Differential requirements of naïve and memory T cells for CD28 costimulation in autoimmune pathogenesis

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Summary. Experimental autoimmune encephalomyelitis (EAE) is the most extensively studied animal model of the human disease multiple sclerosis (MS). In EAE, CNS demyelination is induced by immunization with myelin proteins or adoptive transfer of myelin-reactive CD4⁺ T cells. Since the antigen specificity of the immune response believed to be responsible for the pathology of MS is not well defined, therapies that target aspects of T cell activation that are not antigen specific may be more applicable to the treatment of MS. As a result, understanding the role of costimulatory molecules in the activation of naïve and memory T cells has become an area of extensive investigation. Naïve T cells require two signals for activation. Signal one is provided by engagement of the T cell receptor (TCR) with MHC/peptide complexes and provides antigen specificity to the immune response. The second signal, termed costimulation, is usually provided by B7 molecules on APC to CD28 molecules expressed on T cells and is antigen-independent. This review will discuss our current understanding of costimulation in the induction and perpetuation of EAE, as well as the potential of costimulation blockade in the treatment of MS.

Key words: Autoimmunity, CD28, CNS, Costimulation, T cells

Experimental autoimmune encephalomyelitis as a model for multiple sclerosis.

Multiple sclerosis is hypothesized to be a T cell mediated inflammatory disease of the Central Nervous System (CNS). Inflammatory T cells, macrophages, and their soluble mediators have all been implicated in contributing to the destruction of myelin. This CNS demyelination results in impaired nerve conduction and loss of function. This is a dynamic process and is characterized by a series of recurring episodes.

During recent years, the understanding of immunological mechanisms involved in demyelination has advanced greatly through the investigation of experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS) which can be induced either by immunization of susceptible animals with components of myelin or adoptive transfer of CD4⁺ T cells specific for the myelin antigens (Zamvil and Steinman, 1990; Martin et al., 1992). These adoptive transfer experiments have clearly established that EAE is a T cell-mediated autoimmune disease. Studies of various inbred mouse strains have demonstrated that their ability to develop EAE following immunization with myelin varied significantly (Fritz and McFarlin, 1989). MHC class II background was initially thought to be the most important factor conferring disease susceptibility, but recent studies have shown that other loci are also involved in disease susceptibility (Fritz et al., 1985). Another variable in EAE studies has been the antigen used to induce disease. Myelin basic protein (MBP) and proteolipid protein (PLP) are the major protein components of myelin and have been most often used as the disease initiating antigen (Zamvil and Steinman, 1990; Martin et al., 1992). Although EAE produced by immune responses against MBP or PLP is T cell mediated, it has also been shown that addition of antibodies to myelin oligodendrocyte glycoprotein (MOG), a minor glycoprotein on the outer surface of the oligodendrocyte, dramatically enhances demyelination in MBP-induced EAE (Linington et al., 1988).

Another important observation was that encephalitogenic T cells capable of causing EAE are part of the normal T cell repertoire and are not deleted during thymic deletion (Schluesener and Wekerle, 1985). Interestingly, recent data suggests that MBP is present in the thymus and is capable of stimulating encephalitogenic T cell lines (Fritz and Zhao, 1996). The recent development of a mouse with a transgenic TCR specific for the immunodominant epitope of MBP suggests that in addition to having autoreactive T cells, an additional initiating event must occur for the onset of disease.
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(Goverman et al., 1993). A major focus of recent work by our group has been to examine the difference in costimulatory requirements (CD28-dependence) of naive autoreactive T cells versus memory T cells that have already participated in the initiation of the autoimmune disease response.

T cell activation and costimulation

T cell activation requires two signals (June et al., 1994). Signal one is provided by engagement of the T cell receptor for antigen (TCR). This interaction provides both the antigen-specific component of the immune response as well as genetic (MHC) restriction. The second signal, termed costimulation, is provided by the interaction of an accessory receptor on the T cell with its ligand on the antigen presenting cell. The presence or absence of costimulation determines the outcome of TCR engagement (Schwartz, 1990; Harding et al., 1992; Gimmi et al., 1993; Boise et al., 1995). TCR occupancy in the absence of costimulation induces anergy or apoptotic cell death rather than activation (Schwartz, 1990; Harding et al., 1992; Gimmi et al., 1993).

