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AUTOIMMUNITY

A tale of two mice

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a new model
of spontaneous
experimental
allergic
encephalo-
myelitis

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Two parallel studies published in *The Journal of Clinical Investigation* describe a double-transgenic mouse that the authors consider is a new model of spontaneous experimental allergic encephalomyelitis (EAE). Because the immunization that is required in current EAE models adds an element of complexity to the interpretation of results, a spontaneous model is in great demand. Approximately half of the mice in both studies spontaneously developed autoimmune demyelination, with lesions occurring in a pattern reminiscent of a severe variant of human multiple sclerosis known as Devic's disease.

Multiple sclerosis is a chronic inflammatory disease in which the myelin that surrounds nerve fibres is attacked by cells of the immune system. In the classic form of multiple sclerosis, demyelinating lesions spread throughout the central nervous system (CNS), leading to various neurological problems. A particularly severe subtype of multiple sclerosis known as Devic's disease is characterized by lesions that are restricted to the spinal cord and optic nerves.

Both groups crossed previously generated myelin oligodendrocyte glycoprotein (MOG)-specific T-cell receptor (TCR)-transgenic mice with MOG-specific

immunoglobulin-heavy-chain gene-‘knock-in’ mice to give double-transgenic mice that had both peripheral B and T cells specific for the same MOG antigen. About 50% of both sets of the double-transgenic mice spontaneously developed a severe form of EAE by 8 weeks of age.

The distribution pattern of inflammatory lesions in the CNS of the double-transgenic mice was similar to that seen in Devic's disease, with lesions localized in the optic nerves and spinal cord. The lesions observed by Krishnamoorthy *et al.* were dominated by macrophages, CD4⁺ T cells and eosinophils but contained few B220⁺ B cells, whereas Bettelli *et al.* observed CD4⁺ T cells and large numbers of B220⁺ B cells but no eosinophils.

Both groups found that MOG-specific B cells from the double-transgenic mice were efficient at presenting MOG autoantigens to the MOG-specific TCR-transgenic T cells and, interestingly, that these B cells undergo class switching of MOG-specific antibody from IgM to IgG1. Krishnamoorthy *et al.* showed

that this class switching occurred even in double-transgenic mice that also lacked MOG, raising the possibility that there might be a non-MOG autoantigen that links T and B cells *in vivo*.

Analysis of cytokine profiles in cell cultures and CNS tissues from double-transgenic mice showed a mix of T helper 1 (T_H1) and T_H2 cytokines. Both groups found increased expression of interferon- γ and interleukin-17 (IL-17). Krishnamoorthy *et al.*, however, found lower levels of IL-17 than did Bettelli *et al.*, and they also found that levels of IL-2 and IL-5 were increased.

Although the discrepancies between the findings of the two groups highlight the need for further study, it seems that this new mouse model will be useful for many applications, particularly for testing novel therapeutics for autoimmune diseases of the CNS, such as multiple sclerosis and Devic's disease.

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ORIGINAL RESEARCH PAPERS

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FURTHER READING Ransohoff, R. M. A mighty mouse: building a better model of multiple sclerosis. *J. Clin. Invest.* **116**, 2313–2316 (2006)

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