TOPICAL REVIEW

CTLA-4 and the genetic predisposition to autoimmunity

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Abstract

Due to the wide spectrum of clinical manifestations and their epidemiological dimensions, autoimmune diseases represent an important medical issue. They are the consequence of the loss of immune tolerance to autoantigens, which in turn is a result of the interaction of environmental, as well as genetic factors. The predisposing role of HLA antigens is widely accepted; nonetheless, it does not fully explain the occurrence of autoimmune disorders. In this topical review, we present the current knowledge on the role of some non-HLA genes (ICOS, CD28 and CTLA-4 in particular) in the development of autoimmunity. ***(Fig. 1, Ref. 106.)***

Key words: autoimmunity, genetic predisposition, polymorphisms, CTLA-4, co-stimulation molecules.

One of the elementary functions of the immune system is to distinguish self and non-self antigens. The change from an immune response eliminating a potentially harmful infectious agent to an immune reaction against self-antigens leading to the destruction of tissue is a continuous one. The balance between these two extremes is strictly regulated by mechanisms, which are only partially understood. A disequilibrium in this immune homeostasis can not only lead to uncontrolled infection, but also to the development of autoimmune processes.

Autoimmune disorders affect 5–7 % (1) of the general population, thus representing a major medical problem. Their ethiopathogenesis is complex, since exogenous (environmental) and endogenous factors contribute to their development. As exogenous factors, viruses and bacteria, stress, synthetic chemicals and in the case of thyroid disorders the intake of iodine, are thought to be involved. However, unequivocal evidence for their pathogenetic role is still missing.

The role of genes in autoimmunity

Autoimmune diseases have been observed to cumulate in families. Up to 50 % of patients with Graves' disease have a positive family history for the disorder. Anti-endomysium antibodies, which are highly specific for celiac disease, can be found in 16.1 % of healthy first-degree relatives of affected patients (2).

The fact that in certain individuals more autoimmune disorders can occur at the same time also speaks for the role of genetic factors in the development of autoimmunity. Thus the prevalence of celiac disease is higher in patients with autoimmune thyroid disease (AIT) (3, 4), anti-gliadin and anti-endomysium antibodies are elevated in 3.3 % to 7.8 % of AIT patients (4, 5, 6). The occurrence of AIT in celiac patients has been found to be 14 % to 30 % (5, 7, 8) and that of elevated titres of anti-tyreoperoxidase and anti-microsomal antibodies 14.4 % to 21 % (2, 9, 10). Up to 7.1 % of celiac patients have elevated titres of more than one type of organ-specific autoantibodies (2). In the population of diabetes type 1 (DM1) patients 3.5–6.8 % are affected by celiac disease (11, 12, 13), which is 10 to 20 times the risk in the general population. Anti-transglutaminase antibodies, which are highly specific for celiac disease, are positive in 2.3–11.6 % of diabetic patients (14, 15) and in one third (32 %) of diabetic patients carrying the predisposing HLA-DQ2 allele in the homozygous form (15). In celiac patients, antibodies characteristic for diabetes are present depending on their type in 2.2 % to 6.6 %, or at least one type in 11.1 % of celiac patients. (2, 16, 17).

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Note: According to the new nomenclature of 1995 CTLA-4 is denoted as CD 152. Since the term CTLA-4 is still being used in the majority of scientific literature, we adhered to this.

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A representative multi-centre study demonstrated that the co-occurrence of thyroid disease represents an independent risk factor for the development of celiac disease in diabetic patients (12) and independent studies confirmed, that associated autoimmune disorders predispose to the development of autoimmunity in other organs (18, 19).

The inheritance of autoimmunity

The inheritance of autoimmune disorders is not determined by Mendelian laws, and is complex – polygenic. Thus the disorder is the result of the interaction of a number of genes and environmental factors. Every predisposing gene contributes to the occurrence of disease, however is neither able to cause the disease by itself, nor absolutely necessary for its development.

