



Lecture 13 - T Cell Activation pt2

▼ Summary

- How naïve T cells migrate to LNs? (homing)
 - selectin, chemokine, and integrin
 - Rolling (L selectin)
 - naive mature b cell express L-selectin or CD62L
 - traveling at fast speed when there is CD62L or L-selectin, on naive t cell in ligand on HEV will slow down and start to roll on side wall
 - allowing them to get chemokine signal produced by HEV (specialized blood vessel in secondary lymphoid organ) add on CCR7 that give them activation signal to activate the integrin LFA-1 expressed on naive t cells
 - the naive cell express chemokine receptor and leads to activation of integrin of LFA-1 also expressed on naive t-cells to bind with ICAM-1 the adhesion molecule on HEV with strong binding affinity → stop arrest allowing them to leave to secondary lymphoid organ
 - Activation (CCR7)
 - exit blood vessel and get into secondary lymphoid organ go to where HEV is reside there until they are activated by DC
 - when DC bring in info → they phagocytose
 - Arrest and Diapedesis (LFA-1:ICAM-1)

- T cell priming by DCs in LNs
 - short contact (LFA-1:ICAM-1 interaction)
 - initiate short interaction btwn naive mature t cells through LFA-1 on t cells and ICAM-1 on DC
 - not stable bc not activated
 - buy time for tcells expressing the TCRs to see whether they can find the peptide MHC complex on the DC that they can recognize
 - if they can recognize it, it can deliver activation signal to LFA-1 and ICAM-1 interaction → provide much stronger binding, stabilize interaction and give naive t-cell a proper time to activate those t-cells
 - stable interaction (TCR:peptide/MHC - signal 1)
 - signal 1 is not enough need another signal → co-stimulatory signal
 - provided by DC through expression of B7 binding to receptor on the t-cell CD28, this interaction give t cell a proper activation signal: signal 1 + 2
 - no signal 2 just 1 cells become anergic → take even more effort to reactivate them

- co-stimulation (CD28:B7 - signal 2)
 - ensure only activate right t cells bc DC don't always express B7 all the time
 - mature signal provided by toll-like receptor or PRRs
 - when PRR recognize PAMP will give them maturation signal so DC can upregulate B7, MHC II, and other molecule associated with antigen presentation can also up regulate the migration homing molecules bc DC need to move to secondary lymphoid organ to activate naive t cells
 - naive t cell become effector cells and down regulate all the cells that help them get there in the first place like L-selectin, CCR7,LFA-1
 - can upregular BLA4, allow them to bind to a different ligand or weaken one instead of ICAM-1 at site of infection can leave secondary lymphoid organ and move to site of infection and do their job.
 - this is how t-cell after they leave thymus and get into secondary lymphoid organ they get proper activated and move to the site of infection and do their job.

- Three mechanisms for preventing activation of self-reactive T cells (all required none sufficient on own)
 - no AIRE and AIRE → expressed in mTEC cells allowing mTEC cells express tissue specific antigens bc there is self antigen in thymus that is normally expressed in the thymus
 - MHC molecules will always be there but no antigen specific to (i.e pancreas, heart, only specific in brain)
 - AIRE is critical to ensure mTEC cells can express those antigens allowing mTEC cells to mediate neg selection against those self-antigens
 - DC are also involved in neg selection even though they don't necessarily express AIRE but can phagocytose mTEC cells
 - are also capable to express tissue antigen, specific antigen on MHC molecule presented to the developing t-cells
 - no AIRE → Apex syndrome (multi-organ)
 - have neg selection against antigen in thymus but not antigen from other tissues
 - development of regulatory t-cells → specific subset of CD4 t-cells that recognize self antigens but instead of being negatively selected out, they become regulatory t-cells through expression of another TF called FOXP3
 - FOXP3
 - can control DC, control their function to activate naive t-cell, or directly inhibit cell reactive t cells
 - IPAC syndrome → pt die from autoimmune disease
 - How activated T cells migrate to tissues
 - Anergic induction is through signal 1 without signal 2
 - signal 1 is more important because having signal 2 nothing will happen
 - after signal 1 and 2, the naive t-cells are now activated

