The Innate Immune System
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Lecture 2. Recognition and effector mechanisms (II)
Integration

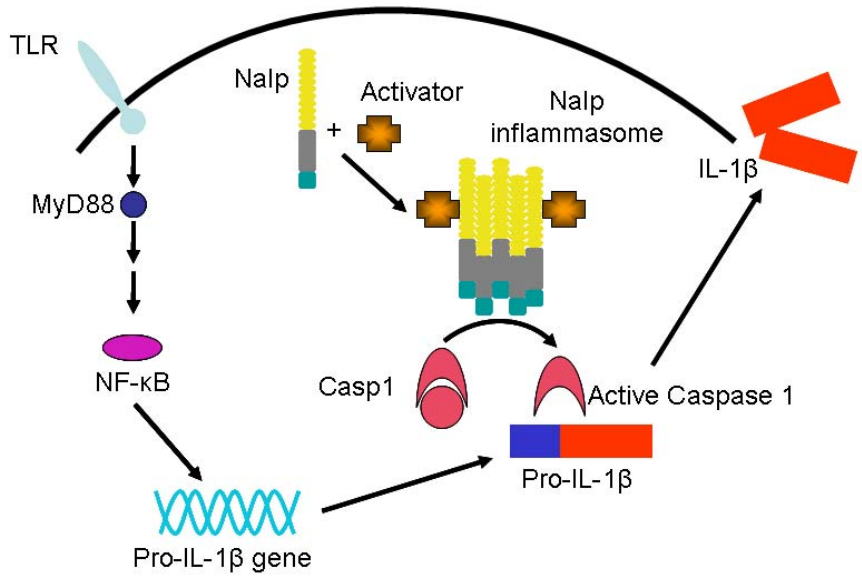
Lethal Toxin

- Dimeric toxin from anthrax delivering a proteolytic subunit to the cytosol
- C57BL/6 macrophages resistant, 129/S1 macrophages sensitive
- Single dominant locus on Ch11
- Currently 5 different alleles in 18 mouse strains (2 resistant; 3 susceptible)
- Protein is Nalp1b
- Caspase 1 deficient cells are protected

The inflammasome

- Inflammation involves the co-ordinated upregulation of a number of genes
- These are co-ordinated by specific transcription factors, particularly NF-κB
- Multiple different 'danger' signals are co-ordinated to a common final pathway
- This common final pathway has been called the inflammasome
  - Immunity 27: 549-559 (2007)
  - Current Opinion in Immunology 2007, 19:615–622

Activation of the inflammasome



Multiple activators for the inflammasome through Nalp1 and Nalp3
Common activation pathway leading to IL-1β secretion
Genetic defects lead to inherited inflammatory conditions
Treatment with anti-IL1R is effective

Co-ordinating the innate immune response

Several cells have roles in the interface between innate and adaptive immunity. Neutrophils and macrophages are the predominant cell type in early inflammation. Here we focus on the macrophage, but also include some data from experiments on DCs.

Macrophages integrate innate immune signals

Extracellular signals

- PAMPs/MAMPs
- Danger
- Complement, proteolysis of extra-cellular matrix, chemotaxis, etc. acting as endogenous adjuvants

Leading to cellular responses

- Receptor recruitment of neutrophils and then macrophages in early inflammation
- MyD88 adapter protein is a key signalling molecule
- Leads to NF-kB driven gene transcription

Macrophages

Large mononuclear phagocytic cells. Phagocytosis was described by Elie Metchnikoff whose first experiment was to introduce a splinter into a starfish larvae and to observe next morning that it was surrounded by mobile cells. In 1891 he proposed that this was important in human inflammation and immediately came under severe and protracted attack by the humoralists, who believed that immunity depended on soluble factors.

Macrophages express class II MHC and are therefore professional APCs. The other professional APCs are DCs, which share overlapping lineage, but are more associated with the ability to initiate immune responses.

Macrophages in the unactivated state.

