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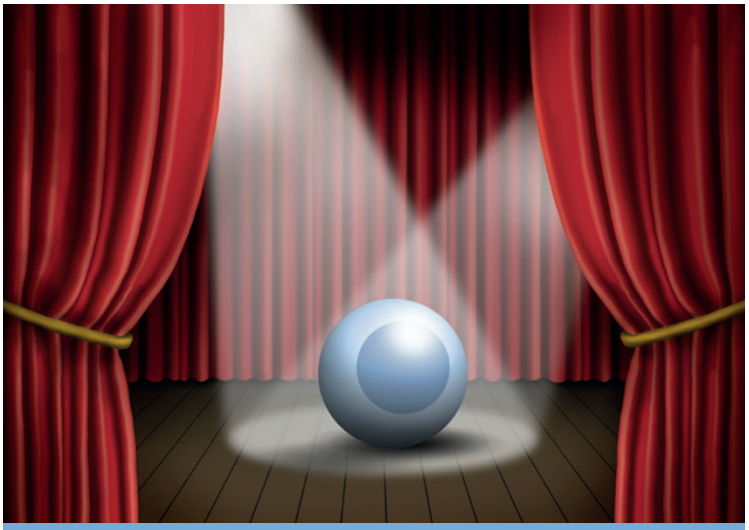

B CELLS

Resetting the scene

T cells and myeloid cells have a central role in the immunopathology of multiple sclerosis, but it is unclear how B cell depletion therapy efficiently controls the inflammatory response in relapsing-remitting multiple sclerosis (RRMS). Now, Li *et al.* show that the frequency of B cells expressing granulocyte–macrophage colony-stimulating factor (GM-CSF) is increased in patients with RRMS and that these B cells activate myeloid cells. Furthermore, B cell-depletion therapy reduced the pro-inflammatory responses of myeloid cells, and this anti-inflammatory effect persisted as new B cells reconstituted.

The authors compared the cytokine profiles of B cells from healthy donors with those from patients with RRMS. In healthy humans, a population of pro-inflammatory effector memory B cells expressing GM-CSF, high levels of interleukin-6 (IL-6) and tumour necrosis factor was identified. The frequency of these GM-CSF$^+$ B cells was increased in blood samples from patients with RRMS, and B cell receptor activation further augmented the difference in the frequency of GM-CSF$^+$ B cells between the two study groups.

Next, the authors examined the effect of GM-CSF$^+$ B cells on myeloid cells. Supernatants from cultures enriched in GM-CSF$^+$ B cells enhanced human macrophage secretion of pro-inflammatory cytokines, such as IL-1β, IL-6 and IL-12, and decreased secretion of the anti-inflammatory cytokine IL-10. Of note, this effect was abolished when GM-CSF was blocked in B cell supernatants. The production of GM-CSF was regulated by signal transducer and activator of transcription 5 (STAT5) and STAT6, as phosphorylation of these proteins induced B cell expression of GM-CSF and decreased induction of IL-10. Interestingly, RRMS-derived GM-CSF$^+$ B cells produced more GM-CSF and induced higher pro-inflammatory cytokine responses in macrophages of both healthy controls and patients with RRMS compared with GM-CSF$^+$ B cells from healthy controls. Thus, GM-CSF from B cells can promote inflammation, and this effect is enhanced in RRMS-derived GM-CSF$^+$ B cells.

Finally, the authors compared the responses of monocyte-derived macrophages from samples collected before and after patients with RRMS underwent B cell-depletion therapy with a CD20-specific antibody. Macrophages obtained just after B cell depletion showed reduced secretion of IL-6 and IL-12, and increased secretion of IL-10, compared with pre-treatment macrophages from the same patient. Moreover, these less inflammatory macrophages persisted after B cell reconstitution, in keeping with lower frequencies and reduced responses of GM-CSF$^+$ B cells within the reconstituted B cell population.

Taken together, the results indicate that modifying the profile of B cells can modulate myeloid cell responses, including reduced pro-inflammatory myeloid cell responses in patients with multiple sclerosis who are treated with B cell depletion therapy.

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> “RRMS-derived GM-CSF$^+$ B cells produced more GM-CSF”

ORIGINAL RESEARCH PAPER Li, R. *et al.* Proinflammatory GM-CSF-producing B cells in multiple sclerosis and B cell depletion therapy. *Sci. Transl Med.* **7**, 310ra166 (2015)
FURTHER READING Shen, P. & Fillatreau, S. Antibody-independent functions of B cells: a focus on cytokines. *Nat. Rev. Immunol.* **15**, 441–451 (2015)