The degree, to which genes contribute to the development of polygenic disorders, can be estimated from concordance rates in monozygotic and dizygotic twins. The genome is identical only in monozygotic twins, while environmental factors affect monygotic as well as dizygotic twins. In Graves' disease and Hashimoto thyroiditis the concordance in monozygotic twins is 35–75 %, in celiac disease 71 % (20), as compared to only 1–9 % in dizygotic twins (21, 22). The high concordance in monozygotic twins speaks for a strong influence of genetic factors. Nonetheless, in spite of the identical genetic background, the concordance in monozygotic twins never reaches 100 %, which demonstrates either the influence of different environmental factors or post-zygotic genetic modulation.

Autoimmune predisposing genes

Presently, it is known that autoimmune disorders are the result of a pathological autoimmune response directed against self-antigens and thus of a disturbed immune tolerance. It's striking that autoimmune diseases resulting from apparently opposing immune mechanisms (e.g. the destruction of thyroid tissue by cellular immunity mechanisms driven by a Th1 lymphocyte response in Hashimoto thyroiditis opposed to the Th2 response leading to the production of autoantibodies in Graves' disease) can occur in the same family, or even in the same patient. Therefore there have to be predisposing genes, which affect universal immune mechanisms. Cytokines and co-signalling molecules control and modulate the quality and intensity of immune reactions. Hence, their genes are attractive candidates for genetic research attempting to unravel the genetic factors contributing to the development of autoimmunity.

The role of HLA antigens

So far, the unequivocal predisposing role for autoimmunity of only one gene region has been confirmed; this being the HLA region located on the long arm of the 6th chromosome. HLA genes are the "tray" antigen presenting cells (APC) "serve" the antigen to T lymphocytes on. The presentation of antigens represents a key event in the interaction of APCs with T lymphocytes. Modifications in the structure of HLA antigens can affect crucial steps of the immune response such as the quantity of presented antigen. This, in turn, determines the initiation of the immune response, which may be particularly importantant in the case of autoantigens, which are normally presented at levels insufficient for the initiation of an immune response (23). The HLA region is highly polymorphic and the effect of individual polymorphisms on the structure and function of HLA binding sites has still not been completely explored. However, it is well known, that the HLA-DR3 allele predisposes to Graves' disease (24), Hashimoto thyroiditis (25) and together with the HLA-DR4 allele to diabetes type 1 (26, 27). As more HLA alleles can contribute to the development of autoimmune disorders, technical advances have enabled the identification of specific predisposing haplotypes such as HLA DRB1*03-DQB1*02-DQA1*0501 for Graves' disease (28, 29) and DQB1*02 DQA1*0501 for celiac disease (30).

More detailed analysis has show, that the asoociation of autoimmune disorders cannot fully explain the occurence of autoimmunity (31). The genetic risk conferred by HLA polymorphisms has been estimated to be only 36 % (32) and 32–40 % (33) of the overall genetic risk for coeliac disease and diabetes type 1, respectively. The different concordance rates in monozygotic twins and HLA identical siblings with celiac disease (71 % vs 30 %) (30) indicate the effect of genes outside the HLA gene region. This is confirmed by the fact that characteristic predisposing HLA polymorphisms are missing in some affected patients (34, 35). These observations justify the search for predisposing non-HLA loci as in the case of genome-wide screening studies. In this way a number of potentially important predisposing gene regions have been identified. Among these, the 2q33 region of the long arm of chromosome 2 is one of the most promising ones. It harbours the genes of co-signalling molecules CD28, CTLA-4 and ICOS, whose functional variants could affect the immune homeostasis.

Co-signalling molecules and their function

Every autoimmune disorder is the result of a disturbed immune tolerance toward tissue autoantigens. The activation of the T lymphocytes represents a key event in initiation of every specific immune reaction and is a two-step process. First, the antigen is processed and presented in conjunction with HLA molecules on the surface of the APC to a specific T cell receptor (TCR). In order for the T lymphocyte to proliferate and produce activating cytokines further antigen-independent co-stimulatory signals are required (36, 37). These determine, whether a specific immune reaction is initiated on interaction with an antigen. In the absence of co-stimulating signals the engagement of the TCR becomes ineffective and leads to the inability of the T lymphocyte to react to further stimuli. Anergy and apoptosis of the T lymphocyte are the result.

