LINK TO ORIGINAL ARTICLE

B-cell-derived interleukin-10 in autoimmune disease: regulating the regulators

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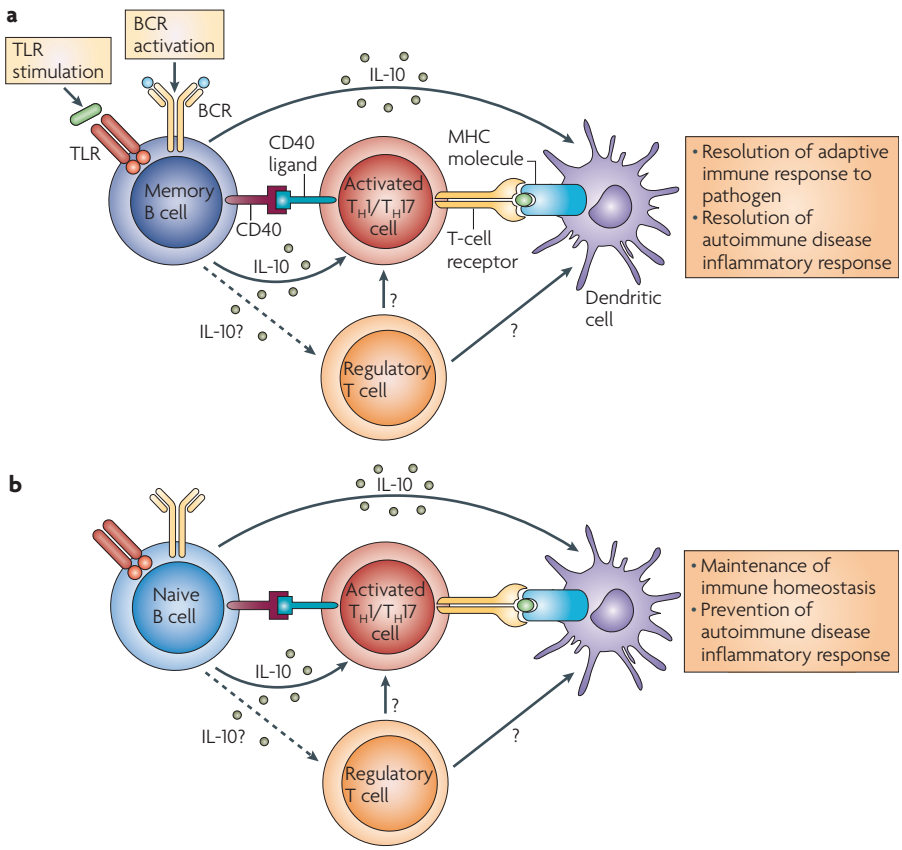
In their recent Opinion paper (Not always the bad guys: B cells as regulators of autoimmune pathology. *Nature Rev. Immunol.* **8**, 391–397 (2008)), Fillatreau *et al.*[1] focus on the important concept of how Toll-like receptor (TLR) stimulation may influence the production of interleukin-10 (IL-10) by B cells and, consequently, the capacity of B cells to downregulate immune responses. Extending their prior work on B cells in autoimmunity[2], the authors recently showed that mice lacking either TLR2, TLR4 or the key TLR signalling molecule MyD88 (myeloid differentiation primary-response gene 88) fail to remit from central nervous system (CNS) inflammatory attack in experimental autoimmune encephalomyelitis (EAE) owing to deficient IL-10 production by B cells[3]. On the basis of this work, they propose the interesting teleological explanation that exposure to certain microbial infections evolved a TLR-mediated mechanism wherein B-cell IL-10 protects from the development of chronic inflammatory diseases, such as multiple sclerosis.

