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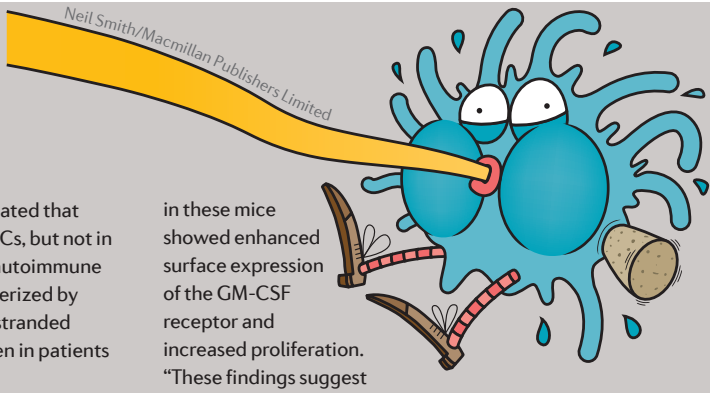
> “cholesterol efflux pathways in DCs have a key role in maintaining immune tolerance”

LUPUS NEPHRITIS

Cholesterol accumulation in DCs promotes autoimmunity



Cholesterol accumulation in dendritic cells (DCs) activates inflammatory signalling pathways that promote autoimmunity. This new finding from Marit Westerterp and colleagues suggests that suppression of DC cholesterol efflux pathways might have a role in the pathogenesis of autoimmune diseases such as systemic lupus erythematosus (SLE).

“Patients with autoimmune diseases have low plasma levels of HDL and several studies in animal models have suggested a link between cellular cholesterol accumulation and autoimmunity,” explains Westerterp. “As HDL mediates cholesterol efflux from immune cells via the ATP binding cassette transporters A1 and G1 (ABCA1 and ABCG1), we hypothesized that impaired cholesterol efflux pathways might have a role in autoimmune diseases.”

To investigate this hypothesis, the researchers characterized the phenotype of mice deficient in both *Abca1* and *Abcg1*. After 40 weeks on a chow diet, these mice showed glomerulonephritis and enlarged lymph nodes, consistent with autoimmunity. Further analysis using tissue-specific knockout mice indicated that deficiency of *Abca1* and *Abcg1* in DCs, but not in macrophages or T cells, led to this autoimmune phenotype, which was also characterized by increased plasma levels of double-stranded DNA antibodies similar to those seen in patients with SLE.

The researchers report that *Abca1* and *Abcg1* deficiency resulted in cholesterol accumulation and inflammasome activation in DCs. These cells showed enhanced cytokine secretion, which led to the expansion of T-cell and B-cell subsets that have previously been shown to contribute to the pathogenesis of lupus nephritis. Deficiency of the *Nlrp3* inflammasome, which is activated in SLE, partially abrogated the autoimmune phenotype of DC-specific *Abca1* and *Abcg1*-deficient (DC-ABC^{DKO}) mice, suggesting that this phenotype is partly inflammasome dependent.

Further analysis of T-cell and B-cell subsets identified an expanded population of granulocyte-macrophage colony-stimulating factor (GM-CSF)-secreting T helper type 17 (T_H17) cells in DC-ABC^{DKO} mice. Moreover, CD11b$^+$ DCs in these mice showed enhanced surface expression of the GM-CSF receptor and increased proliferation. “These findings suggest crosstalk between DC cytokine secretion, production of T_H17 cells, and DC proliferation,” comments Westerterp.

The researchers conclude that cholesterol efflux pathways in DCs have a key role in maintaining immune tolerance. “Our data suggest that agonists for the liver X receptor that upregulate ABCA1 and ABCG1 in DCs, as well as reconstituted HDL particles that mediate cholesterol efflux from these cells might have therapeutic benefit in patients with SLE,” says Westerterp.

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ORIGINAL ARTICLE Westerterp, M. *et al.* Cholesterol accumulation in dendritic cells links the inflammasome to acquired immunity. *Cell Metab.* http://dx.doi.org/10.1016/j.cmet.2017.04.005 (2017)