Adaptive Immunity Is the Key to the Understanding of Autoimmune and Paraneoplastic Inflammatory Central Nervous System Disorders

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There are common aspects and mechanisms between different types of autoimmune diseases such as multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSDs), and autoimmune encephalitis (AE) as well as paraneoplastic inflammatory disorders of the central nervous system. To our present knowledge, depending on the disease, T and B cells as well as antibodies contribute to various aspects of the pathogenesis. Possibly the events leading to the breaking of tolerance between the different diseases are of great similarity and so far, only partially understood. Beside endogenous factors (genetics, genomics, epigenetics, malignancy) also exogenous factors (vitamin D, sun light exposure, smoking, gut microbiome, viral infections) contribute to susceptibility in such diseases. What differs between these disorders are the target molecules of the immune attack. For T cells, these target molecules are presented on major histocompatibility complex (MHC) molecules as MHC-bound ligands. B cells have an important role by amplifying the immune response of T cells by capturing antigen with their surface immunoglobulin and presenting it to T cells. Antibodies secreted by plasma cells that have differentiated from B cells are highly structure specific and can have important effector functions leading to functional impairment or/and lesion evolvement. In MS, the target molecules are mainly myelin- and neuron/axon-derived proteins; in NMOSD, mainly aquaporin-4 expressed on astrocytes; and in AE, various proteins that are expressed by neurons and axons.

Keywords: T cell, B cell, major histocompatibility complex, human leukocyte antigen, multiple sclerosis, neuromyelitis optica spectrum disorders, autoimmune encephalitis, paraneoplastic disease

INTRODUCTION

Various autoimmune and paraneoplastic disorders of the central nervous system (CNS) share many immunological similarities. In these disorders, immunologic tolerance to self-antigens is broken (1). This failure can be on the T cell as well as on the B cell side or on both sides. The reasons why tolerance is broken in autoimmune diseases are multiple and can differ from paraneoplastic diseases (2). In autoimmune disease, the initial trigger that leads to breaking of tolerance is not as well understood (3). Possibly viral, bacterial and fungal antigens that share antigenic properties with self-antigens can result in activation of T or/and B cells that also recognize self-antigens in the CNS (4). Another possibility could be that in certain autoimmune-prone individuals compared

with non-autoimmune-prone individuals, the T and B cell repertoires contain higher quantities of cells with a high avidity for self-antigens that can be activated and can gain access to the CNS in which they find relevant target structures. Such a scenario has been underscored in rodent models of CNS autoimmune diseases (5). In paraneoplastic diseases of the CNS, epitopes from a neoplasm are exposed on antigen-presenting cells to T cells which subsequently also recognize an epitope of similar structural appearance in the CNS (6).

Importantly, the T and B cell epitopes can differ depending on antigen processing in autoimmune disease and possibly also paraneoplastic disease (7, 8). In many autoimmune and paraneoplastic diseases of the CNS, the B cell response is much better characterized as compared with the T cell response (1, 9). T cell help is required for differentiation of B cells into plasma cells and affinity maturation of antibodies (10, 11). There are also B cells which do not require T cell help in autoimmunity, but these do not seem to be of major importance in CNS autoimmunity and CNS paraneoplastic diseases as far as one knows to date (12–14).

ENDOGENOUS FACTORS

Endogenous factors that contribute to the induction of autoimmunity or paraneoplastic diseases are multiple. First, genetics is of paramount importance. Most autoimmune diseases are complex genetic diseases (15). This means that certain allelic variants of genes predispose to autoimmunity. There are also few examples of autoimmune diseases in which single mutated genes predispose to autoimmunity (16). For CNS-directed autoimmune diseases, no confirmed single genes with mutations have been discovered so far. Much work has been done in elucidating genes that contribute to the complex genetic etiologies (17). Most probably also in CNS immune-directed disorders with paraneoplastic origins, complex genetics are of importance. RNA expression levels have been shown to be altered in autoimmune and paraneoplastic diseases of the CNS (18–20). Tissue with altered RNA expression levels as compared with healthy tissue might predispose to autoimmunity and paraneoplastic diseases (21). There is increased understanding that epigenetics is very crucial in susceptibility to autoimmunity and paraneoplastic disorders (22, 23). Much will be learned in the next years regarding epigenetic regulation of immunity and autoimmunity.

