

components of the phosphatidylinositol-3-OH kinase (PI(3)K) signaling pathway. These include activating mutations in *PIK3CD* (which encodes the p110 δ subunit of PI(3)K), and loss-of-function mutations in *PIK3R1* (which encodes the p85 regulatory subunit of PI(3)K) or *PTEN* (which encodes a molecule (PTEN) that antagonizes PI(3)K by dephosphorylating its substrates)¹². Despite the effects on distinct genes, these variants manifest biochemically as hyper-activation of PI(3)K signaling, revealed by the constitutive phosphorylation of downstream targets, including the kinase Akt and the ribosomal protein S6. Notably, the metabolic regulator mTOR is activated by Akt and controls cellular metabolism. Patients with mutations in *PIK3CD*, *PIK3R1* or *PTEN* all have B cell and antibody defects¹², which highlights the need to explore metabolic functions in lymphocytes from these patients, in addition to

predictable assessment of B cell activity. As these patients can be treated with rapamycin and other inhibitors of mTOR, it is likely that the failure to regulate the metabolic and mitochondrial changes described by Pierce and colleagues² contributes to impaired lymphocyte function in these groups of patients. Thus, while these studies have shown that B cells must ‘race against the clock’ to get their ‘second wind’, it is likely that insights from these and future studies of B cell metabolism will provide a boost to the understanding of B cell responses in vivo.

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Competing interests

The authors declare no competing interests.

ANTITUMOR RESPONSES

$\gamma\delta$ T cells and IgE team up to prevent tumors

In response to epithelial DNA damage, tissue-resident $\gamma\delta$ T cells initiate and shape a tumor-protective IgE response that requires CD4⁺ T cells and immune effector cells expressing the high-affinity IgE receptor Fc ϵ RI.

J. Michael McGraw and Wendy L. Havran

$\gamma\delta$ T cells that reside in epithelial tissues, also known as ‘ $\gamma\delta$ TCR⁺ intraepithelial lymphocytes’ (IELs), provide host protection against insults such as infection, wounding and malignancies¹. The $\gamma\delta$ TCR⁺ IEL population in mouse skin is critical for the maintenance of skin homeostasis and responds to self stress antigens via their invariant V γ 5V δ 1⁺ TCR and other co-receptors, such as NKG2D. These cells are critical for tumor immunosurveillance and can directly target and kill malignant cells, yet their role in promoting a broader antitumor response is not well defined². In this issue of *Nature Immunology*, Crawford et al. show that in response to DNA damage in epidermal tissue, $\gamma\delta$ TCR⁺ IELs also initiate and shape a tumor-protective immunoglobulin E (IgE) response that requires interleukin 4 (IL-4)-producing CD4⁺ T cells and Fc ϵ RI⁺ effector cells³. This finding builds on published work linking $\gamma\delta$ TCR⁺ IEL responses to humoral immunity⁴ and elucidates a previously unknown role for $\gamma\delta$ TCR⁺ IELs and IgE in antitumor immunity.

Epithelial tissues, such as the skin, lungs and intestine, act as a physical barrier against a constant barrage of pathogens and environmental hazards, but chronic tissue damage caused by infection, inflammation or exposure to carcinogens can lead to tumor development. Indeed, the majority of human cancers arise in epithelial tissues^{5,6}. $\gamma\delta$ TCR⁺ IELs are continuously engaged in immunosurveillance, and studies of mice have shown that these cells are required for the prevention of tumor development in epithelial tissues⁷. Furthermore, transcriptome analysis of human cancer has found that the presence of intratumoral $\gamma\delta$ T cells, across all leukocyte populations, is the most significant prognostic indicator of overall survival⁸. However, relatively little is known about how $\gamma\delta$ TCR⁺ IELs function and promote a broader adaptive response that helps maintain tissue homeostasis and limit tumorigenesis.

Skin-resident $\gamma\delta$ TCR⁺ IELs produce IL-13, a type 2 immunity cytokine, in response to epithelial DNA damage, which

in turn promotes the proper turnover of epithelial cells and helps prevent tumor formation⁹. This ability of $\gamma\delta$ TCR⁺ IELs to produce IL-13 is in line with published work showing that $\gamma\delta$ TCR⁺ IELs can promote an allergic response and the production of IgE following tissue abrasion and epicutaneous immunization⁴. However, the link among type 2 allergy responses, tissue homeostasis and the development of cancer has remained an enigma^{10,11}. Furthermore, whether $\gamma\delta$ TCR⁺ IEL-mediated type 2 immunity prevents tumor development beyond the local production of IL-13 in the skin has not been characterized.