Several receptor:ligand interactions are capable of providing costimulation. However, the primary signal appears to be through interaction of T cell CD28 with its ligand, either B7.1 (CD80) or B7.2 (CD86) (Thompson et al., 1989; June et al., 1990, 1994). Studies with the CD28 “knockout” (CD28−/−) mice, have demonstrated the importance of CD28 in T cell-mediated immune responses (Shahinian et al., 1993; Lucas et al., 1995). T cells from CD28−/− mice exhibit deficient IL-2 secretion, increased apoptosis, and lower levels of the high affinity IL-2 receptor (CD25) after lectin stimulation (Shahinian et al., 1993).

Some immune responses have an absolute requirement for CD28. For example, CD28−/− mice do not produce TNF-α when challenged with toxic shock syndrome toxin-1 and do not develop fatal toxic shock syndrome (Saha et al., 1996). However, other immune responses remain either partially or completely intact, suggesting the significance of other costimulatory pathways (Shahinian et al., 1993; Lucas et al., 1995). In an autoimmune myocarditis model, CD28−/− mice developed autoimmune heart disease, although it was less severe than that observed in heterozygous littermates (Bachmaier et al., 1996). In addition, breeding NOD mice to CD28−/− mice exacerbated autoimmunity, suggesting CD28 plays an important regulatory role in that disease model (Lenschow et al., 1996). More recently, we have shown that CD28−/− mice develop experimental autoimmune meningitis (EAM) instead of EAE following primary immunization with the neuroantigen myelin oligodendrocyte glycoprotein (MOG) (Perrin et al., 1999a). EAM is characterized by a polymorphonuclear neutrophil-dominated infiltrate within the leptomeninges. In contrast to EAE, there is not infiltrate within the CNS parenchyma.

The B7 ligands can also bind a second T cell receptor, CTLA-4 (CD152) (Freeman et al., 1993a-c). The mechanism whereby CTLA-4 regulates immunity is still being defined and is somewhat controversial. CTLA-4 has been described as both a negative (Walunas et al., 1994, 1996; Waterhouse et al., 1993; Karandikar et al., 1996; Krummel and Allison, 1996; Perrin et al., 1996a; Anderson et al., 1997; Chambers et al., 1997; Hurwitz et al., 1997; Perez et al., 1997) and a positive regulator (Linsley et al., 1992; Wu et al., 1997; Blair et al., 1998) of T cell immunity.

The balance of B7:CD28 and B7:CTLA-4 interactions might determine the outcome of antigen recognition. For example, the opposing effects of costimulatory CD28 and negative CTLA-4 signals can regulate T cell activation and the amplitude of the immune response (Kearnley et al., 1995; Krummel and Allison, 1996; Walunas et al., 1996). B7:CTLA-4 may also provide a signal, which is independent of CD28 that induces peripheral tolerance (Perez et al., 1997).

Other studies have suggested that CTLA-4 provides a costimulatory signal which results in activation or increased cell survival (Linsley et al., 1992; Wu et al., 1997; Blair et al., 1998). B7.1:CTLA-4 interaction can costimulate CD28−/− T cells (Wu et al., 1997). Furthermore, a mutant B7.1, which binds CTLA-4, but not CD28, can induce T cell activation (Wu et al., 1997). Although CTLA-4 inhibits IL-2 secretion by human T cells, it also induces bel-2, a survival gene that protects cells from apoptosis due to IL-2 deficiency. Finally, CTLA-4 can influence T cell differentiation. CTLA-4 blockade in vivo can promote differentiation of IL-4 producing T cells (Walunas and Bluestone, 1998).

Differences in the phenotype of naive and memory T cells

The ability of the immune response to initiate and effect defense upon first contact with an antigen is critical to the defense against foreign pathogens. Understanding the requirements for clonal expansion of T cells specific for a particular antigen is not only important for host defense, but also important in understanding the initiation and perpetuation of an autoimmune response. Cell surface expression of various molecules correlates with the differentiation of T cells into memory cells. Naïve T cells, which have not encountered their antigen since exiting the thymus express high levels of CD45RA or RB and L-selectin and low levels of CD44. In contrast, memory T cells, which have encountered their antigen one or more times, have low expression of CD45RA/RB (or high CD45RO in humans), low L-selectin, and high CD44 (Croft et al., 1994).