EXOGENOUS FACTORS

Much has been discovered regarding exogenous factors that affect autoimmune diseases of the CNS. These exogenous factors cooperate with endogenous factors in susceptibility to autoimmune diseases of the CNS (24). Low vitamin D levels as well as low sun light exposure have been shown to contribute to susceptibility to multiple sclerosis (MS) also independently of other factors (25–27). So far, the influence of vitamin D and sun light exposure has not been defined to the same degree for neuromyelitis optica spectrum disorders (NMOSDs) and autoimmune encephalitis (AE) (28). Smoking has a negative influence on MS (29, 30). This influence is controlled to some degree by human leukocyte antigen (HLA) genes underscoring that HLA-presented autoantigens

are possibly modified and promote a more vigorous autoimmune response (29). It has been shown that in MS there is a change of the gut microbiome (31, 32). Also in NMOSD, changes in the gut microbiome have been observed with overrepresentation of *Clostridium perfringens* (33). In experimental autoimmune encephalomyelitis (EAE), it has been experimentally proven that the gut microbiome contributes to disease susceptibility (34). So far, in most types of diseases it is not well defined what specific bacteria of the gut microbiome drive autoimmune disease. It has been shown that Epstein–Barr virus (EBV) infection has an influence on MS susceptibility (35, 36). The influence is mainly mediated in childhood and most likely affects the T cell repertoire. Even though a direct role of EBV infection in MS lesion development was claimed, this could not be confirmed (37). Also, salt intake has been shown to influence EAE susceptibility (38). So far, it is not clear if levels of salt intake are influencing susceptibility or disease course in MS (39). The elucidation of the influence of nutritional factors in various autoimmune diseases of the CNS is presently investigated in more detail. Regarding paraneoplastic diseases, no such influence has been elucidated so far.

MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)/HLA HAPLOTYPES

Most autoimmune diseases are associated with certain MHC/HLA haplotypes (40). Such associations also exist for some paraneoplastic diseases such as paraneoplastic pemphigus (41). So far, influences of HLA haplotypes on paraneoplastic diseases have not been investigated in much detail. The reason for the haplotype preferences of specific autoimmune diseases is not known.

The most likely scenario for influences of HLA haplotypes on autoimmune diseases indicates that during early tolerance development certain HLA haplotypes select for a T cell repertoire that can be self-biased to certain autoantigens and certain organs (42–44). In the emergence of tolerance, there is selection of a broad range of T cell receptors (TCRs) on various self-antigens. In a first step, only T cells are selected that recognize self MHC-peptide complexes (45–47). In the next step, T cells with TCRs with a too high affinity for such complexes are deleted from the repertoire (48, 49). MHC displayed peptide repertoires influence positive and negative selection (50). Based on the expressed HLA haplotypes, the predetermined T cell repertoire differs in individuals (51, 52). The TCR repertoire has a bias depending on the HLA haplotype in avidity for certain self-antigens (53, 54).

In MHC congenic rat strains, we have shown that there is an autoantigen preference that can result, depending on the expressed MHC alleles, in disease susceptibility or protection from certain diseases (5, 55). Interestingly with increasing complexity of the disease driving autoantigen, the MHC haplotype-dependent effects alleviate (56, 57). Also, we have shown that the amount of autoantigen that leads to disease induction can differ between different MHC haplotypes (5, 58). This means that in one MHC haplotype minute amounts of antigens are sufficient to induce severe disease, while in others much higher amounts would be necessary. These findings underscore the influence of the antigenic load in context with genetic factors. It has been shown that depending on the expressed MHC haplotype,

the cytokine preference of the selected T cell repertoire differs (44, 59). Recently in an experimental model of rheumatoid arthritis (RA), it has been shown that MHC alleles that drive disease are associated with a T helper cell type 1 (Th1) response with secretion of interferon-gamma (IFN-γ) (60). By contrast, protective MHC alleles promoted an interleukin-17 T helper (Th17) cell response. Such a predetermination of cytokine responses to disease-inducing factors is potentially also shaped early in tolerance development and can also contribute to the finding that certain HLA haplotypes predispose to certain autoimmune diseases while others protect from disease.