The authors' work[3], however, primarily highlights the role of memory B-cell IL-10 in downregulating the active inflammatory response in EAE (that is, disease remission), less so the role of B-cell IL-10 in the prevention of chronic inflammatory disease. Is it the authors' opinion that we largely rely on infectious agents to generate the regulatory B cells that contribute not only to recovery from exacerbation of autoimmune disease, but also to the maintenance of immune homeostasis and thus our ability to avoid the initial development of autoimmune disease?

As an alternative teleological explanation for these findings[3], we suggest that TLR-induced immune downregulation by memory B-cell IL-10 evolved as a mechanism that limits otherwise adaptive pathogen-specific responses (T_H1-cell and/or T_H17-cell responses) from becoming overly aggressive. This would be expected to occur when memory B cells integrate sufficiently strong stimulatory signals, such as combined engagement of TLR, B-cell receptor (BCR) and CD40, during vigorous adaptive immune responses, such as pathogen-specific responses. IL-10 induced in these B cells could then contribute through a 'negative-feedback loop' to downregulate the local immune response, thereby limiting excessive self-tissue damage. The existence of such a mechanism as part of the normal resolution of pathogen-specific responses could also contribute to the remission from a dysregulated adaptive immune response, such as exacerbation of a T_H1- or T_H17-cell-driven autoimmune disease[4].

We further propose that B-cell IL-10 has evolved for more than one regulatory purpose relevant to autoimmune disease, and that the expression of regulatory IL-10 from B cells depends on both the context of activation and the B-cell subset involved. Although IL-10 induced from B cells by TLR signalling may be most relevant to the remission phase of autoimmune disease, there are examples of B-cell IL-10 contributing to protection from the development of both induced and spontaneous autoimmune diseases[5,6]. Fillatreau *et al.* nicely highlight the context wherein mouse memory B cells produce IL-10 when activated by the combination of TLR stimulation and BCR and CD40 engagement. They comment that combined BCR and CD40 stimulation is insufficient to elicit IL-10 production from naive B cells and suggest that naive B cells require TLR signals to produce IL-10. In contrast to these observations in mice, however, recent human data indicate that isolated CD40 stimulation (in the absence of either TLR signalling or BCR engagement) induces significant IL-10 production from naive B cells[7,8]. One potential explanation is that in humans, who live in a 'dirtier' environment than laboratory housed animals, the naive B cells are primed *in vivo* with TLR signalling, and can then more readily be induced to make IL-10 on partial signalling[3,9]. Although such an explanation would be in keeping with the authors' reference to the hygiene hypothesis, it seems insufficient, as human memory B cells from the same individuals do not produce IL-10 under either isolated CD40 stimulation or combined BCR and CD40 engagement[7,8].

Our preferred explanation is that both naive and memory B cells have evolved the capacity to produce immune regulatory IL-10, and that such production depends on the signals they receive in a particular activation context (see figure). We propose that memory B-cell IL-10



production evolved primarily to downregulate vigorous adaptive pathogen-specific immune responses (involving combined TLR, BCR and CD40 signalling) and would also contribute to the resolution of autoimmune disease exacerbation (see part a of figure). By contrast, naive B cells produce IL-10 when stimulated in a 'bystander' activation context through non-cognate interaction with an activated T cell (CD40 signalling only, independent of either TLR or BCR signalling). This IL-10 production by naive B cells (that normally harbor the autoreactive B-cell repertoire) is probably most relevant to early B-cell–T-cell interactions and the maintenance of normal immune homeostasis (see part b of figure). So, in the context of autoimmune disease regulation, naive B-cell IL-10 production may function primarily in the prevention of inflammatory responses in autoimmune disease, whereas memory B-cell IL-10 production may function primarily as a mechanism of resolving active disease exacerbation.

Evidence is mounting that B-cell IL-10 can regulate immune responses in both health and disease. As Fillatreau *et al*. note in their Opinion paper, TLR-mediated IL-10 induction represents one such context. It is likely that B-cell-derived regulatory IL-10 has evolved to serve distinct immune functions, and that these functions are in turn carefully regulated in a cell-subset- and context-dependent manner.

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