Activation of T cells by DCs

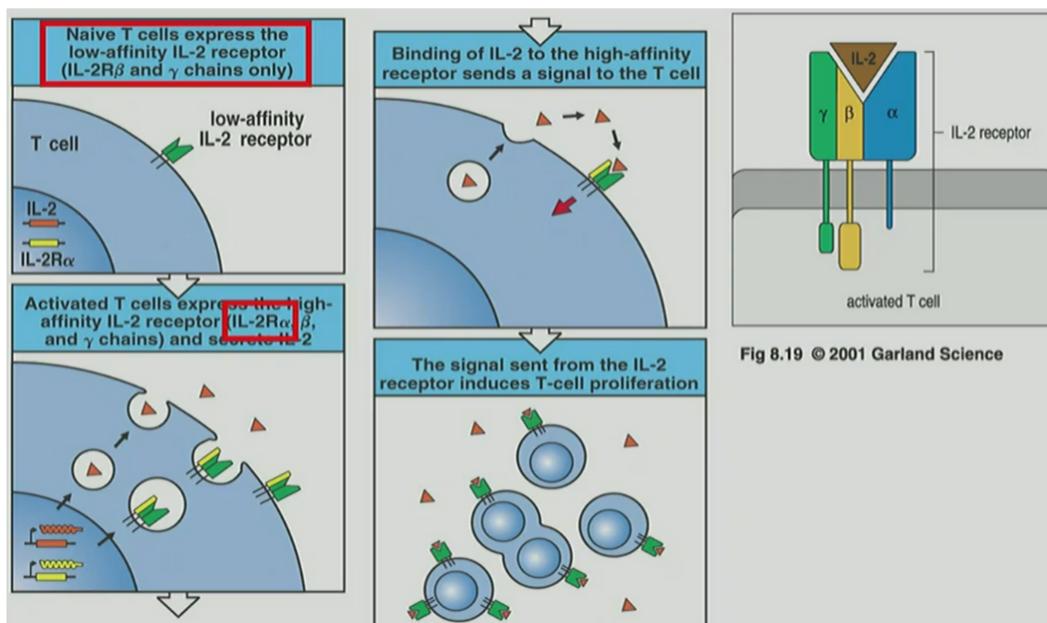
- activated t-cells are now capable of producing GF IL-2 → a cytokine that activate t cell will produce and also drives expansion/ proliferation of this antigen specific t cell
- IL-2 when produced by t-cells is target mostly themselves → autocrine manner but can also act as a paracrine manner



autocrine: act on same cell, expresses both cytokine and receptor for it

paracrine: IL-2 produced by this cell can act on neighboring cells

- IL-2 is needed for t cell expansion
- and IL-2 receptors also expressed on t cell
- in naive t-cell express a low affinity IL-2 receptor, composed of two subunits: beta and gamma chain
- but during t cell activation, when t cell receives signal 1 and 2, properties of t-cell activation will lead production of IL-2, but IL-2 high affinity receptor, alpha chain
- when alpha chain pair up with beta and gamma chain, gives us high affinity IL-2 receptor
- will also express IL-2 receptor alpha chain makes IL-2 more sensitive



- immune cells interact with each other
- CD4 can also come back and further activate DC → induction of a ligand → CD40 ligand on the activated CD4 t cells to bind to receptor on CD40 DC

- Dc express CD40 and naive t-cell do not express CD40 ligand
- activate T-cell not only produce IL-2, high affinity IL-2 receptor, upregulate CD40 ligand
- this helper t-cell through expression of CD40 ligand can help DC
- CD4 t cell can also help DC → DC licensing

