SIgN Immunology Seminar

Prof Nicholas King

Discipline of Pathology, School of Medical Sciences and Bosch Institute, University of Sydney

Immunopathology and the Myeloid Response to Neurotropic Flavivirus Infection

Host
Prof Paola Castagnoli
Singapore Immunology Network, A*Star

Date
Tuesday, 15 January 2013

Time
2pm – 3pm

Venue
SIgN Seminar Room,
Immunos Building
Level 4
Biopolis

Accumulation of myeloid-derived activated microglia and macrophages are hallmarks of viral encephalitis, however mechanisms of recruitment, differentiation and function in neurotropic viral infection are poorly defined. In investigating the role of myeloid lineage cells in West Nile Virus (WNV) encephalitis in a murine model we have shown intranasal infection caused a 3-fold increase in numbers of $CD45^{int}/CD11b^{+}/CD11c^{-}$ microglia by d6-7 post-infection (p.i.). BrdU incorporation showed that few microglia were proliferating, while systemic monocyte depletion during infection prevented this increase, suggesting an alternative migratory precursor cell source. Bone marrow (BM) reconstitution experiments and adoptive transfer of fluorescently-labelled BM monocyte subsets confirmed this: transferred cells migrated into the infected brain parenchyma to express a microglial or macrophage phenotype. Antibody neutralisation of CCL2, highly expressed only by infected neurones, significantly reduced the number of infiltrating myeloid cells and prolonged survival of WNV-infected animals. However, in VLA-4 integrin antibody blockade, the 66% reduction in inflammatory monocyte infiltration results in 60% long-term survival with sterilising immunity, likely mediated by infiltrating T cells. Survival is further increased by the use of immune-modifying particles (IMP), which reduce CNS macrophage infiltration and divert monocytes to the spleen, an effect abrogated by splenectomy. Since viral titres are unaffected by migration inhibition, this also excludes a macrophage-mediated Trojan horse effect in the CNS. Indeed, peripheral human blood monocyte-derived macrophages control virus within three days *in vitro*, evidently using induced indoleamine 2,3 dioxygenase to deplete L-tryptophan and prevent new macrophage infection *in vitro*.

Interestingly, similar CCL2-dependent myeloid cell migration and differentiation also occurs in the early phase of skin infection by WNV *in vivo*, where accumulation of dendritic cells (DC) around dermal infection and in draining auricular lymph nodes (ALN) demonstrate simultaneous migration of bone marrow-derived monocytes to these two sites. Here, migration of monocyte-derived DC from infected dermis to ALN is derived exclusively from $Ly6C^{lo}$ BM monocytes. The differential fates of BM-derived monocyte subsets *in vivo* lead us to propose that BM may be a reservoir of multi-functional "pre-inflammatory" monocytes for rapid deployment during virus infection.