NEOANTIGENS

Tolerance can be broken by presentation of neoantigens on MHC molecules to T cells recognizing antigens that share structural similarities to self-molecules (61). Recently, it has been shown that neoantigens for presentation on MHC I molecules can be generated by fusion of different fragments of degraded proteins during antigen processing (62). In addition, endogenous neoantigens could evolve by mutation or translational defects. So far, the experimental data that such novel antigens could play a role in the induction or maintenance of autoimmune disease of the CNS are still lacking but an interesting avenue of future research efforts.

Posttranslational modifications of antigens can also lead to induction of autoimmunity (63). This has been shown for RA in which citrullinated epitopes have been shown to be disease inducing (64, 65). Also for MS, a role for citrullination has been proposed but so far there is no proof for the relevance in the experimental or human setting (66, 67). Possibly transpeptidation could be of importance as has been shown in a model of diabetes (68). Changes in glycosylation can affect induction of autoimmunity (69). Also, other types of posttranslational modifications could be of great relevance but have not been investigated in much detail regarding CNS autoimmunity or CNS paraneoplastic diseases. We have shown that even the conformational state of an autoantigen can have different consequences on disease induction capacity (8). Therefore, different conformations of an antigen can be seen be the immune system in a "neoantigenic" fashion and lead to autoimmunity (70).

SPECIFIC DISEASES

Multiple Sclerosis

In MS, the target of the autoimmune response, which seems to be predominantly T cell driven, is mainly directed against proteins of the myelin sheath which is produced by oligodendrocytes (1) (**Table 1**). Myelin basic protein (MBP) is thought to be the major autoantigen which is involved (71, 72). Many researchers have addressed this topic and found additional myelin proteins that can be the target of the autoimmune response (1). There are strong indications that the humoral immune response is important as well (73). Nevertheless, the exact autoantigens driving this B cell response are not known to date in detail. Myelin oligodendrocyte glycoprotein (MOG) is a model antigen which has been shown to be of major importance driving the B cells response in rodent and primate models (74). This protein, which is expressed on

the outer surface of the myelin sheath, seems to be involved in children but not to the same extent in older people with MS in the immune pathogenesis of MS (75). Especially young children with MS with an age under 10 years have a robust anti-MOG antibody response. This finding underscores that potentially early in life immunological events are taking place that predispose to development of MS later in life. CNS lesions of MS patients show antibody-dependent complement destruction underscoring the importance of the antibody response in MS (73). Moreover, proteins expressed on neurons and axons have also been discussed to be targets of the immune response in patients with MS based on work in EAE (76). Recently, in patients with MS, we have shown that peptides can be eluted from MHC molecules from CNS tissue that are recognized by T cells secreting IFN-γ (Th1) (72, 77). Importantly, the increased immune reactivity against such peptides is observed in patients with active MS, i.e., in patients with MS who have an acute bout- or/and contrast-enhancing lesions in the CNS indicating active inflammation. This finding underscores that the adaptive immune response against CNS-derived autoantigens is of significance in MS. Importantly, the T cell reactivity is directed not only against MBP but additional autoantigens and differs between individuals.

Neuromyelitis Optica Spectrum Disorders

In NMOSD, it has been demonstrated that the immune response is targeting aquaporin-4 (AQP4), a water channel protein on astrocytes (127) (**Table 1**). Certain cases of NMOSD are associated with an immune response against MOG (128). In both types, antibody-dependent tissue destruction is of major importance (96). The role of T cells is presently analyzed in more detail (94). In rodent models, it has been delineated that direct injection of anti-AQP4 antibody in the CNS can lead to severe pathology without the presence of T cells (129). Also, antibody-dependent destruction of tissue by complement seems to be of paramount importance and dependent on the antigen conformation and the presence of antibodies (130). It is not excluded that also additional target molecules will be discovered, which are associated with seronegative forms of NMOSD in the future.

Autoimmune Encephalitis

There are a high number of diseases in which the autoimmune response is directed against neuronal antigens (1) (**Table 1**). The target molecules can be localized intracellular or extracellular (9, 98). Some of the intracellular antigens are nuclear proteins. Most of the diseases in which the immune response is directed against intracellular neuronal targets are of paraneoplastic origin. Mainly, CD8+ T cells, which are MHC I restricted, are involved in the immune pathogenesis of these types of AE (131). In affected patients, most important is the search for the underlying neoplasm and its treatment. In addition, immunotherapy is meaningful (132).

In diseases in which the target structures are exposed extracellular as membrane proteins, more diseases are of autoimmune origin and less paraneoplastic. A prototype is the anti-*N*-methyl-ᴅ-aspartate receptor (NMDA) receptor encephalitis in which the NMDA receptor is the target molecule of the immune response

TABLE 1 | Human diseases and autoantigens, main cellular expression, and cellular compartment of expression as well as involved immune responses as presently known.

Disease	(Auto)antigen	Target cell	Main cellular localization	Established role of		
				T cells	Antibodies	Complement
MS	Actin	U	C, CS, ES	+ (72)	ND	ND
MS	Alpha-synuclein	N	U, not P	+ (72)	ND	ND
MS	CNPase, 2′,3′-cyclic-nucleotide 3′-phosphodiesterase	O, N	ES, CS, N	+ (78)	+ (79)	ND
MS	GFAP, glial fibrillary acidic protein	A	C, CS	+ (72)	− (80)	ND
MS	Glutamate dehydrogenase	U	M	+ (72)	ND	ND
MS	MAG, myelin-associated glycoprotein	O	PM	+ (81)	+ (81)	ND
MS	MBP, myelin basic protein	O	PM, C, N	+ (72, 82, 83)	+ (79)	ND
MS	MOBP, myelin-associated oligodendrocyte basic protein	O	PM	+ (84)	+ (79)	ND
MS	MOG, myelin oligodendrocyte glycoprotein	O	PM	+ (85, 86)	+ (87)	+ (88)
MS	Neurofilament-3	N	CS, C, N	+ (72)	+ (89)	ND
MS	PLP, proteolipid protein	O	PM	+ (90)	+ (79)	ND
MS	S100β, S100 calcium-binding protein B	A	E, C, N	+ (91)	− (80)	ND
MS	Survivin	U	C, CS, N	+ (72)	ND	ND
MS	Transaldolase	U	E, C, N	+ (92)	+ (93)	ND
NMOSD	AQP4, aquaporin-4	A	PM	+ (94)	+ (95)	+ (96)
NMOSD	MOG, myelin oligodendrocyte glycoprotein	O	PM	ND	+ (97)	+ (88)
AE	AK5, adenylate kinase 5	N	C, ES	ND	+ (98)	ND
AE	AMPAR, glutamate ionotropic receptor AMPA type	N	PM	ND	+ (99)	ND
AE	Amphiphysin	N	PM, C, CS, GA	ND	+ (100)	ND
AE	CASPR2, contactin associated protein-like 2	N	PM, E, GA	ND	+ (101)	ND
AE	CRMP5, dihydropyrimidinase-like 5	N	C	ND	+ (102)	ND
AE	DNER (Tr), delta-/notch-like EGF repeat containing	N	PM, E	ND	+ (103)	ND
AE	Dopamine receptor D2	N	PM, C	ND	+ (104)	ND
AE	DPPX, dipeptidyl peptidase	N	ES, L, PM, V	ND	+ (105)	ND
AE	GABAaR, gamma-aminobutyric acid type A receptor	N	PM	ND	+ (106)	ND
AE	GABAbR, gamma-aminobutyric acid type B receptor	N	PM	ND	+ (107)	ND
AE	GAD65, glutamate decarboxylase 2	N	C, PM	+ (108)	+ (109)	− (108)
AE	GlyR, glycine receptor	N	PM	ND	+ (110)	ND
AE	Hu, ELAV-like RNA-binding protein 4	N	C, N	+ (108, 111)	+ (112)	− (108)
AE	IgLON5, IgLON family member 5	N	ES, PM	ND	+ (113)	ND
AE	LGI1, leucine-rich glioma-inactivated 1	N	ES, PM	+ (108)	+ (114, 115)	+ (108)
AE	Ma1, paraneoplastic Ma antigen 1	N	N	ND	+ (116)	ND
AE	Ma2, paraneoplastic Ma antigen 2	N	N	+ (108)	+ (117)	− (108)
AE	mGluR1, glutamate metabotropic receptor 1	N	PM, C	ND	+ (118)	ND
AE	mGluR5, glutamate metabotropic receptor 5	N	ES, PM	ND	+ (119)	ND
AE	Neurexin-3a	N	PM	ND	+ (120)	ND
AE	NMDAR, glutamate ionotropic receptor NMDA type	N	PM	+ (108)	+ (121)	− (108)
AE	P/Q type VGCC, calcium voltage-gated channel	N	PM	ND	+ (122)	ND
AE	Ri, NOVA alternative splicing regulator 1	N	N	ND	+ (123)	ND
AE	Yo, cerebellar degeneration-related protein 2	N	N	ND	+ (124, 125)	ND
AE	Zic4, Zic family member 4	N	N	ND	+ (126)	ND

