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Review

Cellular immunity and immunopathology in autoimmune Addison's disease

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ABSTRACT

Autoimmune adrenocortical failure, or Addison's disease, is a prototypical organ-specific autoimmune disorder. In common with related autoimmune endocrinopathies, Addison's disease is only manageable to a certain extent with replacement therapy being the only treatment option. Unfortunately, the available therapy does not restore the physiological hormone levels and biorhythm. The key to progress in treating and preventing autoimmune Addison's disease lies in improving our understanding of the predisposing factors, the mechanisms responsible for the progression of the disease, and the interactions between adrenal antigens and effector cells and molecules of the immune system. The aim of the present review is to summarize the current knowledge on the role of T cells and cellular immunity in the pathogenesis of autoimmune Addison's disease.

Contents

Abbreviations: 17OH, steroid cytochrome P450 17-alpha-hydroxylase; 21OH, steroid cytochrome P450 21-hydroxylase; AAD, autoimmune Addison's disease; ACA, adrenal cortex autoantibodies; ADCC, antibody dependent cellular cytotoxicity; AIRE, autoimmune regulator; APC, antigen presenting cell; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; APS I, autoimmune polyendocrine syndrome type 1; APS II, autoimmune polyendocrine syndrome type 2; CIITA, class II, major histocompatibility complex, transactivator; CTL, cytotoxic T lymphocyte; CTLA4, cytotoxic T lymphocyte antigen 4; DCs, dendritic cells; FasL, Fas ligand; FcγR, Fc gamma receptor; IFN-γ, interferon-γ; IL, interleukin; IP-10, interferon-inducible protein-10; LT, lymphotoxin; MHC, major histocompatibility complex; MHC2TA, MHC class II transactivator; MIC-A, MHC class I chain-related A; NALP1, NACHT leucine-rich-repeat protein 1; NK cells, natural killer cells; NOD, non-obese diabetic; PRRs, pattern recognition receptors; PTPN22, protein tyrosine phosphatase, non-receptor type 22; SCC, cholesterol side chain cleavage enzyme; StCA, steroid-producing cell autoantibodies; T1D, type 1 diabetes; TcR, T cell receptor; TLRs, Toll-like receptors; TNF, tumor necrosis factor; VNTR, variable number of tandem repeat.

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1. Introduction

In 1855, Thomas Addison suggested that the adrenal glands were vital organs when he described from the autopsies of 11 patients who had succumbed to an apparent "diseased condition of the suprarenal capsules", characterized by wasting and hyperpigmentation (Addison, 1855). Although not immediately acknowledged by the medical community, the original findings of Thomas Addison was subsequently verified by experimental adrenalectomy in animals, and the term Addison's disease was eventually proposed by Armand Trousseau (Brown-Séquard, 1856). At least six of the 11 patients Addison originally studied probably had tuberculous adrenalitis, and in the developing world this remains a prevalent cause of Addison's disease to this day (Patnaik and Deshpande, 2008). However, in one of the 11 cases, an adrenal fibrosis of unknown origin was described by Addison as having "been occasioned by an actual inflammation having destroyed the integrity of the organs, which finally led to their contraction and atrophy". This was probably the first description of autoimmune adrenalitis, which is the major cause of Addison's disease in the developed countries nowadays (80–90% of the cases) (Arlt and Allolio, 2003; Betterle et al., 2002; Myhre et al., 2002).

Autoimmune Addison's disease (AAD) is one of the classic organ-specific autoimmune diseases, resulting from selective destruction of steroid hormone-secreting cells of the adrenal cortex by immune-mediated inflammation (adrenalitis). It may occur isolated, but in at least half of the cases it is associated with non-adrenal organ-specific autoimmunity such as type 1 diabetes (T1D) and/or autoimmune thyroid disease; designated autoimmune polyendocrine syndrome type 2 (APS II); although non-endocrine conditions (i.e. vitiligo and celiac disease) are also typical features (Michels and Eisenbarth, 2009). AAD is also frequently present in the unique disorder autoimmune polyendocrine syndrome type 1 (APS I), most often accompanied by hypoparathyroidism and mucocutaneous candidiasis but also by a range of other endocrine and non-endocrine manifestations (Perheentupa, 2006). In both isolated AAD and AAD in polyendocrine syndromes, steroid cytochrome P450 21-hydroxylase (21OH) is the dominant antigen targeted by the immune system (Erichsen et al., 2009; Soderbergh et al., 2004). Still, how autoimmune adrenalitis is initiated and perpetuated remains enigmatic. The mechanisms behind the obliteration of the adrenocortical cells are largely unknown, but T cells are thought to play a major role. This review will therefore provide an overview of the current knowledge about cellular immunity and immunopathology in AAD.