Functional differences must exist between naïve and memory T cells to account for host protection against many pathogens following initial infection or immunization. The dependence of memory T cells on costimulation for reactivation has been controversial. We...
and others have demonstrated that proliferative responses to recall antigens do not appear to be dependent on the CD28/B7 pathway (Damle et al., 1992; Croft et al., 1994; Lovett-Racke et al., 1998). However, the recall response may be more efficient in the presence of costimulation, resulting in greater proliferative responses (Yi-qun et al., 1996).

Costimulation therapy for MS

Although there is epidemiological evidence for a viral etiology in MS, there is also ample evidence that MS is a T cell-mediated autoimmune disease. Several recent studies in the EAE model have suggested that exposure to environmental pathogens may result in shifts in the repertoire or expansion of T cell populations crossreactive with myelin antigens that could subsequently mediate inflammatory demyelination (Carrizoza et al., 1998; Ufret-Vincenty et al., 1998). These T cells are appropriate targets for therapeutic intervention and the EAE model is useful for investigating strategies that may eventually be applied to MS.

Neither the viral agent that may possibly initiate MS nor the identity of the myelin-derived autoantigen(s) recognized by the T cells have been defined in MS. Furthermore, T cell antigen recognition is genetically restricted and influenced by the highly polymorphic major histocompatibility complex. Therefore, strategies that target antigen recognition will be difficult to generalize across an outbred patient population.

Costimulation therapy prevents the CD28 signal during antigen presentation. In contrast to the trimolecular TCR:Ag:MHC complex, the B7 ligands and the T cell CD28 are monomorphic. Because the B7 ligands or the CD28 receptor is targeted, costimulation therapy is independent of T cell antigen specificity and is not genetically restricted. Costimulation therapy is specific for activated cells and regulates the T cells mediating an inflammatory response.

Blockade of the B7 receptors with the B7-binding fusion protein CTLA4-Ig, without interfering with TCR/CD3 engagement, prevents T cell activation and may result in antigen-specific tolerance (Schwartz, 1990; Gimmi et al., 1993). CTLA4-Ig is a fusion protein consisting of the extracellular domain of CTLA4 and human IgG1 Fc (Gimmi et al., 1993).

CTLA4-Ig has been used to demonstrate a central role for B7-mediated costimulation in EAE induced by active immunization with myelin protein (Cross et al., 1995; Racke et al., 1995; Perrin et al., 1996b) and by adoptive transfer of myelin-specific lymph node T cells (Perrin et al., 1995; Racke et al., 1995). These studies demonstrated that B7-mediated costimulation plays an important role during initial immune cell interactions, enhancing proliferation and cytokine production, and determining encephalitogenicity. These studies also demonstrated that the effects of CTLA4-Ig were schedule dependent. CTLA4-Ig administration can result in either suppression or enhancement of clinical disease in at least one active model of EAE (Racke et al., 1995).

The roles of the individual B7 molecules, B7-1 and B7-2, during the initiation of EAE have been investigated by us (Racke et al., 1995; Perrin et al., 1996b) and others (Miller et al., 1995; Kuchroo et al., 1995; Vanderlugt et al., 1997). It appears that the effects of anti-B7-1 and anti-B7-2 reagents in vitro and in vivo depend upon the model of EAE studied. However, it is clear that anti-B7-1 treatment ameliorates subsequent disease development, while anti-B7-2 treatment tends to exacerbate disease. The mechanism of differential regulation of EAE by the B7 molecules involves differential regulation of cytokines. The effects of repeated injections of antibody on differential regulation of T helper 1 and T helper 2 differentiation are still unclear (Kuchroo et al., 1995). Recent observations using mice deficient in either B7-1 or B7-2 suggest that both molecules can make significant contributions to the production of both IL-4 and INF-γ (Schweitzer et al., 1997). The effects a single injection involves regulation of the encephalitogenic cytokine TNF-α (Perrin et al., 1996b). Blockade of B7-1 during ongoing EAE prevents epitope spreading and subsequent relapse (Miller et al., 1995; Vanderlugt et al., 1997).

