The role of macrophages in autoimmune pathology

Immunopathology lecture 11
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Macrophages

- Multi-potential role
  - During infection
  - During inflammation
  - During repair
  - Tissue-specific(?) homeostasis

Evidence for tight regulation of function in tissue?
Are macrophages heterogeneous or do they show plasticity during course of inflammation, degeneration or repair?
Macrophages

- First discovered by Elie Metchnikoff
- Large mononuclear phagocytic cell
- Professional Antigen Presenting Cell
Differentiation, distribution and activation of macrophages in vivo
Resident Tissue Macrophages

- Parenchymal
  - Slow turnover
  - Regulate homeostasis

- Perivascular
  - Turnover every 2-3 weeks
  - Immunogenic
Microglia – the retinal macrophage or dendritic cell?

• MG express low MHC Class II

• IFNγ suppresses Co-stimulatory molecule Expression, reduces Migration and reduces phagocytosis

• MG produce IL-10
Retinal APC are directed at limiting cell responses

  
  Microglia, unlike perivascular macrophages induce T cell apoptosis on presentation

- Gregerson et al *J Leuk Biol* 2004; *J Immunol* 2004
  
  Allogeneic APC adoptive transfer showed that recruited APC were essential not resident cells. Retinal APC only weakly induced b-gal TCR T cell proliferation and not naïve T cells.
Ocular Granulomata
Sympathetic Ophthalmia

Chorioretinal Granulomata

CD3

MAC-1
Granulomata can form throughout the eye

- Granuloma in vitreous as a consequence of chronic fungal infection in an intravenous drug abuser

- Granulomata in conjunctiva of a patient with sarcoidosis
Sarcoidosis

- Multisystem granulomatous disease characterised by
  - Langhan’s cells and epitheliod cells

Lung, skin, eye, heart, liver, brain.
Granulomatous responses to infection lead to tissue and microbe death and necrosis accumulating in centre of lesion

- *Caseation*

Acid-fast bacilli of *M Tuberculosis*
Innate and Humoral activation

β-glucan
Receptor
DECTIN-1
Fc receptors

TLR

NO
ROS
IFN α/β
TNF

Cytolytic activity
Classical vs alternative activation

Classical
- Trigger - LPS
- IFN-γ receptor
- Upregulation of MHC class II
- TNF, IL-6, IL-1
- NO ROS

Alternative
- TGF-β/IL-4/IL-13 receptor
- Ag endocytosis (Mannan-dependent)
- MHC class II upregulation
iNOS expression, Nitrite production, and nitrotyrosine expression are indicators of classical activation.

IL-4/13, IL-10

Arginase* → Ornithine → L-Arginine → Citrulline

iNOS (NOS2)

IFN-γ, TNF

Cell proliferation, Proline production

Nitric oxide, Cytolytic activity
Experimental Autoimmune Uveitis (EAU)

- Rat model of posterior uveitis
- Target organ destruction of retinal rod photoreceptors
- CD4$^+$ T cell mediated
- Mφ and CD4$^+$ T cell infiltrate
- Delete mφ => reduced disease
Experimental autoimmune uveoretinitis (EAU)

- Chronic, monophasic
- CD4\(^+\) T cell mediated
- IRBP or IRBP peptide specific
Macrophage derived iNOS only expressed during peak EAU

iNOS/ED1 | nitrotyrosine

peak resolution
Macrophages respond in response to their conditioned environment by:

- They respond hierarchically to cytokines generated to:
  - Respond to remove danger (autoimmune or infectious stimuli) – by generating cytotoxicity or phagocytosis
  - Facilitate repair of tissue
  - Maintain homeostasis
Increased MG numbers during neurodegeneration

Hughes et al *IOVS* 2003; *Exp Eye Res* 2004
Tonic suppression or acquired de-activation

Siglecs (sialoadhesin/CD33)
Receptor-Ligand
CD200R
CD47
MHC class II down regulation
Reduced endocytosis
Cytokine-Autocrine control
TGF-β/IL-10/m-CSF
Fc receptors
TGF-β
IL-10
PGE₂
Gene delivery to the posterior segment of the eye
AAV-IL-10 subretinal injections suppresses EAU and maintains ERG responses

Nitrotyrosine expression

Regulation of Cellular Immunity by Activating and Inhibitory Receptors

**Activation Signal**
- T cell receptor
- CD4
- B cell receptor
- CD20
- FcγRIII
- TREM 1, 2, 3

**Costimulatory Signal**
- CD28
- CD40
- Adhesion molecules
- NKG2D

**Inhibitory Signal**
- CTLA-4
- CD94
- SIRPs
- FcγRIIb
- CD200R

**Homeostasis**
Hypothesis
CD200R is an Inhibitory Receptor

non-myeloid cells

CD200

binding

CD200R

myeloid cells

DOWN
CD200 is expressed widely within the retina on neuronal and endothelial cells.

The CD200-receptor is not detected within the normal retina, but observed on both resident and infiltrating myeloid cells during EAU.
In the absence of CD200 retinal MG are activated constitutively.
CD200 receptor ligation with specific mAb inhibits EAU following intravenous administration.

Intravitreal administration of CD200Receptor mAb inhibits EAU

CD200

Activation
NO\textsubscript{low}
MHC class II\textsubscript{low}
CD86\textsubscript{low}
CD40\textsubscript{low}

TGF\beta

T cell Apoptosis
?via CD200RII

RPE
Further reading: