unaffected skin areas, suggesting a protective effect for IgE in human epithelial carcinogenesis.

Next, the authors explored the modes of induction of class switching to IgE. Mice that lacked αβ T cells failed to induce IgE following DMBA exposure. Similarly, mice given a blocking antibody against the B cell-stimulatory molecule CD40 ligand or mice lacking IL-4 had reduced IgE responses, supporting a role for αβ T cells and IL-4 in class switching to IgE. Indeed, only IL-4-producing αβ T cells and not IL-4-deficient αβ T cells could restore the defective IgE response in αβ T cell-deficient animals.

In the skin, γδIELs are known to protect against chemical-induced carcinogenesis and are strong inducers of type 2 immune responses. Strid and colleagues found that mice lacking γδ T cells had significantly impaired DMBA-induced IgE responses compared with wild-type mice. Specifically, skin γδ T cells seemed to shape the IgE repertoire in response to DMBA exposure, driving direct switching from IgM to IgE and the selection of specific variable–diversity–joining rearrangements and unique characteristics of the complementarity-determining region H3.

These observations suggest that the IgE response is polyclonal. In fact, the authors detected reactivity of DMBA-induced IgE against numerous self-antigens in human and mouse epithelial cells, such as nuclear antigens, stress granules and dsDNA. Interestingly, mice treated with the inflammatory chemical 12-*O*-tetradecanoylphorbol-13-acetate (TPA) generated an IgE response with a less diverse and distinct repertoire compared with that induced by DMBA. Together, the data support the idea that DMBA drives a unique, autoreactive IgE repertoire that protects against epithelial tumour development.

*Lucy Bird*

**ORIGINAL ARTICLE** Crawford, G. et al. Epithelial damage and tissue γδ T cells promote a unique tumor-protective IgE response. *Nat. Immunol.* https://doi.org/10.1038/s41590-018-0161-8 (2018)

and generating mixed bone marrow chimeras, the authors demonstrated that LAG3$^{+}$CD138$^{hi}$ cells control the expansion of LAG3$^{-}$CD138$^{hi}$ plasma cells in a LAG3-dependent manner. LAG3$^{+}$CD138$^{hi}$ cells did not display an amplified response upon re-challenge or undergo isotype switching, indicating that they do not acquire features of memory cells.

Adoptive transfer experiments of different B cell subsets into Rag2$^{-/-}$ mice, as well as cell fate mapping, indicated that LAG3$^{+}$CD138$^{hi}$ cells can develop from several different B cell subsets and that they have a distinct B cell receptor (BCR) repertoire. Their frequency is strongly reduced in *Btk*$^{-/-}$ mice, which have defective BCR signalling. In contrast, mice deficient for TLR signalling, CD40 or the αβ T cell receptor, had normal numbers of these cells. This suggests that the development of LAG3$^{+}$CD138$^{hi}$ cells is BCR-dependent but does not require TLR signalling or T cell help. However, the induction of IL-10 expression was found to be strictly dependent on TLR signalling (except in the bone marrow, where some LAG3$^{+}$CD138$^{hi}$ cells constitutively expressed IL-10).

Further experiments showed that LAG3$^{+}$CD138$^{hi}$ cells were also less abundant in mice deficient for CD19, a positive regulator of BCR signalling, and more abundant in mice lacking CD72, which negatively regulates BCR signalling. CD72$^{-/-}$ mice had impaired immunity against salmonella, which could be reversed by treatment with anti-IL-10 or anti-IL-10 receptor.

Together, these results indicate that LAG3$^{+}$CD138$^{hi}$ cells are natural regulatory plasma cells that rapidly provide a first layer of B cell-mediated immune regulation in response to TLR signals. The authors observed that frequencies of LAG3$^{+}$CD138$^{hi}$ cells in mice increase with age, leading them to speculate that they may react against antigens released by damaged cells. This may provide a feedback mechanism that senses the number of damaged cells, downregulating immunity accordingly.

*Alexandra Flemming*

**ORIGINAL ARTICLE** Lino, A. C. et al. LAG-3 inhibitory receptor expression identifies immunosuppressive natural regulatory plasma cells. *Immunity* **49**, 120–133 (2018)

# Journal club

## CHANCE FAVOURS THE PREPARED MIND

The 1980s was a heady time for T cell immunology at the US National Institutes of Health, with pioneering research leading to the cloning of the T cell receptor and the elucidation of MHC restriction, thymic selection and T cell subset differentiation. I was studying immune tolerance, trying to figure out how T cells are regulated, but the field was on the ropes. The two main concepts — the idiotype network and CD8$^{+}$ T suppressor cells — had been discredited. Then one day I heard Marc Jenkins, a post-doc in Ron Schwartz's lab, talk about an in vitro model of T cell suppression he was developing by exposing T cell clones to antigen-pulsed spleen cells (known as fixed antigen-presenting cells (APCs)), a method he had used during his graduate training to induce a profound state of tolerance in vivo.

The hope was that T cell clones stimulated by fixed APCs would convert into suppressor cells. The model didn't work as the stimulated T cells were totally unresponsive, not immunosuppressive, but this failed experiment changed my view of T cell activation. The exposure to antigen was not inert, as the size of T cells was shown to increase (Marc was fastidious in looking at the cells through a microscope). In response to antigen recognition, the cells had become 'anergic' — shut down by the lack of a co-stimulatory or 'second signal' required for full activation.

This discovery changed the field and, for me, it was an epiphany that altered my thoughts about T cell tolerance. It seemed simple — all one needed to induce tolerance was to identify the second signal, develop a drug that blocked that signal and test the ability to induce tolerance in vivo! A concerted, multi-lab effort led to the identification of CD28–B7 interaction as the key second signal (reviewed by June et al., 1994). Cytotoxic T lymphocyte antigen 4 (CTLA4)–Ig was developed as a potent CD28 antagonist (Linsley et al., 1991). This allowed us to show that co-stimulation blockade could lead to robust, antigen-specific and permanent tolerance in mice (Lenschow et al., 1992).

Ultimately, these key discoveries led to approved drugs for the treatment of autoimmune disease and organ transplantation and to the discovery of CTLA4 as the first of many cell surface molecules that turn off activated T cells, giving birth to the field of checkpoint inhibition for the treatment of cancer. Science is a team sport but Marc's contribution was a game changer for the field of T cell immunology and for me personally.

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