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EDITORIAL

The Role of the Fc Receptor in T-Cell Activation

The repertoire of T-cell specificities is determined during the maturation of T cells in the thymus. The available evidence suggested that T cells are selected into an individual's T-cell compartment on the basis of their ability to recognize auto-major histocompatibility complex (MHC) antigens [12]. T-helper (T_H) cells recognize class II antigens, and cytotoxic cells recognize class I antigens [9, 17]. The specificity of T cells for a given MHC antigen epitope is controlled by its clonotypic T-cell receptor (TCR) [8].

After their recruitment T cells exit from the thymus into the periphery, where they recognize auto-MHC antigen in conjunction with foreign antigen but no longer do so spontaneously. The question arises as to what causes T cells to lose their ability to interact effectively with auto-MHC antigen. There are basically two possibilities: the T-cell receptor either diminishes its affinity for MHC antigen, or the organism installs down-regulatory mechanisms to reduce the consequences of auto-Ia recognition. There is no evidence to support the former assumption, although this possibility has been actively investigated. We believe that the second possibility deserves increased attention, and we present here the idea that the mixed lymphocyte stimulation (MLS) locus encodes a molecule which conveys a down-regulatory signal to T_H cells when these cells interact with completely syngeneic antigen-presenting cells (APC). Whereas the normal function of the MLS signal is to counteract autoreactivity, our model also provides an explanation for the MLS effect. When T cells are mixed with accessory cells from MHC-identical individuals which differ at the MLS locus, this inhibitory signal can occasionally become inoperative, or less effective, and T-cell activation occurs on the basis of unobstructed autostimulation.

The MLS reaction

MLS refers to the activation of T_H cells as a result of coculture with APC which differ at the MLS locus but are otherwise fully syngeneic [2]. Hallmarks of this response are the involvement of the T-cell clonotypic receptor [10] and the genetic restriction to MHC class II antigen [7]. The MLS reaction has been explained as a recognition of a minor, or foreign, antigen (i.e. the MLS product) in an Ia-restricted fashion. However, the very high frequency of responsive T_H cells, estimated to involve 1 in 10 T_H cells, make the explanation as antigen-specific recognition unlikely. Furthermore, although the repertoire of T_H and cytotoxic T cells employs the same set of receptor genes, only T_H cells are responsive to MLS differences.

An alternative explanation for activation by the MLS mechanism must be sought in the realm of regulation. Since recognition of class II antigen by the TCR seems to be an essential component, the MLS reaction can be considered basically as a form of autologous mixed-lymphocyte reaction (AMLR) which may come to pass because the MLS-mismatched APC fails to impart the down-regulatory signal that would normally neutralize the auto-Ia signal (see hypothesis below).

The MLS molecule

The MLS reaction is controlled by an autosomal dominant gene localized on chromosome 1. Five alleles have been discerned on the basis of their ability to stimulate MLS responses [2, 6]. Recently, the gene encoding the Fcγ2b receptor has been mapped to the MLS region [4]. It has first been shown

that the MLS region encodes a surface molecule designated Ly 17 (formerly termed Ly m20 [11]). Subsequent studies revealed that the Ly 17 alloantigen and the Fc receptor are biochemically identical, as antibodies to the Ly 17 polymorphism and the 2.4G2 antibody defining the Fc receptor [13] compete for binding at the cell surface as well as for purified Ly 17 antigen preparations, and coprecipitate the same glycosylated polypeptide (molecular weight, 65,000). Mendelian genetics indicate that the Ly 17 alloantigen is controlled by a locus which is inseparable from the MLS locus [11], suggesting that the product of the latter is the FC receptor (FcR). This assumption is corroborated by the known tissue distribution of the FcR, which is expressed on B lymphocytes, monocytes, macrophages, and Langerhans cells, in short on all those cell types collectively known as APC and as cell types capable of inducing an MLS response.

The hypothesis

We propose that control of the AMLR (i.e. the failure of T_H-cell activation by autologous class II antigen) and the activation of T_H cell by the MLS mechanism are consequences of the same regulatory principle. As stated before, all T_H cells, as a heritage of the selection process in the thymus, are clonotypically restricted and recognize individual class II epitopes through their clonotypic receptors. Mature T cells retain the TCR specificity that facilitated their recruitment in the thymus. Therefore mature T_H cells are subject to persistent latent autoactivation. This autostimulation would normally not reach the threshold necessary for triggering because the T_H cell is down-regulated by interaction with the FcR of APC. Central to our idea is the assumption that the FcR imparts a negative signal to the T_H-cell via an as yet unidentified ligand on the surface of the T_H-cell. Hence auto-MHC stimulation and FcR-mediated down-regulation from an antagonistic signal pair, keeping the T_H cell in balance. The arrival of foreign antigen would tip this balance towards activation by increasing the positive signal through synergistic action with class II antigen. It follows, furthermore, that T_H-cell activation would occur when T_H cells encounter auto-MHC antigen in the absence of a down-regulating signal. We propose that this situation is given in the MLS response when the MLS receptor no longer adequately communicates properly with its ligand as a consequence of genetic divergence. The MLS reaction could therefore be viewed as a decontrolled AMLR.

