MHC based suppression

(First major revision)

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(An outline summary of the suggested role of MBS signal in normal immune responses, Simplified, as short as possible, un-referenced)

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INTRATHYMIC DEVELOPMENT OF T CELLS

The thymus has a crucial role in perinatal development of the immune system, contributing a steady stream of immunocytes, termed T cells which then continues into adulthood, but at a much slower pace. The thymus is first populated with bone marrow derived lymphoid progenitor stem cells which continuously divide to produce a constant stream of new lymphocytes. These undergo somatic mutation and differential splicing of genes to produce a highly variable T cell receptor (TCR). Several hundred copies of this unique TCR are then produced and distributed on the T cell membrane. It is important to note that unlike the B cell receptor the TCR does not undergo adaptation at any

stage. At this point the T cells produced look like small lymphocytes and express both CD 4 and CD 8.

The thymic cortical epithelium expresses high levels of MHC class 1 and class 2 on the surface epithelium, the peptide groove of these MHC molecules being occupied by a peptide derived from self proteins, (and importantly) predominantly MHC derived. Each T cell tests its ability to bind to one combined MHC/Peptide complex, chosen at random. Dependant on whether the chosen MHC molecule is MHC Class 1 or Class 2, the appropriate co-receptor is retained, CD8 for MHC Class 1, CD4 for MHC Class 2.

95% of the newly produced single positive T-cells have random TCRs which, when tested, fail to bind securely to the chosen MHC/peptide. The T cell precursor may have several attempts to produce a TCR that binds to the MHC/peptide, but if it is still unsuccessful the cell undergoes apoptosis. The` positive selection process is completed by setting the baseline, gain and maximum levels for MBS signalling with the bound MHC-derived peptide in the MHC groove. This peptide/MHC combination is thereafter able to deliver maximal inhibitory MBS signal to this same T cell or clones derived from it, because the TCR remains constant.

Immediately after positive selection the T cell then begins to receive a stream of inhibitory MBS signal from repeated contact with self MHC.

The molecules delivering the inhibitory signal are proposed here as being those molecules which are to be found adjacent to the TCR, to have known involvement in activation and regulatory function, yet are not vital to the bare minimum molecular set necessary for activation signal. The identity of the molecular components, role and proposed mechanism in generating the MBS signalling are most easily explained diagrammatically (Gray, DWR, Open Transplantation Journal 2008), but to summarise the principle in one sentence: the extent of mechanical engagement of TCR to those MHC/peptide residues which are OUTSIDE the binding groove is transduced into changes of enzyme induced phosphorylation which normally keeps the activation threshold of the T-cell and thereby the specificity, high.

The CD4 or CD8 T cells, as they are now known then move to the thymus medullary cortical junction where bone marrow derived dendritic cells present large numbers of copies of all 12 expressed MHC molecules which are all bearing a wide range of peptides derived from self proteins (including MHC derived peptides). T cells which have receptors that produce activation signal with any self peptides are deleted by apoptosis,

being allowed through only if there is sufficient MBS signal detected on local sampling, this being necessary to prevent invaders avoiding the immune response by infiltrating the thymus itself.

CIRCULATION OF LYMPHOCYTES

T cells which have survived positive and then negative selection are finally released as naive T cells into the circulation, where their recirculating pathway and targeting to sites of inflammation and potential invader attack is determined by TLRs, chemokines and adhesion molecules of various types, the details of which are beyond the scope of this presentation. However one aspect of the circulation of T cells that is relevant is the need to maintain repeated contact with MHC in order to prevent reduction of the MBS suppression signal causing the activation threshold to reduce, raising the chance of activation of T cells in the circulation. To prevent this unwanted occurrence the T cell receives constant MBS signalling from soluble MHC. Within the lymphoid tissue, if the number of cells presenting MHC should fall, the low MBS signal in the absence of activation signal causes homeostatic proliferation.

PRIMARY ACTIVATION OF A NAIVE T CELL: (MBS NOT PROPOSED TO USUALLY HAVE A ROLE)

The first detection of a peptide/MHC combination that binds strongly to the TCR of a naïve T cell and gives maximum activation signal is probably a rare event but must be responded to, even if it is initiated by just one molecule of peptide binding. Generally the event will take place within organised lymphoid tissue and the stimulating cell will often be a migratory dendritic cell, presenting the peptide bound within the groove of an MHC molecule alongside co-stimulatory molecules which are enhancers acting upon the responding cell to increase the activation signalling. This ensures that activating signal threshold levels are achieved, and normally will over-ride MBS signalling so MBS is not a factor here. Activation and expansion directed by cytokines results in clonal expansion, brought to a halt after 4 or 5 days, then release of these cloned cells, all of which carry the same TCR and are variously called "antigen experienced," "primed""or the term to be used here which is “armed effector cell “ (AEC), They are importantly different from naive T-cells in that their threshold for activation has reduced to a level which no longer requires co-stimulatory signalling, possibly by the mechanism of lowering the gain factor for MBS signalling,

ACTIVATION VS SUPPRESSION OF AECS

If the original site of origin of the peptide is still undergoing some form of attack the local expression of adhesion molecules will target the recently released AEC into the area. And if the same peptide / MHC combination is detected this is the point at which the crucial decision must be taken that distinguishes between the peptide having originated from an invader or from normal tissues which are producing a peptide that has not undergone thymic negative selection.