A number of co-signalling molecules are expressed on the surface of T lymphocytes (Fig. 1), whose activation, inhibition and interaction are responsible for keeping up the immune homeostasis and hence the initiation of immune responses against

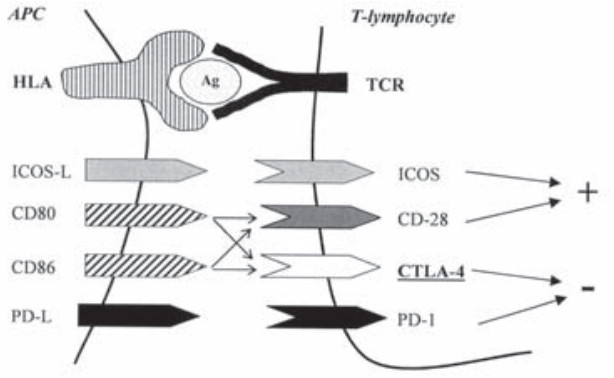

Fig. 1. The interaction of the antigen presenting cell (APC) with a T lymphocyte. The HLA-II molecule presents the antigen Ag to the antigen specific T cell receptor (TCR) Co-stimulation is transmitted via the interaction of B7-type molecules (CD80, CD86, ICOS-L) with their receptors CD28 and ICOS. The interaction of CD80 or CD86 with CTLA-4 (DD152) results in negative signalling to the T lymphocyte, decreased proliferation rate and cytokine production and termination of cell cycle progression.

the right antigen at the right place and time. The equilibrium of stimulatory and inhibitory signals is crucial for both peripheral immune tolerance as well as the protective immune reaction against foreign antigens.

PD-1, CD28, CTLA-4 and ICOS molecules belong to a family of immunoglobulin-like receptor molecules located on the surface of T lymphocytes. By regulating T cell activation in a stimulatory or inhibitory manner they all contribute to immune homeostasis.

CD28 is a co-stimulatory receptor constitutively expressed on the surface of CD4+ T lymphocytes and about a half of CD8+ T lymphocytes (38). Stimulation via CD28 leads to T-lymphocyte proliferation, production of cytokines and acquirement of some T cell effector functions important in specific cytotoxic and humoral immunity (39). CD28-deficient mice are immune suppressed (40) and blocking its ligands by neutralizing antiCD28 and antiCD86 monoclonal antibodies induces T cell anergy (41). CD28 polymorphisms have been excluded to play a major role in the predisposition to autoimmunity in a number of studies (42, 43).

The inducible co-stimulator (ICOS) is another co-stimulatory molecule, whose actions are qualitatively and quantitatively comparable to those of CD28. ICOS is expressed only on the surface of activated T lymphocytes and on interaction with its ligand ICOS-L (B7h, B7-H2) enhances T cell reactions to foreign antigens – proliferation, lymphokine secretion and antibody production by B lymphocytes (44). There is evidence, that ICOS predominantly induces TH2 responses, as demonstrated by the insufficient production of IgG1 and IgG2 antibodies to T-dependent antigens in ICOS-deficient mice. Thus it seems that ICOS has an important role in the interaction of T and B lymphocytes and humoral immunity against T-dependent antigens.

CD80 (B7-1) and CD 86 (B7-2, B70) belong to the B7 family of surface molecules. They are expressed on the same cell type (APC), share the same receptors (CTLA-4, CD28) and have similar functions. CD80 has a higher affinity and avidity for CTLA-4 than CD86 and therefore it is possibly its primary ligand.

CTLA-4 structure and localisation

The cytotoxic T lymphocyte associated antigen (CTLA-4) is the best-explored co-signalling molecule since it is considered to be one of the best candidates for predisposition to autoimmune diseases.

CTLA-4 is a 34-kDa glycoprotein belonging along with CD28 and ICOS to the family of B7 receptor molecules. The B7 binding domain is located extracellularly in the so called complementarity-determining regions. The CTLA-4 molecule has been detected on activated CD4+ and CD8+ T and B lymphocytes. CTLA-4 mRNA transcript production is induced on activation of T lymphocytes (45, 46, 47), leading to an increase of its surface concentration, that is very low in naive cells. Even on activated T lymphocytes the maximum expression of CTLA-4 is only 2–3 % that of CD28 (48). The binding affinity and avidity of recombinant CTLA-4 to CD80 a CD86, however, is 20 to 50 – fold (depending on the ligand) that of CD28 (48, 49). Therefore, although being a low abundance receptor, due to its high affinity to its ligands it is a very potent regulator of T cell function.

Apart form the T cell surface, CTLA-4 can also be found intracellularly. Following transcription and translation, the CTLA-4 molecule binds to the clathrin adaptor complex AP-1 (50, 51) and is transported into vesicles of the Golgi apparatus. (45). During T cell activation, vesicles containing CTLA-4 are quickly transmitted to the interacting TCR and CTLA-4 is translocated to the T cell surface (52), where it can fulfil its inhibitory function. Eventually, it is quickly internalised by the process of endocytosis. Thus it is obvious that only a minority of the synthesized CTLA-4 is situated on the surface of naive T lymphocytes and its concentration is dynamically regulated by the transmission from the intracellular stores to the surface. Intracellular transport may therefore be one of the mechanisms of quantitative regulation of CTLA-4 function.

CTLA-4 function

As opposed to CD28, CTLA-4 has been demonstrated in a number of experimental systems to be a negative regulator of T cell activation (53, 54, 55, 56, 57, 58). Eliminating the CTLA-4 gene sequence from the murine genome by "genetic knock-out" (59) leads to early death within a few weeks after birth from multi-organ failure. This is a result of a lymphoproliferative disorder with massive infiltration of organ tissues by polyclonally proliferating lymphocytes. Blocking the B7-CTLA-4 interaction by monoclonal antibodies under anti-CD3 and anti-CD28 antibody stimulation leads to an increase of antigen specific T lymphocyte proliferation and to an exacerbation of animal experimental models of autoimmune disease (60, 61). Also, CTLA-4 monoclonal antibodies significantly increase the efficacy of xenogenic DNA vaccines in experimental tumour rejection by mice (62). Corresponding humanized monoclonal antibodies (MDX-CTLA-4) in monotherapy as well as adjuvant therapy have shown promising results in oncologic patients (63).

CTLA-4Ig is a recombinant chimeric soluble form of CTLA-4 that is a result of the fusion of the CTLA-4 extracellular domain with the Fc constant region of the immunoglobulin IgG1 heavy chain at the gene level (64). It binds CTLA-4 ligands CD80 a CD86 with high avidity. CTLA-4Ig has been used successfully in prolonging allo-transplant tolerance (65), in suppressing antibody production to T cell dependent antigens as well as in delaying the onset of Th mediated disorders in autoimmune disease-prone animal models (66). CTLA-4Ig is a promising molecule, which can suppress immune reactions in both a fully developed or evolving autoimmune disease.

On B7-CTLA-4 interaction biochemical reactions are initiated which suppress the on-going immune response (67): accumulation of IL-2 and its receptor IL2-R are diminished, eventually cell cycle progression and T lymphocyte proliferation are stopped (68). Due to its high affinity for its ligands, redistributing even small amounts of intracellular CTLA-4 stores to the T cell surface might lead to effective competition with CD28 for the ligands. Therefore, in suboptimal stimulation conditions as present during the presentation of endogenous antigens, CTLA-4 possibly serves as an important immune attenuator of stimulatory signals transmitted via TCR and CD 28. In this way it can control the adaptation of T lymphocytes to the state of immune tolerance and thus unresponsiveness to self-antigens. A defect in this immune tolerance mechanism could be a crucial factor in the development of autoimmune disease.

Soluble CTLA-4 (sCTLA-4)

Cloning CTLA-4 mRNA by RT-PCR a shorter soluble form of CTLA-4 (sCTLA-4) has been discovered in animal (69) as well as human sera. On comparison, the extracellular domains of sCTLA-4 and CTLA-4 were shown to be completely identical in their nucleotide and amino acid sequences. Therefore, sCTLA-4 seems to be a fully functional CD80 and CD86 receptor. The transmembrane region of CTLA-4, which is responsible for keeping the molecule membrane-bound, is missing in the structure sCTLA-4. Elevated concentrations of sCTLA-4 have been found in the sera of patients with autoimmune thyroid disease (70) and myasthenia gravis (71). Also speaking for a role of sCTLA-4 in autoimmune processes are the decreased production rates of sCTLA-4 on activation of T lymphocytes (69,72). In summary we can say, that sCTLA-4 is produced as a soluble functional B7 ligand receptor by T lymphocytes in dependence of their level of activation that interferes with B7-CTLA-4 and B7-CD28 interactions and therefore may affect T cell immune responses in a paracrine manner.

CTLA-4 mechanisms of action

Since CTLA-4 shares its ligands with CD28 and has a higher affinity to them than CD 28, it may compete for them with the alternative receptor (73, 74) and thus prevent CD28 mediated stimulation. Also sCTLA-4 might exert its actions by competition for the ligands, however it is unclear whether sCTLA-4 tips the balance in favour or against the development of autoimmunity, since it prevents the interaction with both, the stimulatory (CD28) and inhibitory (CTLA-4) receptor. The striking similarity of sCT LA-4 with the immunoadhesive molecule CTLA-4Ig speaks in favour of an inhibitory action of sCTLA-4 on T lymphocyte activation. It has been shown, that CTLA-4 inhibits CD28 stimulation. However, inhibitory affects of CTLA-4 in the absence of CD28 (75, 76) clearly demonstrate that CD28-independent inhibitory mechanisms must exist. Functional (75, 76) and biochemical (77) evidence for the direct inhibition of TCR-signalling by CTLA-4, probably by an independent signalling cascade, has been provided. CTLA-4 is constitutively expressed on the surface of a small but significant population of CD25+ regulatory (suppressive) T lymphocytes (Treg) (78). These have a crucial role in keeping up peripheral immune tolerance and the development of autoimmunity. (79, 80). By the action of CTLA-4 these cells might be able to produce factors, which prevent the activation of neighbouring T cells (81). In conclusion, it is clear that the actions of CTLA-4 can not be explained by a single mechanism and evidence exists for a number of mechanisms, that might all act simultaneously, which ads both complexity and importance to the molecule of CTLA-4.

The genetics of CTLA-4

Until recently, only few polymorphisms in the CD28-CTLA-4-ICOS gene region on the long arm of chromosome 2 were known. From these only CTLA4(-318)C/T (82), CTLA4(+49)A/G (83) and CTLA4(AT)n (25, 83, 84) have been examined in more detail in a number of studies.

The CTLA4(-318)C/T polymorphism is located in the promoter region of the CTLA-4 gene. Not surprisingly, it affects the intensity of CTLA-4 expression (85). The CTLA4(+49)A/G exon 1 polymorphism is the only one that alters the structure of the CTLA-4 molecule. The adenine to guanine change leads to an amino acid interchange from treonine to alanine and thus to an insertion of a hydrophobic amino–acid into a highly conservative region of the leader peptide. Although the leader peptide is lost by the time the molecule reaches the surface of the T lymphocyte, it has an important role in directing the synthesized peptide to the membrane of the endoplasmic reticulum and secures its transmission to its lumen (86). Therefore even these slight alterations of the leader peptide may affect the intracellular transport of CTLA-4 and its availability on the cell surface. CTLA4(AT)n is a microsatellite polymorphism of repetitive dinucleotide adenine and tymine sequences at the 3' terminal untranslated region of the CTLA-4 gene. Its numerous polymorphic variants differ in the number of AT dinucleotide repeats. These are thought to represent one type of adenylate-rich elements (ARE), which are known to be the most important determinants of mRNA stability (87).

In a recent study, *Ueda et al.* (88) sequenced the 300 kB sequence in the 2q33 gene region incorporating the CD28, CTLA-4 and ICOS genes and discovered up to 108 different polymorphisms. Of these, four polymorphisms (CT60, JO31, JO30 and JO27-1), which have not been studied so far, were strongly

associated with Graves' disease and diabetes type1 and with low levels of soluble sCTLA-4 mRNA. These new data open an entirely new chapter in the study of the predisposing role of the 2q33 gene region to autoimmunity.