A number of experimental findings suggest the possible involvement of the FcR in T_H-cell activation. The probable identity between the MLS product and the FcR has already been mentioned. The autoactivation of T_H cells by aggregated immunoglobulin, antigen–antibody complexes, or Fc fragments of immunoglobulin should also be mentioned. Morgan *et al.* [15] described the mitogenicity of these reagents as a pleotropic effect on lymphocytes. The effect can be reduced to an Ia-dependent and APC-dependent activation of T_H cells [16] which in turn release lymphokines to set in motion secondary effects on B lymphocytes. A stimulatory 23-amino acid peptide has been isolated from human immunoglobulin. Jamming of the down-regulatory signal imparted by the FcR would provide a reasonable explanation. We have seen that the mitogenic Fc fragments of aggregated gammaglobulins act synergistically, not additively, with the MLS effect (U. Hammerling & E. Morgan, unpublished). This finding suggests that the MLS constitutes a partial rather than a complete loss of the FcR-mediated inhibitory signal. Contrary to expectation, we found it impossible to influence the MLS reaction or to induce autoactivation with monoclonal Ly 17 or 2.4G2 antibodies. This antibody apparently does not obstruct FcR regions critical for the MLS response. In contrast, polyvalent rabbit antibody to FcR shows a marked synergism with MLS stimulation. Rabbit anti-FcR also induces APC-dependent syngeneic activation of T_H cells (J. Unkeless, E. Pure & U. Hammerling, unpublished). A third relevant observation is the increased sensitivity of antigen-specific T_H-cell clones to MLS-disparate APC [5]. Although such T cells need not be spontaneously MLS reactive, they show a heightened sensitivity when their corresponding antigen is presented by MLS disparate, rather than fully syngeneic, APC. A spectrum of MLS effects can thus be envisaged. One set of cells becomes spontaneously autoreactive upon removal of the negative MLS signal, others experience a stronger net activation through the specific antigen stimulation, and yet another subset seems to remain unresponsive.

Whereas most key observations of the MLS are adequately explained by the proposed mechanism, one seems to be in conflict. The genetics of MLS show dominance of the controlling gene in a heterozygous situation [2], whereas the negative interaction proposed by us would be more in tune with recessive control. An inhibitor should be an inhibitor, whether presented on parental or F_1 cells. Failure to inhibit could be dominant when the MLS product, the FcR, is physically linked to the stimulatory class II molecule. It is of interest that such a physical association between FcR and Ia was indeed described many years ago by Dickler & Sachs [1]. Thus the chance interaction of the TCR with class II antigen associated with a nonfunctional FcR of an MLS-heterozygous APC could lead to activation, because in this circumstance a functional FcR may be sterically excluded from the interaction and unable to exert its restraining effect.

Our hypothesis attributes to the FcR another biological significance beyond its role of binding immunoglobulin Fc domains. We suggest that the primary function is that of a receptor for cell communication, and that the Fc binding function was acquired secondarily. Expression of Ly 17 indeed occurs earlier in ontogeny (and may therefore be evolutionarily older) than the production of immunoglobulin. Both in vivo colony-forming units (CFU) of spleen and in vitro CFU-C express the Ly 17 polymorphism (W. Mark & U. Hammerling, unpublished).

Conclusion

With this hypothesis we continue to emphasize the key role that autorecognition plays in the control of the immune response. T_H lymphocytes learn to discriminate self from non-self MHC antigen in the thymus. They are presumed to be selected into the T-cell pool on the basis of their ability to recognize self-Ia antigen presented to them by Ia-expressing cells. We have proposed that the effective interaction of the TCR with the Ia epitope that initially caused the T cell's recruitment in the thymus leads to the activation of T cells, and this event must therefore be tightly controlled by the organism. It must be effectively down-regulated so as not to occur spontaneously in the periphery. The concept presented here describes one possible mechanism by which autoreactivity may be controlled. We have previously advanced a concept to explain activation of T cells by foreign antigen as an autoreactive event [3]. The description of the MLS reaction on the basis of down-regulated autoreactivity complements this hypothesis. We anticipate that focus on the recognition of the MHC by the T-cell receptor will lead to a unifying concept of T-cell activation in the allo-MLR, AMLR, MLS reaction, and in the antigen-specific response.

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