IN BRIEF

NEONATAL IMMUNITY

Fetal immune repertoire

Determining the ontogeny of the human fetal adaptive immune system has important implications for defining the infectious risk of prematurely born infants. However, due to technical limitations, little is known about the full diversity of the fetal immune repertoire. In this study, the authors used next-generation sequencing technology to analyse B cell and T cell lymphopoiesis in blood samples from human fetuses from 12 to 26 weeks of gestation. The data confirm that B cell development precedes T cell development and show that there is a progressive increase in both B cell and T cell receptor repertoire diversity during human fetal development. Furthermore, somatic hypermutation and class-switch recombination occur during fetal B cell development, even at a time when there is limited T cell lymphopoiesis. These data help to define the level of immune competency in developing fetuses and may be used as a reference for future studies of fetal immunity.

ORIGINAL RESEARCH PAPER Rechavi, E. *et al.* Timely and spatially regulated maturation of B and T cell repertoire during human fetal development. *Sci. Transl Med.* **276**, 276ra25 (2015)

NEUROIMMUNOLOGY

TREM2 in Alzheimer disease

Several variants in *TREM2* (triggering receptor expressed on myeloid cells 2), including an Arg47His mutation, are associated with increased risk of Alzheimer disease (AD). Two recent papers have examined the effect of *Trem2* deficiency in mouse models of AD (APP/PS1 and 5XFAD mice) but have found contrasting roles for TREM2 in neurodegeneration. Jay *et al.* showed that TREM2 expression is selectively upregulated in myeloid cells that accumulate around β-amyloid deposits in the brains of APP/PS1 and 5XFAD mice, as well as in human AD brain tissue. In APP/PS1 mice, TREM2 was shown to be exclusively expressed by $CD11b^{+}F4/80^{+}CD45^{hi}$ macrophages, which are thought to be derived from peripheral monocytes. $Trem2^{-/-}$ APP/PS1 mice had greatly reduced numbers of plaque-associated $CD45^{+}$ macrophages but there was no effect on the number of cells expressing P2RY12, which is a purinergic receptor expressed by microglia. These mice had reduced inflammation, ameliorated β-amyloid deposition in the hippocampus, and reduced astrocytosis and microtubule-associated protein tau pathology compared with controls. These data suggest that TREM2 has a detrimental role in AD pathology. By contrast, Wang *et al.* suggested that the cells expressing increased TREM2 in 5XFAD mice during β-amyloid deposition are microglia. Furthermore, TREM2 deficiency in 5XFAD mice resulted in increased β-amyloid deposition in the hippocampus compared with control mice. This increased deposition was suggested to be due to dysfunctional microglia, which did not accumulate around β-amyloid plaques and became apoptotic rather than activated. Further analysis showed that TREM2 recognizes anionic and zwitterionic lipids that are exposed during β-amyloid deposition and that the Arg47His mutation reduced the ability of TREM2 to bind anionic ligands. These data suggest that TREM2 senses damage-associated lipids and sustains a protective microglial response. Whether the differences in the role of TREM2 in AD described in these studies are due to differences in the rate of β-amyloid deposition in the mouse models or to other factors remains to be determined.

ORIGINAL RESEARCH PAPERS Jay, T. R. *et al.* TREM2 deficiency eliminates $TREM2^{+}$ inflammatory macrophages and ameliorates pathology in Alzheimer's disease mouse models. *J. Exp. Med.* **212**, 287–295 (2015) | Wang, Y. *et al.* TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease model. *Cell* **160**, 1061–1071 (2015)