The role of macrophages in autoimmune pathology

Immunopathology lecture 11 Andrew Dick

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







Nature Reviews | Immunology

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

Ford et al *JI* 1995; *J Exp Med* 1996

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.



Lung granuloma Acute stage



Granuloma And fibrosis in Healing phase

Tuberculosis

Granulomatous
 responses to infection
 lead to tissue and
 microbe death and
 necrosis accumulating
 in centre of lesion



Acid-fast baciili of *M Tuberculosis*





Innate and Humoral activation







Experimental Autoimmune Uveitis (EAU)

- Rat model of posterior uveitis
- Target organ destruction of retinal rod photoreceptors
- CD4⁺ T cell mediated
- Mø and CD4⁺ T cell infiltrate
- Delete $m\phi =>$ 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 environment they are conditioned 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





Retinal detachment

AAV-IL-10 subretinal injections suppresses EAU and maintains ERG responses



Broderick et al. Mol Ther. 2005 Aug;12(2):369-73.

Regulation of Cellular Immunity by Activating and Inhibitory Receptors

Activation Signal



Hypothesis CD200R is an Inhibitory Receptor



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





Copland et al Am J Pathol. 2007

Intravitreal administration of CD200Receptor mAb inhibits EAU



Copland et al Am J Pathol. 2007



Further reading:

 Gordon S, Alternative activation of macrophages.Nat Rev Immunol. 2003 Jan;3(1):23-35.