A, astrocytes; AE, autoimmune encephalitis; C, cytosol; CS, cytoskeleton; E, endosome; ES, extracellular space; GA, Golgi apparatus; L, lysosome; M, mitochondria; MS, multiple sclerosis; N, neurons; N, nucleus; ND, not determined; NMOSD, neuromyelitis optica spectrum disorder; O, oligodendrocytes; P, peroxisome; PM, plasma membrane; U, ubiquitous; V, vacuoles; +, positive findings; −, negative findings.

(121). It has been shown that antibodies are most important in this type of diseases and that these antibodies can lead to alteration of cellular function with consequences on behavior (104, 133, 134) or tissue destruction by complement (108). There is a requirement for these antibodies to access the CNS in order to be of disease relevance (135). Recently, a strong influence of a specific HLA haplotype has been shown in anti-LGI1 encephalitis in Koreans (136). So far, the role of T cells has not been assessed in detail in these illnesses but deserves much more attention in future efforts. These diseases are treated by immunotherapy (132, 137). In cases in which the origin is paraneoplastic, the neoplasm needs to be treated in addition to immunotherapy.

Paraneoplastic Disease of the CNS

Why is there such a preference of paraneoplastic CNS disorders for neuronal antigens? Why are there no or only few cases of paraneoplastic MS or NMOSD? Possibly the answer lies in the antigen repertoires that are preferentially displayed by neoplasms. In NMOSD, cases with paraneoplastic origin have been reported (138, 139). In addition, certain brain neoplasms might result in paraneoplastic cases of MS even though such cases have not been interpreted as paraneoplastic diseases so far but rather in the opposite way that the molecular changes in the MS lesion have led to development of the neoplasms (140–142). As discussed in the section regarding HLA haplotypes, the

density of the presented disease-inducing antigen expressed by the neoplasms is potentially an important factor that can lead to paraneoplastic disease. Therefore, a higher density of the presented autoantigen would possibly more likely lead to disease induction.

THERAPEUTIC CONSIDERATIONS

Since the adaptive immune response is of such great relevance in various immunologically mediated disorder of the CNS it is obvious that it should be targeted to halt and possibly cure auto-immune and paraneoplastic diseases of the CNS. Of course, in paraneoplastic diseases always the underlying malignancy should be treated by surgical, radiotherapeutic, and chemotherapeutic approaches, since the eradication of the malignancy with pres-ence of the antigens that drive the disease can possibly lead to an improvement of the paraneoplastic disease condition affecting the CNS. It has been proposed that immunotherapeutic approaches should mainly affect the humoral immune response, since the cellular immune response by CD8+ T cells is of great importance in tumor rejection (143). This aspect needs to be investigated in more depth.

In autoimmune diseases of CNS depending on the dominance of the T or/and B cell response, a rational treatment approach should be used. In most diseases in which autoantibodies are of major importance, the depletion of B cells by rituximab a mono-clonal antibody (mAb) that targets CD20 has been shown to be of great efficacy (144–146). This is the case for AE with membrane molecules as target antigens of the immune response (132, 137, 146). In NMOSD, depletion of B cells is well established as a very efficacious treatment approach (145). Also in MS, depletion of B cells has been shown to be of great therapeutic efficacy (144). This has been underscored by recent data with ocrelizumab a novel human mAb also targeting CD20 (147, 148). Since B cells are very potent professional antigen-presenting cells, the deple-tion of such cells leads also to reduced presentation of antigens to T cells (1, 149, 150). This reduction of antigen presentation in individuals that have been treated with B cell depleting agents is potentially one of the most important immunotherapeutic effects of such a therapeutic approach.

