA [133].

Supporting the autoimmune genesis of AA, several studies highlighted its association with other autoimmune diseases [103, 129, 133–140]. In fact, AA patients are often diagnosed with type I diabetes, lupus erythematosus, vitiligo, myasthenia gravis, rheumatoid arthritis, ulcerative colitis, scleroderma and mostly with AITD [27, 103, 129, 134–140]. AA may be encountered in the adult APS, and alopecia universalis has also been described in an unusual form of APS III in association with thyroiditis, isolated corticotrophin deficiency, ulcerative colitis and elevated levels of plasma factor VIII [30]. Regarding the association between AA and AITD, one study on 3568 AA patients showed that AITD represents the most common comorbidity with a prevalence of 14.6%, followed by diabetes mellitus (11.1%), psoriasis (6.3%), system lupus erythematosus (4.3%) and other autoimmune diseases [136]. A retrospective study performed on 298 children with AA, screened for thyroid function, revealed that 20% of the analyzed patients had abnormal thyroid tests [132]. Of these, 49% had hypothyroidism mostly due to Hashimoto thyroiditis, and 20% had hyperthyroidism due to Graves' disease [134]. Several other studies documented the presence of TD with positivity for thyroid autoantibodies in about of 15–20% of AA patients [103, 134–140]. In addition, TD has been associated with the most severe forms of AA [103, 140–142]. Interestingly, AA has been observed together with thyroid

hormone resistance syndrome in one family harboring a heterozygous missense mutation of the TR β (thyroid hormone receptor) gene (I353V) without AITD [143]. The authors speculated that the two diseases were causally related, with AA owing either to unresponsiveness of the hair follicle to thyroid hormones or to the abnormal regulation of the hairless gene, encoding a 130 kDa nuclear transcription factor essential for proper skin and hair follicle functions [144].

3.9 Psoriasis

Psoriasis is a common chronic, immune-mediated inflammatory skin disease characterized by the appearance of sharply demarcated erythematous-squamous plaques histologically branded by acanthosis and hyperkeratosis. The prevalence estimated in children ranges from 0% (Taiwan) to 2.1% (Italy), and in adults from 0.91% (United States) to 8.5% (Norway) [145]. Disease severity may vary from few scattered plaques to the involvement of nearly all body surface. Although clinically well characterized, the etiological and pathogenic mechanisms of psoriasis are far from being completely defined [24]. Currently, an ongoing debate exists on whether psoriasis should be considered an autoinflammatory or an autoimmune disease [22, 24]. Anyway, Th1 and Th17 lymphocyte activation by IL-12 and IL-23, respectively, produced by activated dendritic cells, is thought to play a major role in disease progression [145]. Cytokines released by activated Th1 (i.e. TNF α and IFN- γ) and Th17 (i.e. IL-17A, IL-17F and IL-22) lymphocytes are held responsible for keratinocyte proliferation and release of proinflammatory cytokines, chemokines and antimicrobial peptides that further support the inflammatory process [146, 147]. Inflammation appears to be very similar to that observed in antibacterial responses, and that explains why psoriasis lesions rarely become infected [17]. Both genetic and environmental factors significantly contribute to the pathogenesis of psoriasis. The genetic basis is clearly proven by the increased incidence of the disease in relatives of psoriasis patients, and by the higher disease risk observed in monozygotic twins compared to dizygotic twins [24, 148]. Among the recognized susceptibility genes for psoriasis, the HLA-Cw6 is the major risk allele. In addition, genome-wide linkage analyses found out multiple chromosomal loci statistically linked to psoriasis susceptibility (PSORS1-12) and, similarly, genome-wide association studies identified 50 different genetic loci, either tissue-specific or immune-specific, related with an increased risk of disease [70, 71, 149–152]. Environmental factors thought to contribute to disease pathogenesis in genetically predisposed individuals comprise trauma (Koebner phenomenon), streptococcal pharyngitis, stress, drugs (i.e. lithium, anti-malarial, and beta-blockers), smoking, sunlight (UVB), and alcohol [71, 147].

In a recent study, performed on 8214 participants, the association of psoriasis with anti-TPO autoantibodies, TSH and free thyroxine (FT₄) serum levels was evaluated [153]. The authors found no association between anti-TPO antibodies and the psoriatic disease, while a positive, but non-significant, correlation with TSH and/or FT₄ serum levels was evidenced [153]. However, when the authors performed a meta-analysis including other four published case studies, a significant association between psoriasis and anti-TPO autoantibodies positivity, hypo- and hyperthyroidism conditions emerged [153–158].

3.9.1 Molecular mechanisms underlying thyroid disease (TD) and autoimmune skin disease (AISD).

Data above reported indicate that all AISD described have been associated to some extent with TD, mainly AITD. However, on the basis of the available epidemiological findings, TD associations with bullous pemphigoid, epidermolysis bullosa acquisita, linear IgA dermatosis, and pemphigus appear to be weak and require further clinical, epidemiological and experimental data to be proved. On the contrary, strong evidence has surfaced the association of TD with dermatitis herpetiformis, vitiligo, chronic urticaria, alopecia areata and psoriasis, indicating the presence of shared pathogenetic mechanism(s).

