

Chapter 10
 10/30 8:00 am
 Lymphocyte activation

Most immune responses will start with an APC activating a naive T-cell. However, very few T-cells will recognize the antigen that the APC is presenting. Consequently, it may have to present the Ag to a great number of T-cells before a match is found.

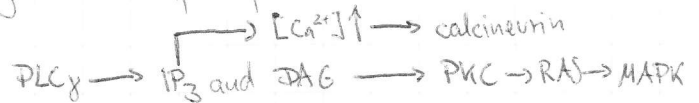
When a match is found, two processes take place: antigen recognition and autocrine stimulation.

⊕ antigen recognition: Upon successful binding, the TCRs will cluster together, packing densely into a region called C-SMAC. The close proximity is important for adhesion and signaling. C-SMAC is surrounded by the P-SMAC region which mostly consists of adhesion molecules (e.g. LFA-1).

⊕ autocrine stimulation: The TCR has no significant cytoplasmic tail, but it is closely associated with ~~various~~ proteins like CD3 (γ E or δ E) and zeta-chains (ζ ← my zeta attempt). Both have ITAM regions with tyrosines that can be phosphorylated by LCK (from the CD4/CD8). Once p'-lated, the ITAMs serve as a SH2 binding site.

An aside on LCK: it is linked to CD4/CD8 via a Zn^{2+} ion and auto-phosphorylates upon CD4/CD8 crosslinking with TCR (when they both bind MHC). While phosphorylated it can p'-late ITAMs. To shut off the signal, CSK will de-p'-late LCK and CD45 will return it to its original conformation.

As said, the p'-lated ITAM now is a SH2 binding site. ZAP70 has two SH2 domains and will bind to ITAM. ZAP70 now can phosphorylate the adapter protein LAT which can recruit two pathways:



If this is the only signal received, the T-cell will die or become anergic. Signal 2 is also needed for activation.

"Signal 1"

absence of LCK or Zap70 leads to selective T-cell defect (STD)

Signal 2

⊕ Signal 2 involves the binding of CD28 to B7. The pathway is not completely known. However, it is known how the signal is turned off: The T cell expresses both, CD28 and CTLA-4, both compete for binding the B7 from the APC. CTLA-4 binding has an inhibitory effect over the CD28 induced pathway.

Both signals are required as they trigger cascades that end with the production of transcription factors. All of the factors are needed to transcribe the α -chain of the IL-2 receptor and to express IL-2 itself. (autocrine signaling)

It may be clinically necessary to reduce T-cell activation (e.g. transplants). This can be achieved by administration of CSA or FK506, both which block calcineurin and thereby signal 1.

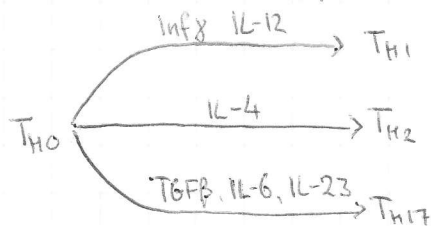
Chapter 11

10/30 9:30 am

T-cell effector function I

The autocrine signal IL-2 leads to proliferation. It binds the IL-2R which consists of 3 subunits: α , β and γ . They are associated with a tyrosine kinase ("Jak") which phosphorylates STAT. STAT then serves as a transcription factor. Not having IL-2 signaling can be compensated for by receiving IL-4 or IL-15 signals. However, the three signaling pathways all require the γ -chain of IL-2R as well as Jak and STAT. Defects here result in severe immune deficiencies (SCID)

At first, the T cell ($CD4^+$) is a T_H0 and will differentiate depending on the signals in its microenvironment:



⊕ T_H1 : These guys activate macrophages. This allows the macrophage to use the respiratory burst to kill pathogens inside its endosomes. Without T_H1 activations, the pathogens can survive in the macrophage.

The Machness experiment showed the importance of this: Macrophages engulfed mycobacteria (tuberculosis) but were not able to clear them in the presence of T cells primed to Listeria. However, co-infection with Listeria allowed for macrophage activation and successful destruction of mycobacteria.

Macrophage activation is important for delayed type hypersensitivity (DTH). Activation occurs by CD40/CD40L interaction and IFN γ from T-cell.

⊕ T_H2 : This $CD4^+$ subclass activates B-cells. A B-cell can internalize its BCR and display the antigen on its MHC II. If a T-cell recognizes the antigen, it will permit the B-cell to proliferate and produce antibodies. In addition to CD40/CD40L binding, IL-4, IL-5 and IL-6 are the signal. Furthermore, CD40/CD40L is required for class switching. A defect here will lead to hyper IgM syndrome.