The effect of CTLA-4 and CD28 blockade per se on EAE have also been examined. As expected, CD28 blockade suppressed EAE (Perrin et al., 1999b) and CTLA4 blockade exacerbated clinical disease (Karandikar et al., 1996; Perrin et al., 1996a). Anti-CTLA-4 injection during antigen priming had little effect on disease severity, but resulted in increased mortality after disease onset (Perrin et al., 1996a). This increased mortality is associated with increased production of the pro-inflammatory cytokines IL-2 and TNF-α (Perrin et al., 1996a). These results predict that CTLA4-Ig therapy in MS could prevent B7-CTLA-4 interaction and result in enhanced disease.

In the allogeneic transplantation setting, a variety of polyclonal major and minor histocompatibility antigens can provoke rejection. Therefore, as in MS, the development of antigen specific therapy is not practical. In the transplant setting, the time of antigen priming is known. Because of the more predictable kinetics of the allogeneic immune response to transplants, CTLA4-Ig can be administered with reduced threat of interfering with regulatory T cell development.

In contrast, MS is not treated until after the initiation of the immune response when the clinical consequences of that response are manifest. This is the time that CTLA-4 is likely to be required for exerting its negative regulatory influences. Therefore, administration of CTLA-4Ig to a patient with ongoing autoimmunity may have the undesirable consequence of interfering with regulation of the inflammation. Therefore, directly targeting CTLA-4 to enhance regulation or CD28 to prevent activation may represent better approaches for treating autoimmune diseases such as MS.

Another caveat to costimulation blockade has been
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that studies have primarily focused on B7 blockade during initial T cell interactions. While CTLA-4-Ig is effective at preventing disease induction (Perrin et al., 1995; Racke et al., 1995), it is ineffective when administered later in disease (Perrin et al., 1995). These results could reflect a decreased dependence on memory T cells that mediate autoimmune demyelination (Lovett-Racke et al., 1998; Scholz et al., 1998). On the other hand, injection of anti-B7-1 during the first disease episode ameliorates disease and prevents subsequent relapses (Miller et al., 1995). In addition, we have found that anti-CD28 after the onset of EAE can ameliorate disease as well (Perrin et al., 1999b). Therefore, sustained EAE may be contingent upon newly recruited activated T cells that required B7-1:CD28 cosimulation. The proper therapeutic moxey that specifically targets this interaction and avoids interfering with CTLA-4 mediated regulation may be useful for treating EAE and MS.

Expression of B7 molecules in the CNS during EAE

There is presently some controversy regarding the ability of resident cells of the CNS to act as antigen presenting cells (APC). For these CNS resident APC to be able to activate naive myelin-specific T cells, which have been recruited to the CNS, they would need to express the appropriate costimulatory molecules, B7-1 and B7-2, are not normally expressed in CNS tissues, however they have been shown to be upregulated during disease states. Interferon-γ activated astrocytes have been shown to be able to prime naive antigen-specific T cells in vitro and are also capable of activating encephalitogenic precursors. Our own studies have demonstrated that infiltrating T cells are the predominant cell type expressing B7-1 and B7-2 in the CNS during EAE (Cross et al., submitted). These findings suggest that there are several cell types within the CNS during EAE that have the potential to regulate the local activation of T cells.

MOG, a potential ligand for CD28 or CTLA-4

Another possible confounding unknown in developing costimulation therapy for EAE and MS is represented by MOG, which is expressed externally on the myelin sheath. MOG shares significant homology to the extracellular domain of B7 and it has been proposed that MOG is a member of a larger B7 receptor family (Linsley et al., 1994). The homology of MOG to B7 suggests a potential immune function and, as previously suggested, the identification of it’s receptor(s) would shed light on this possibility (Linsley et al., 1994). The peptide that induces EAM is not from this region and is not homologous to B7 (Perrin et al., 1999).