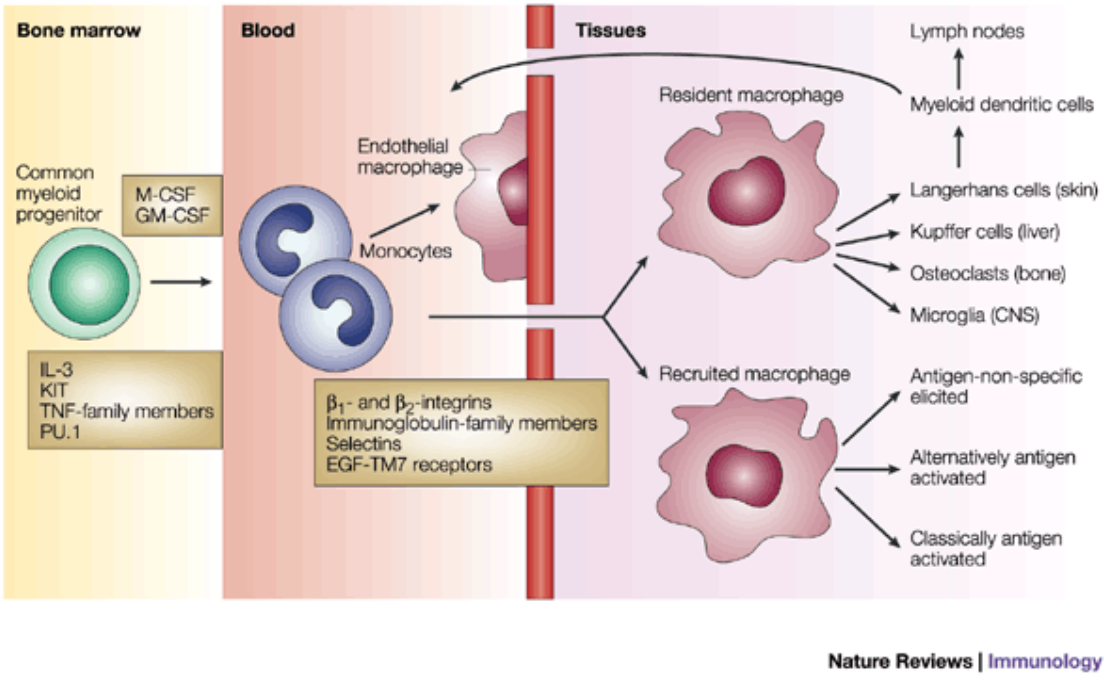
Macrophages have a relatively short programmed life-span.

Van Furth studied the kinetics of monocyte/macrophages; mean turnover time in most tissues <7days.

Site	Number of macrophages ($x10^6$)	Mean turnover time (days)
Liver	9.0	3.8
Spleen	4.0	6.0
Lung	2.0	6.0
Peritoneal cavity	2.4	14.9

Table 1: From van Furth 1989

Monocytes differentiate into resident and recruited cells.
Resident cells (e.g. Langerhans, microglia) may be long lived.
Recruited macrophages do not recirculate, so they die either in the tissue or in the lymph node.
Inflammatory conditions may modulate lifespan.



Nature Reviews Immunology **3**:23 - 35 2003

Macrophages during inflammation

Varol et al. JEM 204:171 (2007)
Kinetics
Inflammation e.g. peritonitis, leads to an increase in promonocyte production and therefore to an increase in

the number of leucocytes in the blood, even though there is also a decrease in the mean half-life of the circulating cells.

Most macrophages and neutrophils at the site of acute inflammation derive from the circulation, although there is some division in situ at later time points. What are the mechanisms that draw cells to sites of inflammation and keep them there?