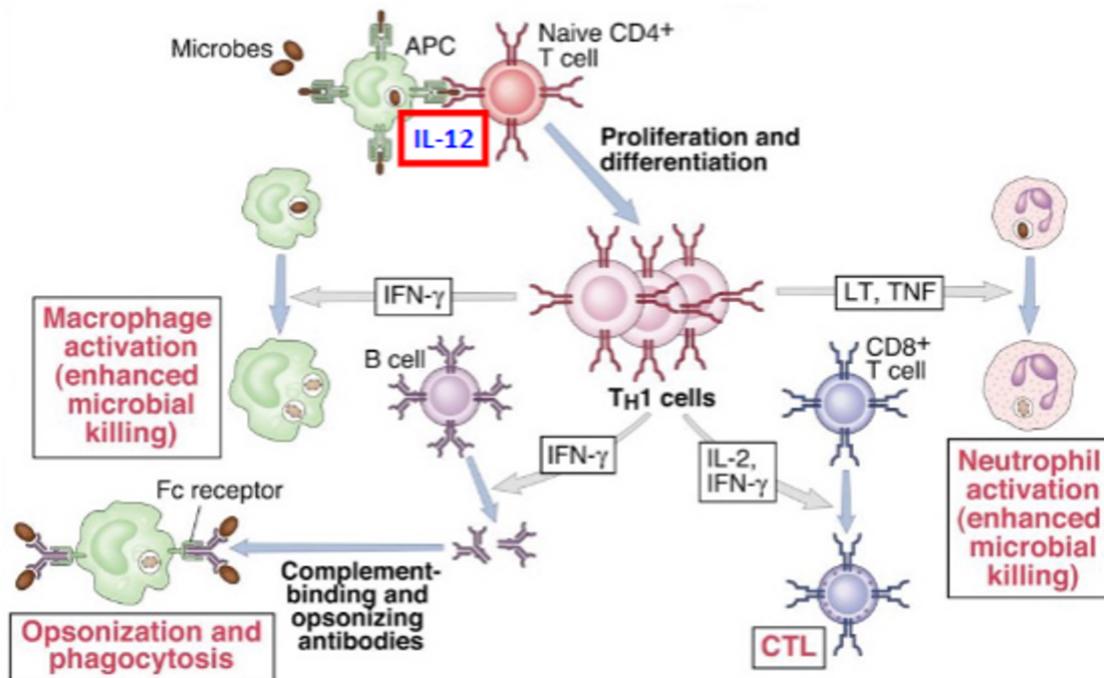


DC Licensing: CD40 stimulation by MHC restricted, antigen-specific CD4 effect t cells enhances DC survival and effector function as well as improves their capacity for cross presentation of antigens for CTL priming

- t cell license cell inside and tell them to do a better job
 - DC can now live longer and activate other t cell
 - so many different peptide, so DC can activate many different t cell
 - but CD40 make DC live long enough to do their job and making them a better APC
 - yes, CD4 t cell affect DC ability to activate CD8 t cells
- Singal 1 → TCR signal
- Signal 2 → costimulatory signal
- signal 3 → cytokine provided by DC

- Dc when they encounter pathogens, phagocytose the pathogen can present antigens, and recognize pathogen through their PRRs, stimulation through the engagement through PAMP is actually not just non-specific mature DC but instruct them to produce the right cytokines
 - that give CD4 helper t cell to activate another instruction to tell them what they need to become
 - dealing with virus → want macrophages, neutrophils
 - CD8 t cells, NK cells → want cells to deal with pathogens
 - those pathogens half the time will act on PRRs to give them DC a signal to produce cytokines that are TH1 driven, so cytokine that is produced by DC act on CD4 t cell together with signal 1 and 2 (proper activation - 2)
 - order of importance
 - not in Th1 or TH2 but at TH0 because they are not good at anything rn
 - but with cytokine produced by DC, become TH1 cell
 - infected with parasite (big) → IgE produced in endosinophil help recognize parasite and attack them
 - need production of antibody
 - want TH2 cells → have PRR recognizing PAMPS on parasites will produce the cytokines that will drive TH2 differentiation → get Th2 cells
 - signal 3 is important to tell TH cells that t-helper cells to differentiate to right type of t-helper cell you need at given infection
 - IL-12 → cytokine drive Th1 differentiation → interferon gamma
 - IL-4 → cytokine → Th2 differentiation → IL-4
 - can then produce cytokines to help their target cell
 - effector helper cells their function mostly decided by what type of cytokine they produce