Crawford et al. utilize a chemically induced model of skin tumorigenesis that involves treating mouse skin with the environmental carcinogen DMBA (7,12-dimethylbenz[a]anthracene), a polycyclic aromatic hydrocarbon³. DMBA induces double-stranded DNA breaks, and repeated, weekly treatment with DMBA results in the development of squamous-cell carcinoma (SCC)⁹. The authors show that a

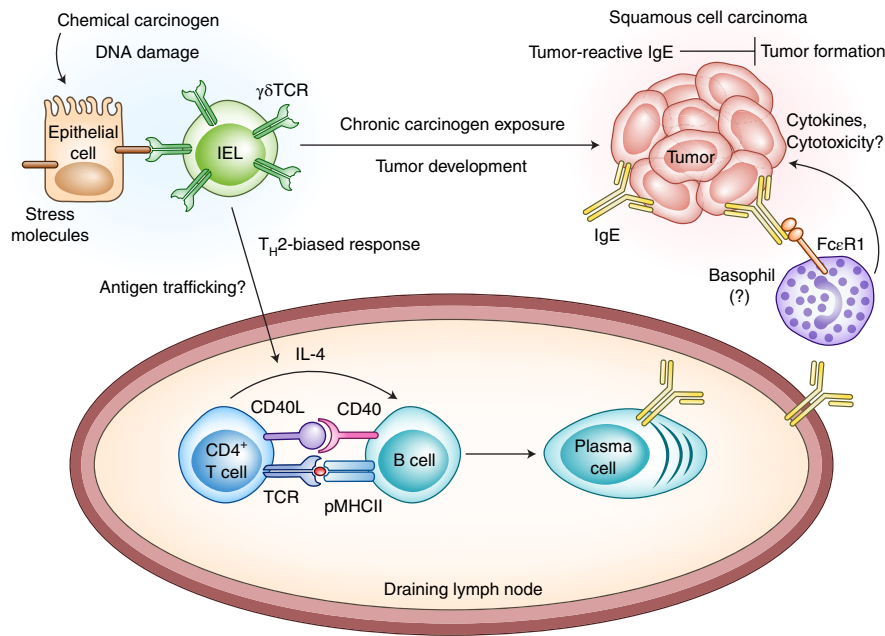


Fig. 1 | Skin-resident $\gamma\delta$ T cells sense epithelial damage and help shape a tumor-protective IgE response.

Crawford et al. show that skin-resident $\gamma\delta$ T cells detect damaged epithelial cells following carcinogen-induced DNA damage and help initiate a T_H2 -biased response³. IL-4-producing $CD4^+$ T cells interact with B cells in skin-draining lymph nodes and promote the generation of IgE⁺ plasma cells. Tumor-reactive IgE limits tumor formation and growth following repeated carcinogen exposure, and this protection requires effector cells that express the high-affinity IgE receptor FcεR1. pMHCII, peptide-major histocompatibility complex class II. Credit: Marina Corral Spence/Springer Nature

single, topical application of DMBA induces a serum IgE response within 4 days. The abundance of IgE⁺ plasma cells in the draining lymph nodes increases with additional weekly applications of DMBA, and IgE is readily detected in tumors at later time points³. Furthermore, mice deficient in the gene encoding the heavy chain of IgE, which thus lack IgE, and mice deficient in the gene encoding FcεR1, the high-affinity receptor for IgE, are more susceptible to SCC than are their wild-type counterparts. The authors also show that the total expression of FcεR1 in human SCC is inversely correlated with tumor malignancy³. These observations indicate that IgE provides protection against tumor formation in response to localized epithelial stress.