CTLA-4 as a universal predisposing gene

Polymorphisms of the CTLA-4 gene are significantly associated with diabetes type 1 (89, 90, 92) and an increased occurrence of the +49GG genotype has been reported in diabetic patients with positive antiGAD antibodies (89, 91). The association was found to be significant for AIT (92, 93, 94, 95), rheumatoid arthritis (96, 97), Addison's disease (98) and multiple sclerosis (99). The association of the A allele in position +49 with celiac disease (100, 101) is all the more interesting, that in the concept of associated autoimmunity, which is mostly associated with the G allele, it has to be considered problematic. It is improbable, that opposing alleles in the gene of a molecule, with a function that central and universal for any immune response, could lead to different autoimmune disorders, in particular because their co-occurrence is well established. This clearly reveals the limits of association studies, demonstrating that positive findings of significant associations may be the result of strong linkage disequilibrium between the studied locus and the causative gene polymorphism in its vicinity.

Although the above data on CTLA-4 suggest that its gene polymorphisms are associated with particular diseases, they are not sufficient to prove their effect on the development of the autoimmune process. From this point of view, experimental data on the affect of CTLA-4 gene polymorphisms on the function of T lymphocytes are highly relevant. A significantly increased T lymphocyte proliferation rate has been found in +49GG homozygotes as compared to +49AA homozygotes (102). On administration of anti-CTLA-4 monoclonal antibodies during antigen stimulation a dose-dependent increase in T lymphocyte proliferation could be observed, which was dependent on the type of +49 allele. The proliferation rate in +49AA genotype carriers was 1.5-fold, as compared to that +49GG individuals. These data indirectly suggest that the AA genotype leads to better CTLA-4 mediated inhibition, the loss of which on inhibition with anti-CTLA-4 monoclonal antibodies is more prominent (103). On the other hand, the +49GG genotype apparently results in diminished suppression of T lymphocytes, which may result in the expansion of auto-reactive T lymphocyte clones. Also, CTLA-4 mRNA production correlates well with the CTLA-4 polymorphism present, as well as with CTLA-4 expression on the cell surface (103, 104). Fluorescent staining of lymphocytes revealed qualitative differences in the distribution of intracellular CTLA-4 dependent on the +49 genotype (102) An increased mRNA production as well as secretion of the activating cytokine IL-2 was associated with the +49GG genotype. On the molecular level, the treonine to alanine substitution results in increased production of incompletely glycosylated CTLA-4, which may affect intracellular transport and thus CTLA-4 availability on the cell surface (105). Recent studies have demonstrated a correlation of CTLA-4 polymorphisms with soluble sCTLA-4 concentrations in the sera of patients with autoimmune diseases. In individuals affected by myasthenia gravis carrying the long (AT)n alleles a diminished CTLA-4 inhibitory function as well as increased IL-2 serum concentrations and telomerase activity (both markers of T cell activation) were demonstrated (106). The length of (AT)n terminal repeats also correlates with soluble IL-2 receptor concentrations (106).

In summary we can say, that CTLA-4 expression (on mRNA and protein level) as well as its intracellular distribution and production of its alternative splice form sCTLA-4 are affected by CTLA-4 gene polymorphisms. Although these are very subtle alterations, in the light of positive associations of CTLA-4 gene polymorphisms with a wide spectrum of autoimmune disorders, it could be these changes in CTLA-4 and T lymphocyte function that tip the balance of the immune equilibrium in favour of the development of autoimmune reactions.

Autoimmune disorders arise by a complex mechanism in which genetic predisposition undoubtedly plays an important role. Intensive research aimed at unravelling the complex function of co-signalling molecules is the consequence of positive results from genome-wide screening studies, which have been confirmed by numerous association studies and by accumulating knowledge on the function of individual co-signalling molecules and their interactions. Even from the definition of polygenic diseases it is obvious, that there is no single predisposing gene and polymorphisms of many candidate genes need to be found that confer the greatest genetic risk to develop autoimmune disorders. By analysis of their mutual linkage disequilibrium and determination of predisposing haplotypes gene regions with a pathogenetic role can be identified. The 2q33 gene region is a "hot" candidate for being a key non-HLA locus, its polymorphisms being possibly universal predisposition markers for the development of autoimmunity.

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