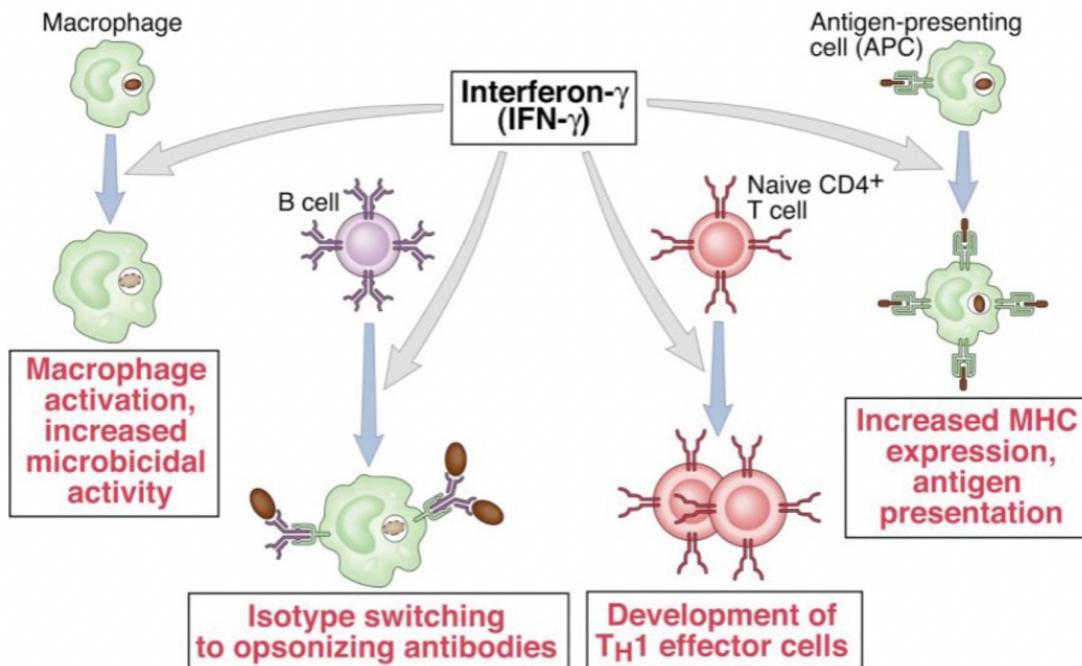
Effector functions of Th1 cells



- APC provide our signal 3 will develop TH 1 cells
- TH1 cell are also healthy cells
- TH1 cell will help b cell in a way that will make the b cell antibody isotype switch to make antibody that facilitate pahgocytosis
 - opsonization → important to deal with antigens that need Th1
- also need to get green light → need to interact with b cell that they help → act on b-cell give b cell instruction to isotype switch to the one that is good for opsonization bc that is the antibody we need to deal with given infection
- not non-specific, they help b-cell they interact with and tell them to make antibody with right isotype that is good for opsonization
- help make Cd8 t cells stronger, neutrophils