⊕ T_H17 : As they have been discovered relatively recent, not much is known about them. They seem to be involved with neutrophil activation. They secrete IL-17, IL-6 and TNF.

Chapter 12

10/30 10:30 am

T-cell effector function II

While the last chapter discussed $CD4^+$ T-cell activation, this one will focus on $CD8^+$. When a $CD4^+$ T-cell gets stimulated by a DC, it may also "license" the DC to go and activate $CD8^+$ T-cells. This is accomplished by allowing the DC to express CD40 and 4-1BBL. When a $CD8^+$ T-cell then binds to the DC, it receives signal 1 (positive Ag recognition) and signal 2 (CD40-CD40L and 4-1BB/4-1BBL) and begins IL-2 autocrine stimulated proliferation.

$CD8^+$ can also be activated without $CD4^+$, but the response is shorter and may not be able to clear the pathogen. Also, no memory is established.

The activated $CD8^+$ T-cell is now a functional cytotoxic T-lymphocyte (CTL). It will patrol the peripheral tissues and may encounter the antigen it recognizes bound to an MHC I of a cell infected by an intracellular pathogen.

Without requiring signal 2, the CTL can exocytose its granules in very close proximity to the plasma membrane of the infected cell. Perforins (similar to C9) will create a pore through which granzymes can enter the target cell. Once inside, the granzymes cleave caspases which triggers apoptosis. Apoptosis is preferential over lysis as it does not release virions from the target cell and thus spread the infection. The CTL is not affected by the perforins. It is not known how it prevents damage to itself.

A second killing pathway is the FAS/FASL receptor. It contains a death domain and can activate caspases. However, the perforin mechanism is far more potent.

Viruses may attempt to avoid CTL detection by latent infection, infecting privileged tissues like neurons (no MHC I), downregulating MHC I or mutating some of the recognized epitopes of itself. Adenovirus' E1A blocks MHC I loading, CMV's US11 retrotranslocates the MHC I from the ER to the cytoplasm. Other viruses may block the TAP1/TAP2 transporters.

Fortunately, there are NK cells (they are ~~not~~ T lymphocytes). They will kill cells displaying little/no MHC I or other stress molecules. Also, they can recognize bound antibodies and will kill the cell with a perforin mechanism. (Antibody dependent cellular cytotoxicity = ADCC).

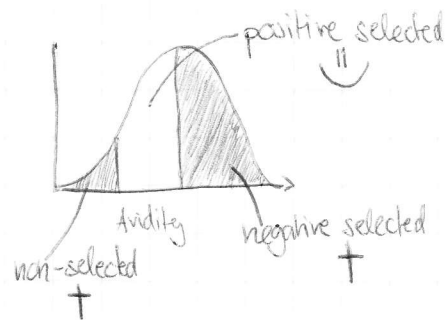
Some tissues, however, do not express MHC I (neurons, RBCs) or display stress molecules during beneficial processes (e.g. wound healing) in those cases, they must express inhibitory signals on their surface to avoid destruction by NK.

Chapter 13/14
10/31 8:00 am
T-cell development and tolerance.

- ⊕ Free-Martin cow
- ⊕ three stages of development: TCR gene rearrangement, selection and maturation.

1) Very similar to Ig heavy chain gene rearrangement. The β chain is arranged first (VDJ) if $\gamma\delta$ rearrangement was not successful (95% of the time). The cell is $CD4^+ / CD8^-$ at this time. The β -chain will now associate with preTCR α and CD3 to test its functionality. If successful, CD4 and CD8 are being expressed and the α chain gene starts to rearrange.

2) Selection can be central (in thymus) or peripheral. The central selection is first positive (T-cell will survive if it can bind MHC*). Afterwards, either CD4 or CD8 is lost and the T-cell undergoes negative selection (T-cell will die if it recognizes self Ag). *non-selected cells will die.



⊕ Since not all proteins are expressed in the thymus, selection must continue in the periphery. Here, the context in which an Ag is encountered is important (Jonger theory). If a T cell only receives signal 1 (MHC-Ag recognition) it either becomes anergic or dies. If signal 2 is present at the same time, an immunogenic response is triggered. Of course, death is irreversible (deletion), yet anergic T-cell can be "woken up" with enough IL-2. If the antigen is at very low levels or sequestered, T cells are ignorant of it. Should they gain access to the antigen or its concentration rises, a response will result.

Treg cells express Foxp3 and can turn off T cells. Important to prevent autoimmunity.