In the case of an invader attack the local environment is likely to be chaotic with activation of toll- like receptors activating chemokines to draw in leukocytes including macrophagesand various granulocytes as well as T and B lymphocytes. IFN gamma will be released into the local environment, causing both MHC class 1 and MHC class 2. to be expressed by most cells and tissuesT The T cells will be responding to a variety of peptides.

In contrast, if the peptide is self-non-deleted, the tissues giving rise to the peptide will usually be normal, expressing only MHC class 1 at low level, but any initiating event (trauma, local infection, chemicals etc) may already have produced a local inflammatory response to TLR engagement and chemokine production causing the arrival of granulocytes, macrophages and lymphocytes. The arrival of lymphocytes (NK, T and B) coincides with local IFN gamma production to which all cells (with the exception of neurons) respond by up-regulating MHC class 1 and de novo expression of MHC Class 2.

DUAL ROLE FOR MHC MOLECULES EXPRESSED BY NON-PROFESSIONAL APCs

The production of IFN gamma is an early event after recognition of MHC-peptide complex and causes up-regulation of MHC class 1 and de novo of MHC class 2 within minutes.
If an invader is present, either inside or outside the tissue cells, these cells may process invader proteins to peptides and act as APCs, particularly in the case of viruses. Uninfected tissue cells can use their MHC molecules to deliver inhibitory signalling to T cells by preferentially loading self-MHC derived peptides (one of which should be the signature peptide for any T cell). This mechanism would be the way uninfected cells could help minimise "collateral" or "by-stander" damage.

THE T CELL DECISION: DETECTING A SINGLETON VERSUS POLYCLONAL T CELL RESPONSE

To fit the known features of the T cell activation process it is proposed that there are 2 stages to T cell activation: The first corresponds to the familiar activation pathway we currently recognize to be signalling through the TCR/CD3/ITAMS/Zap70 pathway, modified by the MBS signalling, which sets the threshold for activation and specificity. Once the activation threshold has been passed the second stage involves a sampling process of the surrounding cells for MHC/peptide, and takes 4-6 hours.
Firstly IFN gamma is produced to ensure high levels of MHC expression on all cells locally, utilizing a promoter pathway which concentrates on MHC-derived peptide loading. Special interest will be taken in any lymphocytes encountered, because if the cell is from the same clone it will express the same TCR, MHC and signal peptide and each cell will both give and receive high level MBS inhibition. If it is from a different clone the MBS signals will be much less. Therefore all that has to be proposed as the simplest way of delivering a molecular device that gives information on whether the T cells are all from the same clone is that the two cells simultaneously engage each other using the TCR / signature peptide ./ MHC combination. It is possible this “reciprocal MBS signalling” model requires internalization of the sampling T cell TCR, dragging in with it a portion of opposing cell membrane with MHC molecules and TCR attached. The molecular pathways mediating and accumulating the MBS signal are unknown but speculatively involve a phosphorylation / dephosphorylation cascade ending with a final common pathway which allows addition or subtraction of the contribution by a number of factors previously shown to influence tolerance induction. Finally the decision is taken based on crossing a threshold level originally set during positive selection in the thymus.

During the second stage sampling period just described changes are being made within the T cell towards the default outcome if the inhibitory threshold is never reached, which will be T cell activation. However if the inhibitory threshold is in fact reached, the progression to activation is stopped.
he changed properties of the T cell and the reversibility of those changes will depend upon the stage reached, ranging from reversible anergy, to non-reversible suppressor cell function and apoptosis.

SUPPRESSOR CELLS ALSO USE MBS SIGNAL TO

SUPPRESS

Suppressor cells arise as a result of armed effector T cells in the periphery being switched off as described jn the last section, these cells have progressed towards activation to the point that when switched they are non-reversibly anergic and have an active role in switching newly arrived (mostly T-cells from the same clone). To do this, migration is halted and MHC molecules selectively loaded with self MHC-derived peptides expressed at high density on the cell membrane. New T-cells taking the decision will receive a strong inhibitory signal which in the absence of other responding T-cells from other clones will ensure autoimmunity continues to be suppressed.

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