Although MOG is a minor constituent of the myelin sheath, representing 0.01 to 0.05% of total myelin protein (Amiguet et al., 1992), several recent studies suggest its importance as an important auto-antigen in both EAE and MS (Mendel et al., 1995; Ben-Nun et al., 1996). Immunization of C57BL/6 (H-2b) mice with MOG or amino acids 35-55 of MOG (MOG35-55) results in chronic, nonremitting EAE (Mendel et al., 1995; Ben-Nun et al., 1996). MOG-reactive, CD4+ T cells can adoptively transfer EAE to naive, syngeneic recipients (Mendel et al., 1995). MOG-reactive T cells predominate in MS patients, suggesting their involvement in the pathogenesis of MS (Kerlero et al., 1993; Ben-Nun et al., 1996; Kerlero de Rosbo et al., 1997). In contrast, the incidences of cells which recognize MBP, PLP, or myelin associated glycoprotein are similar between MS patients and control individuals (Kerlero et al., 1993). Therefore, although these cells represent constituents of myelin can also induce EAE, the elevated frequency of MOG-reactive T cells in patients suggests the importance of MOG in MS (Lucas et al., 1995).

Structurally, MOG is a member of the immunoglobulin supergene family, encoded within the mammalian MHC (Pham-Dinh et al., 1993) and therefore an immunological role for MOG has been suggested (Gardinier et al., 1992; Vernet et al., 1993; Slavin et al., 1997). As mentioned above, MOG might be a member of the B7 gene family (Linsley et al., 1994).

To date, no cellular receptor for MOG has been identified. However, MOG’s homology to B7 may suggest an interaction with costimulatory receptors on naïve autoreactive T cells. Several hypothetical models for a protective role of these interactions can be constructed. Conversely, these interactions might contribute to the activation of neuroantigen specific T cells.

For example, MOG may serve as a B7 “decoy”. In this scenario, MOG binding T cell CD28 does not result in a costimulatory signal. Therefore, engagement of the T cell antigen receptor in the absence of costimulation will prevent T cell activation (June et al., 1994; Kearney et al., 1995). The lack of the CD28 signal may also induce T cell anergy or apoptotic cell death (Schwartz, 1990; Harding et al., 1992; Gimmi et al., 1993). That is, the T cell will not be able to respond upon subsequent encounter with antigen, even in the presence of a costimulatory signal delivered by CD28.

The expression of Fas Ligand in the testes (Bellgaur et al., 1995) and the eye (Griffith et al., 1995) are thought to contribute to immune privilege in these sites. Fas receptor on autoreactive T cells entering these sites bind to Fas Ligand, resulting in the apoptotic elimination of these potentially pathogenic T cells. Likewise, MOG binding to CTLA-4 could contribute to immune privilege. MOG:CTLA-4 might result in a negative signal that inhibits T cell activation (Kearney et al., 1995; Kruegeman and Allison, 1996; Walunas et al., 1996) or induce anergy (Perez et al., 1997).

Alternatively, MOG may contribute to T cell costimulation and activation. MOG:CD28 interaction may mimic B7:CD28 interaction. Furthermore,
MOG:CTLA-4 might also contribute to T cell activation. As mentioned previously, in contrast to its negative regulatory functions, CTLA-4 ligation can enhance T cell activation and survival (Linsley et al., 1992; Wu et al., 1997; Blair et al., 1998). These various hypotheses have yet to be confirmed experimentally.

Finally, MOG appears late in the development of the myelina sheath and it has been hypothesized that it is involved in myelina compaction. It is tempting to speculate a two signal model operative in myelination. Perhaps MOG provides a second signal involved in terminating the myelination process, similar to how B7 provides a signal to regulate the immune response.

**CD28 costimulation requirements in MS patients**

Myelin-reactive T cells are present in both MS patients and controls (Pette et al., 1990; Martin et al., 1993), indicating that autoreactive T cells can exist in individuals without pathological consequences. We have attempted to address whether there is a difference in the costimulatory requirements of MBP-reactive T cells in MS patients versus normal controls. The hypothesis tested was that MS patients would have myelin-reactive T cells that were less dependent on CD28-mediated costimulation because they had an activated or memory phenotype. Understanding the costimulation requirements of potentially pathogenic T cells in MS patients is the first step to determining whether therapies based on costimulation have a future in the treatment of MS patients.

