## *Antigen presentation*

*Learning objectives*
*1)Ag processing, presentation and T cell recognition*
*2)Differences in recognition between B and T cells*
*3)Origins of Ag presented by MHC 1 and 2*
*4)Type of info given by MHC 1 and 2 and the ensuing immune response*
*5)Localisation of Ag processing and formation of the MHC peptide complex*
*6)Components of the MHC 1 and 2 'Ag presentation machinery' and their function*
*7)Steps involved in antigen processing and presentation*
*8)Ability to predict the outcome of interference with steps involved in Ag presentation with drugs, biological agents or genetic manipulations*
*9)peptide editing and optimisation of the affinity of the MHC-peptide interaction*

1)Ag processing (biochemistry); presentation and T cell recognition (cellular immunology)
2)B cells recognise native conformation of Ag: carbohydrate; T cells- peptide (processed and) loaded onto MHC
3)MHC1: antigens are generally made within the cytosol; MHC2: antigens are mostly exogenous. Cross presentation and autophagy are exceptions.
4)MHC1- I'm an infected cell- please kill me; MHC2- DC activating the CD4+ T cell ; T cells giving permission to B cells to produce antibodies; T cells giving permission to Macrophages to kill phagocytosed material
5)MHC1: antigen passing from the cytosol to the ER through the TAP molecule. The ends of peptide are chopped off by ERAP, so that the peptide is more of an optimal size (to fit onto the MHC 1) The pMHC complex then travels to the cell surface via the secretory pathway
MHC 2) CLIP binds to the MHC 2 as it makes its way to meet the endosome containing the Ag. The invariant chain contains a signalling motif that leads it to the endosome. HLA-DM then interacts with the MHC 2 so as to displace the CLIP. The peptide made in the endosome has a higher affinity, so it will bind to the MHC, outcompeting CLIP.

Overcoming inherent physico-chemical barriers (TAP transporter allowing the peptide to go from the cytosol to the ER.
*Multifunctional* machinery: proteasome
*Dedicated* machinery: TAP

Drip hypothesis solves two problems:
1) How come antigen presentation can occur before substantial levels of viral proteins (polypeptides) have even been synthesised?
2) How come polypeptides that are synthesised into the ER can become processed by the proteasome, which is not in the ER, but the cytosol?

It is not the polypeptide that is being degraded by the proteasome, but Defective Ribosomal Products.

The immunoproteasome is induced by IFN-*gamma* and produces *longer* peptides than the normal proteasome.

IFN-gamma also upregulates TAP and MHC 1.

Due to the action of **aminopeptidases** in the cytosol, only 1% of all peptides generated by the proteasome go into the ER to bind with MHC.

The proteasome degrades the polypeptide in such a way that the **C ter** of the peptides generate are **hydrophobic**. Due to the action of the aminopeptidase, the N-ter can be quite varied.

TAP selectively and actively transports 9-12 amino acid length peptides into the ER. In mouse it also prefers to transport peptides with hydrophobic C-ter. In human, this doesn't matter. It is NOT biased towards peptides with a particular internal sequence

Many of the peptides that do get transported into the ER are too long to fit into the peptide binding cleft of the MHC 1 molecule. So this is where ERAP comes in.

HLA-A prefers different anchor residues to HLA-B
The peptide loading complex consists of Calnexin, Calreticulin, ERp57(multipurpose chaperones), tapasin, ERAP, TAP

The ½ life of a pMHC is directly proportional to the affinity of the peptide to the MHC. If the affinity is too low, the peptide will fall off. An empty MHC1 molecule is unstable and will be degraded. However, the threshold for affinity that must be met in order for a peptide-MHC complex to reach the plasma membrane must not be too high, or else only a select few peptides can actually be presented.

Ii zipper region generates the alpha beta 3x Ii nonamer.
If it wasn't for the molecular code that guides the MHC 2 to the endocytic route, it would just move towards the ER.

MHC 2 can sample antigen along the entire endocytic route!

Two models of peptide binding onto MHC 2 (both are probably happening)
1. First trim then bind
2. First bind then trim

'Peptide editing' is mediated by HLA-DM