2. Histopathology

During the course of AAD all three hormone-producing cell-layers of the adrenal cortex are gradually destroyed and replaced by fibrous tissue. As the functional reserve of the adrenal cortex is large, deficiency of its hormones does not appear clinically until at least 90% of the functioning cortical cells have been destroyed (Rosenthal et al., 1978). Residual nodules of adrenal cortex can be seen as the disease progresses, but complete atrophy of the adrenal cortex will eventually occur (Jackson et al., 1988). The histological picture (which is similar in both isolated AAD and in the polyendocrine syndromes) is dominated by a widespread diffuse inflammatory mononuclear infiltrate consisting of lymphocytes, plasma cells and macrophages (Carpenter et al., 1964; Drury et al., 1970; Imam et al., 1988; Irvine et al., 1967). Unfortunately there has never been performed a comprehensive analysis of the cellular and molecular components of the infiltrate, and the mechanism(s) by which the adrenal cortex is destroyed is unknown. However, there is a highly increased expression of class II major histocompatibility complex (MHC) molecules by adrenocortical cells in the active phase of the disease (Jackson et al., 1988). Apparently every single remaining cortical epithelial cell in some glands becomes MHC class II positive, suggesting extensive exposure to interferon-γ (IFN-γ) secreted by activated CD4+ and/or CD8+ T cells (Skoskiewicz et al., 1985; Todd et al., 1985).

3. Genetic predisposition

3.1. HLA risk alleles

A set of genetic, environmental and endogenous factors are required in appropriate combinations in order to initiate adrenal autoimmunity and disease. At present the best characterized factors are the genetic ones, among which most encode proteins involved in antigen presentation and T cell activation. Genetic susceptibility to AAD has primarily been linked to certain class II HLA alleles in the MHC complex. Several reports from different populations have confirmed that the risk for AAD is significantly increased in the presence of the HLA-DRB1*03-DQA1*0501-DQB1*0201 (DR3/DQ2) and DRB1*0404-DQA1*0301-DQB1*0302 (DR4.4/DQ8) haplotypes (Erichsen et al., 2009; Gombos et al., 2007; Maclaren and Riley, 1986; Myhre et al., 2002; Yu et al., 1999). Interestingly, the DRB1*0404 allele is much more frequent among AAD patients than the closely related DRB1*0401 (Myhre et al., 2002; Yu et al., 1999). The protein encoded by HLA-DRB1*0404 (DR4.4) differs from the one encoded by HLA-DRB1*0401 (DR4.1) in only two amino acid residues (Gregersen et al., 1987). These differing amino acids influence the peptide binding capabilities of the HLA molecules (Hammer et al., 1995), which may indicate that peptides from 21OH are particularly well presented to autoreactive T cells in the presence of DR4.4. The biochemical differences in the ability of presenting peptides are due to the fact that DR4.4 has an arginine residue at position 71 of the DR β-chain, while DR4.1 has a lysine residue here (Gregersen et al., 1987; Hammer et al., 1995). Peptides with a negative residue (aspartic or glutamic acid) in the fourth position therefore bind 20–50 fold better to DR4.1 than DR4.4. We used *in silico* prediction tools to search for 21OH peptides preferentially binding to DR4.4 compared to DR4.1, and found a significant association between carriers of the DRB1*0404-DQ8 haplotype and cellular immune responses against a 20-mer peptide consisting of amino acids 342–361 (p342–361) of 21OH among AAD patients (Bratland et al., 2009).

In spite of the intriguing findings regarding DR4.4, it is important to bear in mind that only 15–20% of AAD patient cohorts from different populations are carriers of the DRB1*0404 allele, so other alleles are important as well (Erichsen et al., 2009; Gombos et al., 2007). Recently it was reported that extreme risk for AAD, especially in multiplex families, is strongly associated with the conserved DR3-B8 HLA haplotype (the fully extended haplotype DR3-B8-A1 was less associated) (Baker et al., 2010). Noteworthy, the HLA class I allele B8 was significantly increased in AAD patients independently of DR3. This is an exciting observation, since a B8-restricted T cell epitope of 21OH has just been reported (Rottembourg et al., 2010).

Also in the MHC complex, there is an association between AAD and the 5.1 allele of the non-classical MHC molecule MHC class I chain-related A (MIC-A) (Gambelunghe et al., 1999; Park et al., 2002). It has been suggested that homozygosity for the 5.1 allele of MIC-A in the presence of the high-risk HLA genotype (DR3-DQ2/DR4.4-DQ8) may define subjects with extreme risk of progressing to overt AAD (Triolo et al., 2009). MIC-A is a distant relative of MHC proteins which do not have a role in antigen presentation, but functions as mediators of cellular distress and act as activating ligands for receptors on natural killer (NK) cells and activated cytotoxic T lymphocytes (CTLs) (Spies, 2002; Stephens, 2001).