We decided to use an approach which would minimize the amount of in vitro manipulation, such as that which occurs with T cell cloning. After repeated in vitro stimulation, T cells would have an activated or memory phenotype. Therefore, peripheral blood lymphocytes (PBL) form MS patients, stroke patients, or controls, were tested. PBL were plated at a density of 2.5x10^6 cells/well in the presence of MBP and either anti-CD28 or control antibody (192 wells/condition). In addition, 48 wells without antigen and each antibody were plated. After 6 days in culture, 3H-methyl-thymidine was added and the wells were harvested on day 7. Positive wells were considered to be those with MBP and antibody (either anti-CD28 or control) that had a counts per minute (cpm) of 2 standard deviations above the mean of the control wells and also having a stimulation index greater than 2 (Lovett-Racke et al., 1998). Figure 1 shows the percentage of the MBP response inhibited by blocking CD28 with anti-CD28 antibody. Approximately 80% of the MBP-specific proliferative response was inhibited by anti-CD28 in MS patients (MS vs. control, p=0.036; MS vs. stroke, p=0.0317; control vs. stroke, not significant). These data suggest that MBP-reactive T cells in MS patients are less dependent on costimulation, a characteristic of activated or memory T cells, than the MBP-reactive T cells in controls or stroke patients. The stroke patients represent an important control, because presumably after an infarct, macrophages that are clearing away the infarcted tissue would have the opportunity to present MBP and other myelin antigens to T cells. However, it has been previously shown that B7-1 is expressed in the inflammatory lesions in the brains of MS patients, but not in cerebral infarcts, making it likely that priming to MBP would occur in MS but not in stroke (Windhagen et al., 1995). As another control, we examined the response to tetanus toxoid (TT). As expected, since most people have had multiple immunizations to TT, both MS patients and controls make an excellent response that is...
not blocked by anti-CD28 (Fig. 1). Another important issue is whether the CD28 costimulatory requirements change over time and whether they may be an additional marker for disease activity. As shown in Figure 2, a patient with relapsing/remitting MS who had a very benign course has an MBP response that was clearly blocked by anti-CD28. After clinical exacerbation, not only is there an increase in the proliferative response to MBP and PLP, there is little ability of anti-CD28 to block the response, suggesting that these T cells have a more activated phenotype.

One might expect that costimulation blockade should completely inhibit MBP-specific proliferation in non-MS patients. One explanation for the incomplete inhibition of MBP-reactive T cell proliferation in healthy controls following CD28 blockade may be due to cross-reactivity of MBP-reactive T cells with foreign antigens. Wucherpfennig described MBP-reactive T cells that could proliferate to a variety of antigens derived from common viral pathogens, suggesting that these “MBP-specific” T cells may have been activated in vivo in controls in response to an infection and may have never encountered MBP, which is sequestered behind an intact blood-brain barrier (Wucherpfennig and Strominger, 1995). Limiting dilution analysis of MBP and TT-reactive T cells demonstrated that the frequency of MBP-reactive T cells able to respond when CD28 was blocked decreased 4-6 fold in controls, suggesting that these T cells are naive (Lovett-Racke et al., 1998). In contrast, there was no significant difference in the frequency of TT-reactive cells for the controls or MS patients. This is consistent with the hypothesis that memory T cells are less dependent on CD28-mediated costimulation to mount a proliferative response. This initial study in MS patients suggests that costimulation therapy may not be successful in inhibiting previously activated autoreactive T cells. However, it may be very effective in preventing the expansion of the autoreactive T cell repertoire, which may play a critical role in the progression of the disease.

Conclusion

In this review, we have discussed costimulation in T cell mediated autoimmune disease. B7:CD28 and B7:CTLA-4 interactions are central in initiating, then regulating the inflammatory T cells that mediate disease. Blockade of B7 has the potential pitfall of preventing regulatory CTLA-4 influences. Therefore, B7 mediated therapy must be carefully timed. Alternatively, direct targeting of CD28 or enhancement of CTLA-4 may circumvent this potential problem. In addition, we have discussed the possibility of the involvement of other B7-like molecules. In particular, MOG, a constitutive component of the myelin sheath, has significant homology to B7 and may interact with CD28 or CTLA-4 within the CNS environment, either activating or regulating autoreactive T cells. Finally, the costimulation requirements of potentially autoreactive T cells in MS patients appears to be diminished, suggesting that early intervention with costimulation therapy may have profound effect in slowing progression of disease.

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