- can produce different cytokines

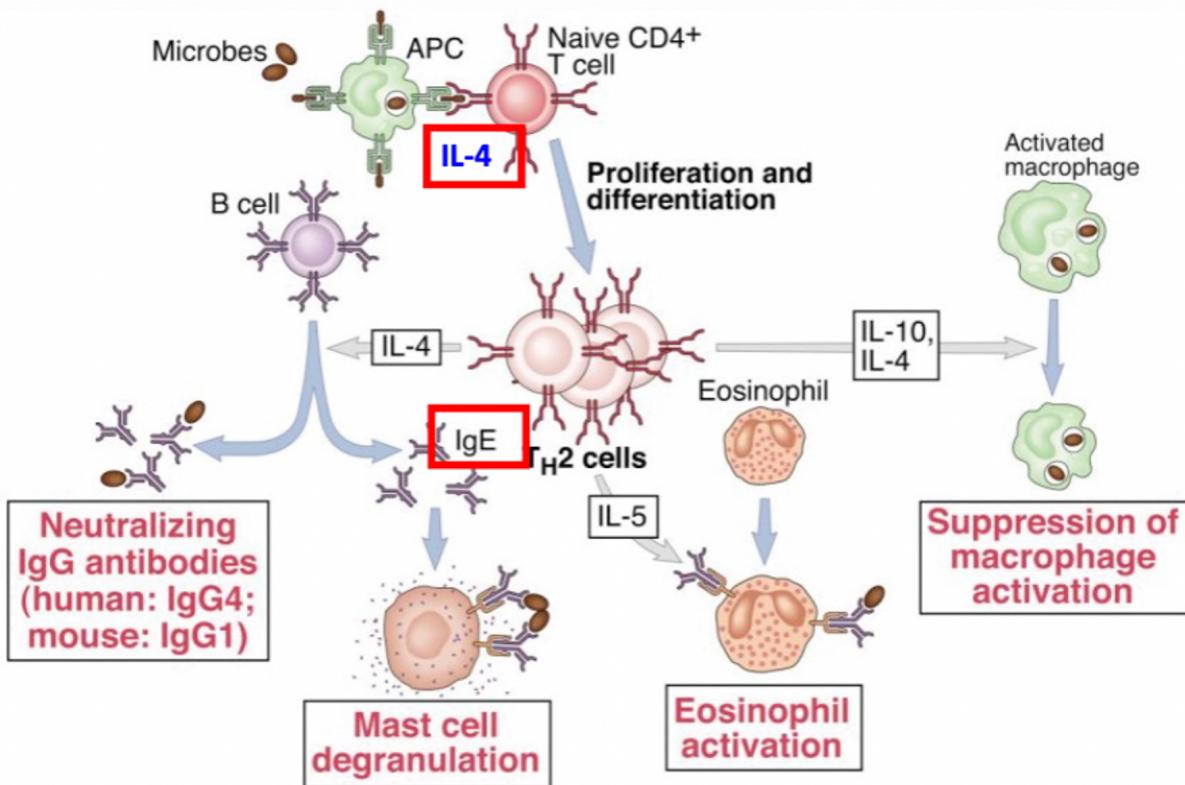
Actions of IFN-gamma



role of interferon gamma

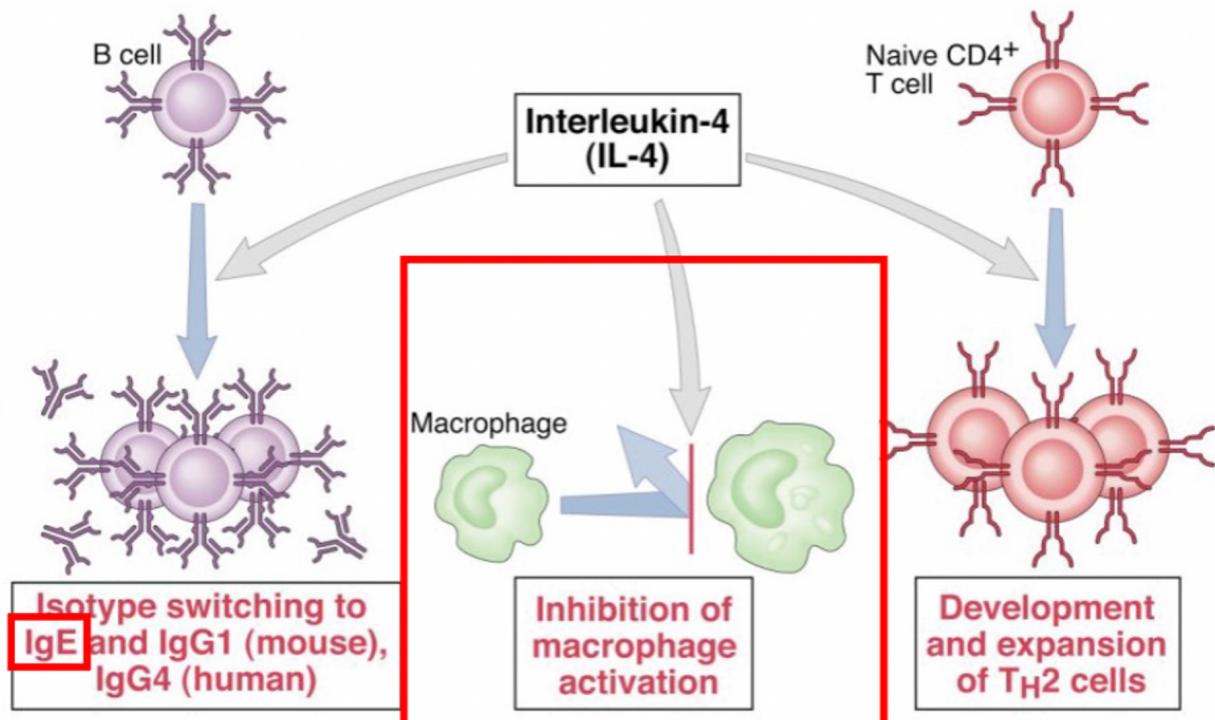
- interferon gamma helps macrophages
- gives b cells instructions to make right isotypes of antibody good for phagocytosis, opsonization \rightarrow interferon gamma dependent
- interferon induce ERAP \rightarrow interferon gamma
- promotes MHC I presentation
 - induce immunoproteasome, ERAP going to make MHC I presentation more diverse and complete
 - directly induces expression of MHC I
 - better processing and more MHC I on surface to present antigen to CD8 t-cells
- Naive CD4+ t cell \rightarrow ensure stability of TH1 cells
 - become TH1 will self ensure they stay as TH1 cells
 - will also act on themselves

Effector functions of Th2 cells



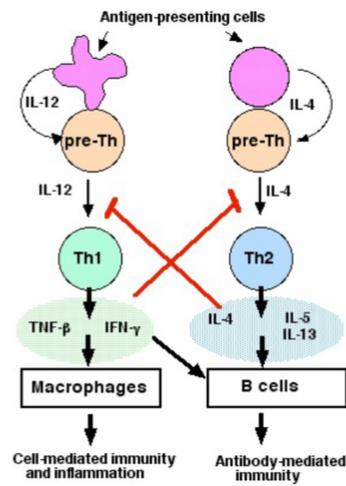
- Th2 is differentiated after they get IL4 produced by DC
 - IL4 is a major cytokine that Th2 produces
 - IL4 can help b-cells by producing IL-4
 - IL-4 important for isotype switching to type of antibody you need to fight parasites
 - IgE
 - IL-4 is a cytokine to instruct b cells to isotype switch to IgE → to fight parasites
 - having Th2 can hurt Th1 response bc IL-4 can also inhibit macrophage activation

Actions of IL-4



- Th2 also use IL-4 to make sure they stay as Th2

The cytokines push the response toward Th1 or Th2 differentiation while inhibiting formation of the other



negative feedback enforcing the polarization!

- when naive t-cell gets activated (Th0) and receive signal 3 from DC such as IL-4 IL-12 to become Th1 or Th2 lineage → at the same time cytokine they produce will inhibit each other
 - interferon stabilizes Th1 and inhibit Th2
 - IL4 stabilize Th2 but inhibit Th1
 - get virus make sure Th1 is made to fight the pathogens
- IL-2 activated by t-cells
- to make sure we get pure Th1 differentiation, give positive signal IL-12 prevent inhibitory signal by anti IL-4 in antibody to neutralize any potential IL-4 in cell culture so that we can get pure TH1
- to get pure Th2 we can add IL-4 and anti IL12 → block any possibility

What about CD8 T killer cells? How do they get activated?