Release of soluble activators effecting endothelium e.g. chemokines
Upregulation of integrins/addressins on endothelial cells
Signals to retain cells in tissues
Signals to the bone marrow

Signals at site of inflammation

Signals	Dual receptor	Single receptor	Diffusible
Cognate interactions	+		
Costimulation	+		
ECM interactions	+/-		
Pathogens		+	
PAMPs		+	
Endogenous Innate immune system ligands		+	
Danger signals		+	
Cytokines		+	
Chemokines		+	
NO; superoxides		+	+

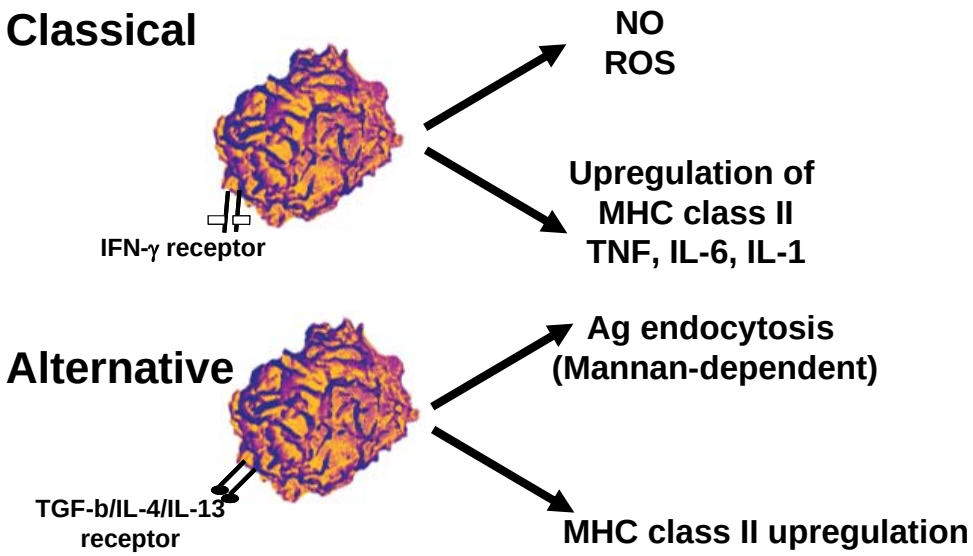
Macrophages are very responsive to environment. External environment controls the gene programs executed by macrophages.

There are different responses to activation by Th1 or Th2 cytokines

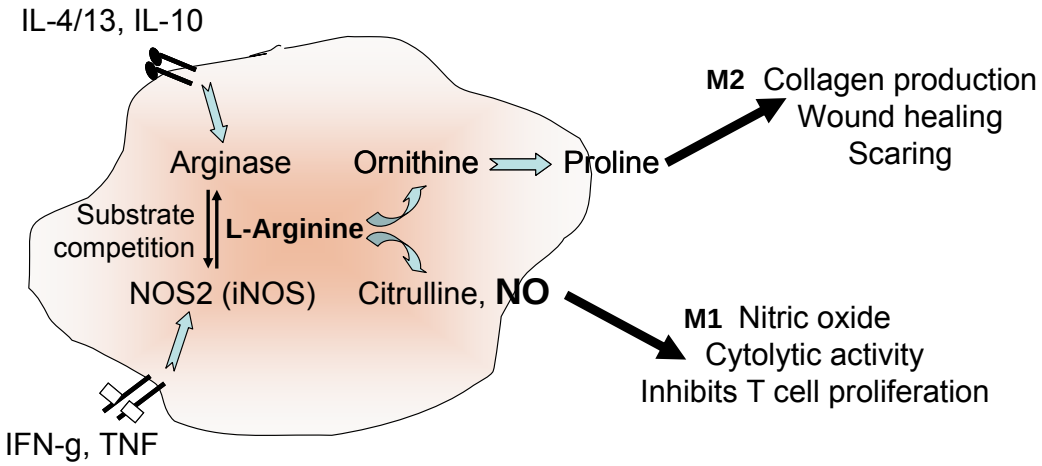
IFNg, IL-12 M1 phenotype; classical activation
IL-4, IL-13 M2 phenotype; alternative activation

But different to T cells:
No clonal burst
Integrating many other environmental cues, such as stimuli from pattern recognition receptors
Degree of reversibility is uncertain

