Nature Reviews Immunology | Published online 14 Mar 2016; doi:10.1038/nri.2016.35

NEUROIMMUNOLOGY

IL-17A mediates a path to autism

Severe viral infection during pregnancy has been linked to increased risk of autism spectrum disorder (ASD) in offspring. Now, a study in mice shows that ASD-like behaviour in offspring in response to maternal immune activation depends on maternal $CD4^+$ T cells expressing retinoic acid receptor-related orphan receptor-γt (RORγt) and interleukin-17A (IL-17A); blocking this pathway restored normal behaviour and brain structure.

T helper 17 (T_H17) cells have been implicated in ASD as IL-17A can be detected in the blood in a subset of children with ASD, and *IL17A* is one of the many genes linked to susceptibility to ASD; however, whether T_H17 cells promote ASD has been unclear. To study the underlying mechanisms causing ASD-like behaviour in mice, Choi *et al.* injected pregnant mice with polyinosinic–polycytidylic acid (poly(I:C)) to mimic viral infection and induce maternal immune activation. At embryonic day 14.5 (E14.5), mothers had increased serum levels of IL-17A and elevated mRNA levels of *Il17a* in placental- and decidua-associated mononuclear cells. Furthermore, offspring from these mice showed increased mRNA expression of the IL-17A receptor in the brain.

> “the maternal IL-17A pathway mediates irregular brain structure”

Next, the authors investigated whether activation of the IL-17A pathway in pregnant mice affects fetal brain development and thereby contributes to ASD-like behaviour in offspring. Analysis of cortical layer-specific markers at E14.5 and E18.5 revealed irregularities in the normally well-defined layers of neurons in the brain cortex in offspring from mice injected with poly(I:C). This was not observed in offspring from control mice or offspring from poly(I:C)-injected mothers pretreated with IL-17A-blocking antibodies. Behavioural studies showed that IL-17A-induced signalling was associated with deficits in social interaction and with repetitive behaviour and abnormal communication in offspring of poly(I:C)-injected pregnant mice. These behavioural defects were corrected in offspring from mothers pretreated with IL-17A-blocking antibodies. Thus, the maternal IL-17A pathway mediates irregular brain structure and behavioural abnormalities in offspring from mice exposed to maternal immune activation.

So, could maternal expression of RORγt — which is an important regulator of the IL-17A pathway — have a role in the behavioural phenotypes of offspring from mothers exposed to immune activation? Female mice with a T cell-specific RORγt deficiency were mated with wild-type male mice, so that offspring had at least one functional copy of RORγt and functional T_H17 cells. Pregnant RORγt-deficient mice failed to produce IL-17A after poly(I:C) injection, and offspring from these mice showed normal cortex structure and normal behaviour. Hence, maternal RORγt-expressing $CD4^+$ T cells, such as T_H17 cells, are required for the ASD-like behaviours seen in mouse offspring after maternal immune activation.

Finally, the authors found that treating pregnant mice with IL-17A-blocking antibodies after induction of maternal immune activation could correct some of the ASD-like behaviours, but pretreatment with this antibody had a greater effect and therefore might have more therapeutic potential. The future will tell whether these findings can be translated to humans.

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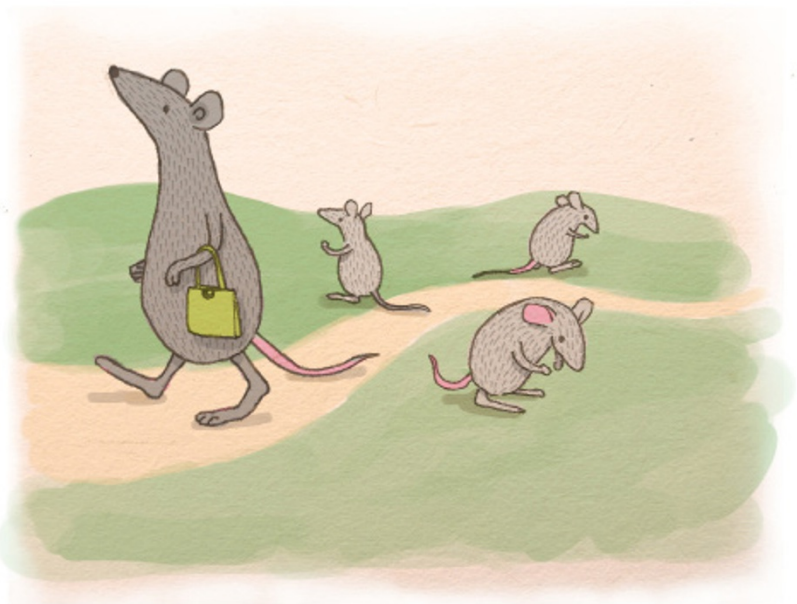

S. Bradbrook/NPG

ORIGINAL ARTICLE Choi, G. B. *et al.* The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. *Science* **351**, 933–939 (2016)