The attendance of shared heritable susceptibility genes has been suggested to explain the association between AITD and vitiligo [77]. As above mentioned, 37 and 15 susceptibility genes have been identified for vitiligo and AITD, respectively [88, 159–166]. Genome-wide linkage analysis and candidate gene association studies identified 9 loci involved in both AITD and vitiligo, including organ-specific genes such as those coding for TYR, thyroglobulin (Tg) and thyrotropin receptor (TSHR) [88, 159–161]. Moreover, in families affected by vitiligo and Hashimoto thyroiditis, autoimmunity susceptibility loci (AIS1, AIS2 and AIS3) have been recognized by genome-wide linkage analysis on chromosomes 1, 7 and 8 [165–167]. Among the 27 genes mapping in the AIS1 locus, the forkhead transcription factor D3 (FoxD3) seems to be the most plausible candidate responsible for the simultaneous occurrence of vitiligo and AITD [165, 168]. Furthermore, a single nucleotide polymorphism of the PTPN22 gene has been shown to be shared between vitiligo and AITD patients [88]. Altogether, these observations support the hypothesis of a common genetic background underlying the association between vitiligo and AITD.

Within the same context, it has been recently reported the expression of melanocyte-specific antigens in thyroid tissues of Hashimoto thyroiditis patients and healthy subjects [169]. Thyroid tissues from Hashimoto thyroiditis patients without vitiligo, as well as normal thyroid tissues, were negative for the expression of NKI/beteb, Pmel17, TRP1, HMB-45 and

S100, but positive for the expression of TRP2, lysosome-associated membrane protein 1 (LAMP1) and CD69. Remarkably, TYR expression was shown to occur only in thyroid tissues from Hashimoto thyroiditis patients. In addition, the levels of LAMP1 and CD69 were higher in thyroid from Hashimoto thyroiditis patients compared to normal thyroid [169]. These findings may provide a rationale for assuming the development of vitiligo secondary to Hashimoto thyroiditis. Moreover, with regard to melanocytes as possible targets of the autoimmune response in psoriasis as well as in alopecia areata, it is tempting to speculate that autoimmune mechanisms primarily directed against thyroid tissue may play a role also in the pathogenesis of secondary alopecia areata and psoriatic skin lesions [134, 156]. On the other hand, different skin cell types, including keratinocytes, melanocytes and dermal fibroblasts have been shown to bear functional TSHR and other thyroid-specific antigens (i.e. Tg, TPO, and sodium/iodide symporter (NIS) [170–174]. The expression of TSH itself has been reported in the normal human epidermis, and its intraepidermal immunoreactivity was shown to be up-regulated by TRH and down-regulated by thyroid hormones [174]. In addition, TSH treatment of organ-cultured human skin has been found to strongly increase the expression of the epidermal markers involucrin, loricrin, and keratins 5 and 14, and to stimulate human keratinocyte proliferation *in vitro* [171, 174]. The presence of functional TSHR has been also demonstrated in mesenchymal cells of human hair follicle [175, 176]. Thus, it may be assumed that in patients affected by vitiligo, alopecia areata and psoriasis the activation of the immune system against either melanocyte-specific or thyroid-specific antigens present at skin level may cause a secondary AITD. In this context, it is worth mentioning a recent study, performed on CU patients with or without Hashimoto thyroiditis, in which women with both CU and Hashimoto thyroiditis showed a greater positivity and larger dimensions at the Autologous Serum Skin Test (ASST), and higher skin TSHR expression [177]. Interestingly, TSHR expression positively correlated with ASST measurements and anti-TPO serum levels, suggesting an association between CU, Hashimoto thyroiditis and skin TSHR expression [177]. Finally, it has been demonstrated that about 60% of CU patients have high levels of IgE-anti-TPO autoantibodies, positively correlated with the levels of IgG-anti-TPO autoantibodies, and this could cause autoallergic mast cell activation in CU patients [178].

The role of thyroid hormones in skin development and functions is well recognized [179, 180]. In particular, thyroid hormones have been demonstrated to play a role in fetal epidermal differentiation, hair growth, sebum production, wound healing, epidermal oxygen consumption, keratinocyte proliferation and keratin gene expression [179–186]. In agreement with these observations, the expression of thyroid hormone receptors, as well as that of thyroid hormone deiodinases, has been demonstrated in different skin cell types

[187–191]. Patients affected by hypothyroidism are typically characterized by generalized myxedema with cool, dry and pale skin, while in the hyperthyroidism condition warm and smooth skin with hyperhidrosis may be present [179]. Further clinical manifestations of thyroid hormone alterations affecting skin physiology have been documented in the above cited reports showing that AA may associate with thyroid hormone resistance syndrome in absence of thyroid autoimmunity, and in the study displaying a reduced expression of thyroid hormone receptor (THR) α and retinoid X receptor, the heterodimer partner for THR, in lesional psoriatic skin [141, 189]. In addition, THAb have been detected in the majority of vitiligo patients, as well as in about half of the patients affected by APS III [105, 108, 113]. On the whole, these findings suggest that perturbing thyroid hormone action per se may directly or indirectly contribute to AISD progression.

3.9.2 Conclusions

Knowledge regarding the pathogenesis of AISD has considerably increased over the last decades starting to clarify the molecular mechanisms underlying disease aetiology and progression, as well as the association with other autoimmune disorders. Shared susceptibility genes and antigens identified to date may contribute to elucidate AISD pathogenesis and the association observed between AITD and AISD. Besides that, the reported evidence showing a relationship between dysregulated TSH, either locally produced or from the pituitary gland, thyroid hormone action and AISD warrant further investigations.

Compliance with Ethical Standards

Conflict of Interest Authors declares that they have no conflict of interest.

Ethical approval This article does not contain any studies on animal or human participants performed by any of the authors.

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