The thymic contribution to T cell tolerance

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The adaptive cellular immune system recognizes pathogenic antigens by means of the T cell antigen receptor (TCR) which interacts with peptide antigens displayed on the surface of antigen presenting cells (APCs) by glycoproteins belonging to the Major Histocompatibility Complex (MHC). The immune system contains millions of distinct TCR molecules, formed by random rearrangement of the gene segments encoding the antigen-recognizing region of the TCR. Each T cell expresses one specific TCR species (clonotype), unique to the T cell and the clone to which it belongs. Since TCR clonotypes are generated at random, a number of them inevitably are autoreactive: their TCR molecule recognizes one or more antigens derived from the body's own proteins (autoantigens). Such autoreactive clones are kept in check by various tolerization mechanisms which prevent their activation and concomitant autoimmune disease. T cell tolerance comprises both central and peripheral tolerance. The T cell repertoire undergoes central tolerization in the thymus, where numerous immature T cells that recognize autoantigens are induced to undergo apoptosis. While this process of negative selection is generally thought to prevent maturation of many autoreactive T cells, it seems likely that some degree of residual autoreactivity remains in the mature repertoire.

The autoreactivity of an individual TCR clonotype involves more than merely the number of autoantigens recognized by its TCR molecule. Equally important for the immunogenic potential of an autoantigen are (i) its ubiquity: the frequency with which a mature recirculating T cell will encounter the autoantigen as it visits secondary lymphoid tissues throughout the body and (ii) its MHC copy number on the surface of the APCs.

Upon conjugation with an APC, a T cell registers a signal through its TCRs due to the peptides presented on the MHC molecules on the APC surface. This signal is represented [see equation (1)] as a weighed sum over the contributions due to the various peptide/MCH (pMHC) species, with weighing factors corresponding to the copy numbers of the various pMHC species on the given APC. The T cell will be assumed to respond when the TCR signal exceeds a cellular threshold. The *threshold hypothesis* states that the T cell becomes activated when the TCR signal is greater than some threshold value. The T cell may be assumed to have various different threshold values, each corresponding to a particular response. Two important examples of such responses are (i) the naïve T cell's decision to commit to differentiation and proliferation, when the TCR signal, W_{iz}, exceeds the *activation threshold* $W_{\rm act}$, and (ii) the thymocyte's entry into apoptosis, when W_{iz} exceeds the *thymic selection threshold* $W_{\rm thy}$. Variability of the TCR signal due to recognition of autoantigens has two major sources: one is the interclonotypic variability, which arises because different TCR molecules recognize different antigens, and another is the intraclonotypic variability due to random fluctuations in antigen presentation. In order to represent both types of fluctuations we partition the autoantigens (self pMHC species) in $K < \infty$ self-presentation *components*, such that all pMHC species belonging to a given component have two characteristics in common: their frequency of occurring in an autoantigen presentation profile (APP) and their copy number. With this partitioning we write the TCR signal that a T cell of clonotype i registers upon conjugation with an APC (with APP z), as follows

$$W_{iz} = \sum_{k=1}^{K} \hat{n}_{ikz}\, Z_k\, \hat{W}\ , \qquad (1)$$

where the indices i and z indicate that the TCR signal, W_{iz}, depends not only on the TCR clonotype i, but also on the particular APP being conjugated, indexed by z. Here $\hat{n}_{ikz}$ is the number of pMHC species that belong to component k and are (i) presented in APP z and (ii) productively recognized by the TCR of clonotype i; Z_k is the MHC copy number of each autoantigen belonging to component k; and $\hat{W}$ is the TCR signal evoked by a single recognized pMHC molecule. In the component model the description of each APP z is given by the parameter set $\{Z_k\}_{k=1}^{K}$, which tells us for each component k how many self pMHC molecules of an autoantigen belonging to k are present on the surface of the chosen APC.

In order to derive from equation (1) qualitative and quantitative results about the nature of the T cell repertoire pre- and post-selection, we present the statistics of the random variable $\hat{n}_{ikz}$. The model allows us to answer the following questions (by making use of the theory of large deviations): (1) what is the probability that a given negatively selected T cell will recognize a randomly selected autoantigen? and (2) what is the relationship between thymic presentation statistics, peripheral presentation statistics and the contribution of negative selection to T cell tolerance?

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[1] Thymic presentation of autoantigens and the efficiency of negative selection, Hugo van den Berg and Carmen Molina-París, accepted for publication in the Journal of Theoretical Medicine.