In MS, it has been demonstrated that decreasing numbers of T cells that enter the CNS can result in reduction of contrast enhancing lesions, numbers of new lesions, and improvement of clinical disease score as well (3). Also, modulating T cell responses regarding the way how these cells react in expression of certain immune mediators can affect disease.

The combined depletion of T and B cells by alemtuzumab by targeting CD52 has been shown to be very efficacious in MS (151–153). In a retrospective case series in NMOSD, this approach failed to be effective (154). The reasons are not clear so far, but the authors recommend caution. The approach has not been used in AE so far. This restricted use is most likely because potential side effects are dreaded. Nevertheless, such a therapeutic approach embodies a great potential for cure in selected patient populations.
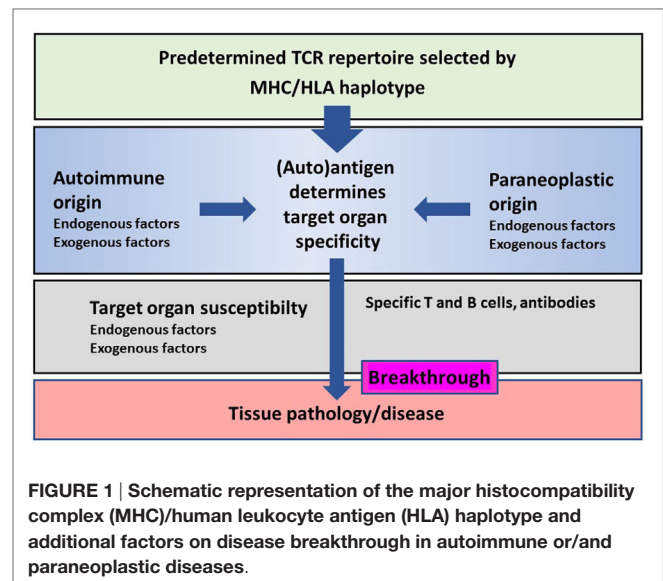

FIGURE 1 | Schematic representation of the major histocompatibility complex (MHC)/human leukocyte antigen (HLA) haplotype and additional factors on disease breakthrough in autoimmune or/and paraneoplastic diseases.

Another approach to affect autoimmune and paraneoplastic diseases would be the blockade of the terminal phase of inflam-mation which is partially mediated by antibodies and that leads to tissue destruction. In this aspect, the use of eculizumab, a mAb depleting the complement factor C5 holds great promise. There are trials ongoing in NMOSD that investigate the efficacy of eculizumab in disease arrest. Initial observations are very promising (155). The use of complement inhibitors could be of great therapeutic potential in MS as well as in certain types of AE in which complement is strongly involved in pathophysiology. So far, the use of eculizumab is restricted due to limited clinical development efforts because of its high cost.

CONCLUSION

There is a great similarity in immune mechanisms of different autoimmune and paraneoplastic diseases of the CNS (**Figure 1**). The adaptive immunity seems to be the main driver of selected organ pathology in autoimmune and paraneoplastic diseases. Specific HLA haplotypes are associated with different autoim-mune and paraneoplastic autoimmune disorders. HLA haplo-types predispose for selection of certain autoantigens that drive such diseases. The phenotype of autoimmune and paraneoplastic diseases of the CNS differs depending on the antigens that drive the immune responses. Neoantigens can possibly contribute to the development of these disorders. The pivotal role of the adap-tive immunity in autoimmune and paraneoplastic diseases of the CNS allows directed immune interventions to modulate T and B cell responses.

AUTHOR CONTRIBUTIONS

RW outlined the subject of the review; searched for, analyzed, and interpreted the literature; wrote the manuscript, and agreed to be accountable for all aspects of the work.

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