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Journal club

THE BIGGER B CELL PICTURE

Decades of discoveries in immunology have elucidated most of the fundamental mechanisms that control lymphocyte development and activation. Technological progress, in particular advances in multi-parameter flow cytometry and genome sequencing, has enabled immunologists to look deeper into the minutiae of immune cell stratification, fine epigenetic regulation and the cellular mechanisms that underpin fundamental immune functions. As a result, immunologists have remained for the most part 'immune-centric' and, by default, view the immune system as an autonomous and self-regulated entity that can be studied in isolation.

As I was clearing my desk a few months ago, I came across an intriguing article by Winer *et al.*, published in 2011, that provides strong evidence that B cells have a pathogenic role in obesity-associated insulin resistance.

> "it is important sometimes to step back from the immune minutiae so as to not neglect non-immune factors"

This study looked at high fat diet (HFD)-induced obesity in mice and showed that there are larger numbers of class-switched B cells in the visceral adipose tissue of obese HFD-fed mice compared with mice fed a normal chow diet. Surprisingly, B cell-deficient mice on a HFD were protected against insulin resistance, which indicates that B cells might have a pathogenic role in obesity-dependent metabolic disease. B cells from HFD-fed mice (but not normal chow-fed mice) were pathogenic, and their pathogenicity depended on MHC class I- and MHC class II-mediated activation of $CD8^+$ T cells and $CD4^+$ T cells, respectively. Remarkably, the pathogenicity of HFD-induced B cell populations was mediated through the production of autoantibodies. The Fc portion of these antibodies is required to induce insulin resistance, which suggests a possible role of complement activation — as a source of pro-inflammatory signalling through complement C3 and complement receptor C3aR — in underpinning inflammation in the visceral adipose tissue.

Reading this work again was a reminder that it is important sometimes to step back from the immune minutiae so as to not neglect non-immune factors. As illustrated by this study and others since (see Further reading), these non-immune factors can profoundly reshape the B cell repertoire with major health consequences, and yet little is known regarding the molecular basis of this interplay.

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ORIGINAL ARTICLE Winer, D. A. *et al.* B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG antibodies. *Nat. Med.* **17**, 610 – 617 (2011)
FURTHER READING DeFuria, J. *et al.* B cells promote inflammation in obesity and type 2 diabetes through regulation of T-cell function and an inflammatory cytokine profile. *Proc. Natl Acad. Sci. USA* **110**, 5133–5138 (2013) | Nishimura, S. *et al.* Adipose natural regulatory B cells negatively control adipose tissue inflammation. *Cell Metab.* http://dx.doi.org/10.1016/j.cmet.2013.09.017 (2013)