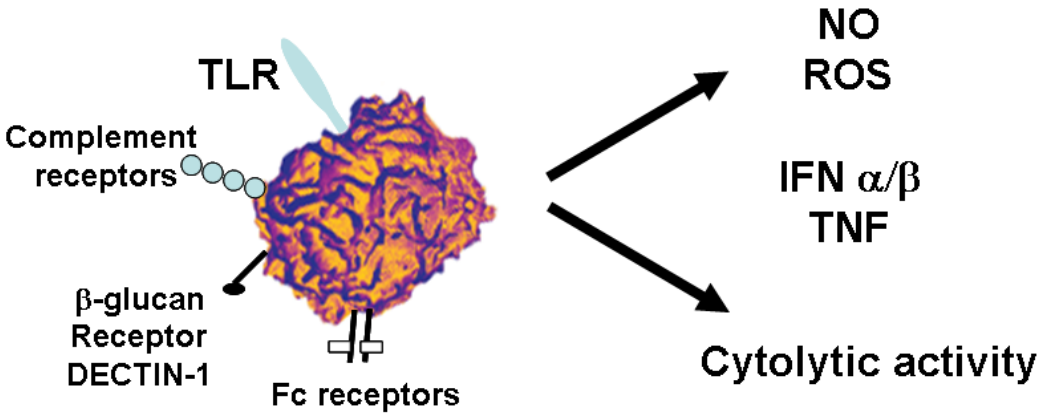
Classical and alternative activation



NOS2 expression, nitrite production, and nitrotyrosination are indicators of classical activation

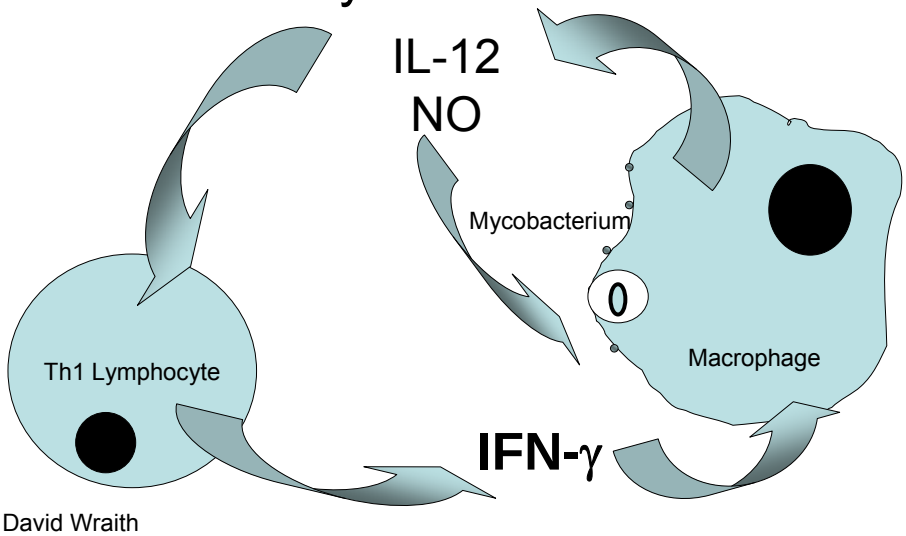


Innate and Humoral activation



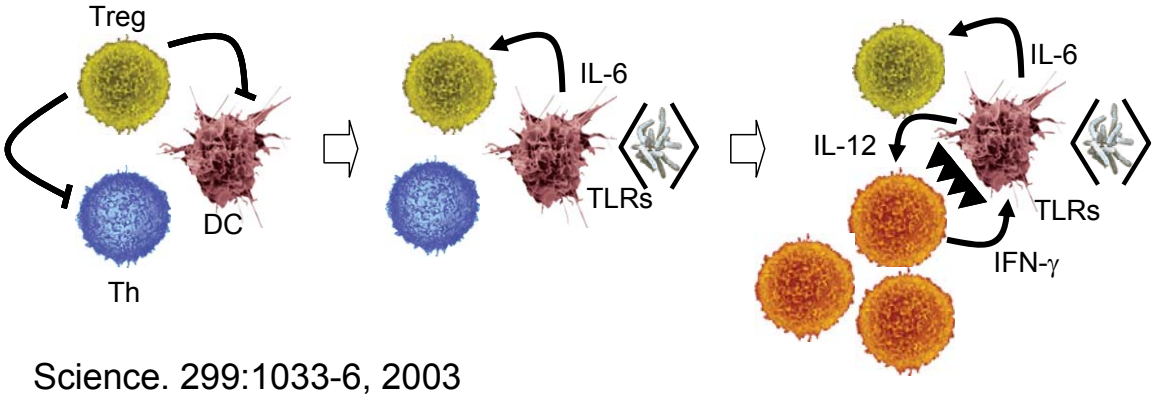
The biological response of macrophages to mycobacteria is enhanced by innate and adaptive signals that activate the macrophage.

Integrated activation 1: killing mycobacteria



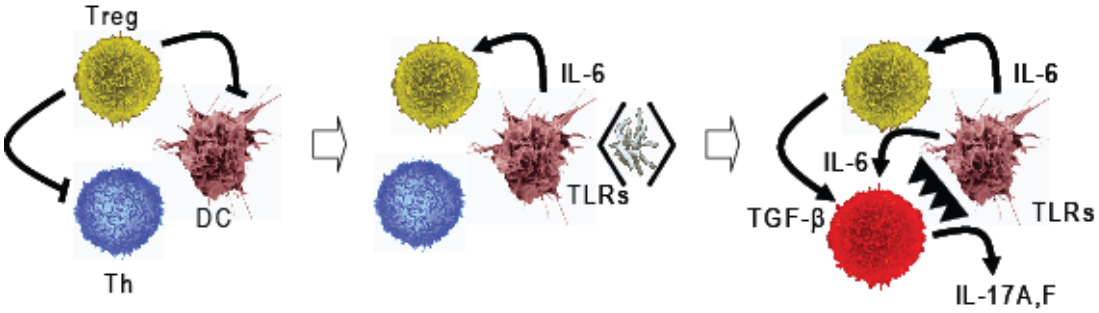
David Wraith

Innate immune signals induce IL-6 which ‘derepresses’ T regulatory cells



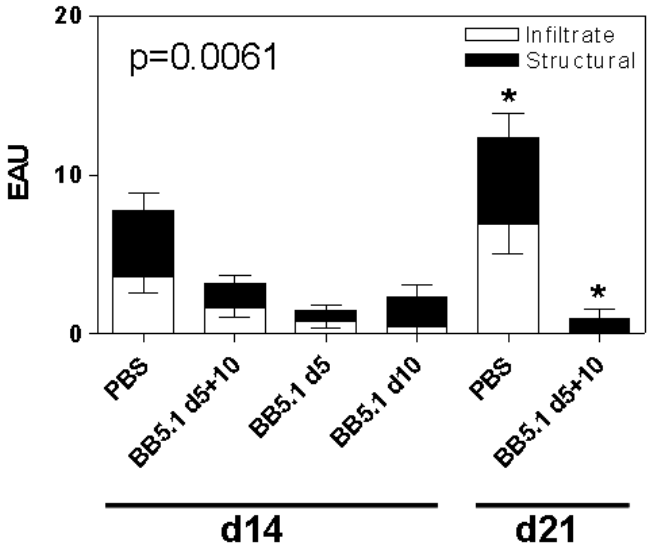
Science. 299:1033-6, 2003

Innate immune signals in the presence of T regulatory cells which supply TGF-□, can lead to the development of T17 effector T cells which have potent pro-inflammatory effects.



Immunity. 24:179-89, 2006
Nature. 441:231-4, 2006
Nature. 441:235-8, 2006

Suppressing innate immune response can limit adaptive immune responses.
In EAU, mice were treated with one or two doses of an antibody (BB5.1) that inhibits the proteolysis of C5. This treatment reduced ocular disease 14 and 21 days after immunisation.



Summary

It is increasingly recognised that innate immune signals play a role in setting the level of inflammation in a particular microenvironment. These signals act as natural ‘adjuvants’ which promote adaptive immune responses. This is good in the case of infection, but bad in the case of autoimmune disease.

Further reading:

S. Gordon. *Alternative activation of macrophages.* Nature Reviews Immunology **3**:23 - 35 2003
Nathan, C. *Points of control in inflammation*. Nature. **420**:846-52 2002