Published work has demonstrated that $\gamma\delta TCR^+$ IELs respond to DMBA-induced SCC⁹; therefore, the authors investigate whether these cells are also required for the production of IgE. They show that mice deficient in the gene encoding the δ -chain of the TCR, which thus lack $\gamma\delta$ T cells, have a distinct defect in the production of IgE following treatment with DMBA³. To pinpoint the critical population of $\gamma\delta$ T cells, the authors generate chimeric mice that have only $\gamma\delta TCR^+$ IELs in the skin or only γ

δ T cells in lymphoid tissue and show that plasma-cell class switching to IgE specifically requires $\gamma\delta TCR^+$ IELs, not other $\gamma\delta$ T cell populations³. High-throughput sequencing of IgE heavy chains indicates that the presence of $\gamma\delta TCR^+$ IELs helps shape the repertoire by supporting specific variable-diversity-joining rearrangements. Finally, the authors show that the tumor-protective IgE response induced by DMBA is autoreactive (for example, it includes antibodies to double-stranded DNA)³. These findings indicate that $\gamma\delta TCR^+$ IELs respond to epithelial damage and initiate an autoreactive IgE response that limits tumor development (Fig. 1).

A key finding of this study is the critical role of IgE in preventing the development of SCC following repeated tissue damage. The authors highlight the findings that expression of FcεR1 has been associated with improved survival in human malignancies and that the clinical use of omalizumab (an IgE-blocking monoclonal antibody) has been associated with a higher incidence of epithelial cancers^{8,12}, although direct evidence of the role of IgE in antitumor immunity is lacking. This tumor-protective role of IgE is dependent on FcεR1⁺ effector cells; however, the identity and effector functions of these FcεR1⁺ cells need further

investigation. Both basophils and mast cells bind IgE in DMBA-treated skin and tumors³. Because *Cpa3^{Cre/+}* mice, which lack skin mast cells due to genotoxicity caused by Cre recombinase expressed via the locus encoding the mast-cell carboxypeptidase (*Cpa3*), do not display any increased susceptibility to DMBA-induced SCC, the authors conclude that basophils are the IgE-responsive population³. Although basophils have roles in type 2 responses to allergens and parasites, characterized by the secretion of histamine, IL-4 and other inflammatory mediators, the role of basophils in cancer is poorly defined¹³. Whether basophils are indeed required for the antitumor effects of IgE and how IgE-responsive cells aid in antitumor immunity remain open to investigation.

The current study extends published work by showing that $\gamma\delta TCR^+$ IELs support the generation of IgE in response to DNA damage in the skin and shape the subsequent IgE response by supporting specific variable-diversity-joining rearrangements³. The interaction of $CD4^+$ type 2 helper T cells (T_H2 cells) with B cells, via the costimulatory receptor CD40 and its ligand CD40L, in draining lymph nodes is required for IgE production³ (Fig. 1), yet how $\gamma\delta TCR^+$ IELs promote this T_H2 -biased response remains unclear. One possibility is that $\gamma\delta TCR^+$ IELs provide local signals, such as IL-13, to neighboring Langerhans cells, which then migrate to lymph nodes and promote a T_H2 response. Another possibility is that $\gamma\delta TCR^+$ IELs selectively recruit antigen-presenting cells from the circulation and bias them to promote a T_H2 response. Of note, basophils have been shown to express major histocompatibility complex class II and IL-4 and drive allergic responses to allergens and helminths¹³. Therefore, $\gamma\delta TCR^+$ IELs might selectively recruit basophils to sites of tissue damage to initiate an IgE response.

The development of cancer immunotherapies, such as checkpoint blockade and chimeric antigen receptor T cells, has generated intense interest in understanding how the immune system prevents and eliminates tumors. However, the roles of $\gamma\delta TCR^+$ IELs and T_H2 responses in antitumor immunity have remained an enigma. In the current study, Crawford et al. define a novel antitumor response that is initiated by $\gamma\delta TCR^+$ IELs following tissue damage and is mediated by IgE and FcεR1⁺ effector cells³. These findings provide novel insight into the role of IgE in antitumor immunity and add to the growing link between $\gamma\delta TCR^+$ IEL responses and broader humoral immunity. Future work should address how IgE-responsive effector cells

help eliminate tumors and if $\gamma\delta$ TCR⁺ IELs in other epithelial tissues, such as the intestine and the lungs, can also promote a tumor-protective IgE response. Better understanding of this link between $\gamma\delta$ TCR⁺ IELs and IgE will help define the delicate balance of allergy, tissue repair and tumor formation. 

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Competing interests

The authors declare no competing interests.

MEMORY T CELLS

An RNA checkpoint that keeps immunological memory at bay

What keeps memory T cells functionally silent in the absence of infection is unclear. New data reveal the existence of a deterministic halt in the protein-synthesis machinery of memory T cells and expose the discriminatory functions of a family of RNA-binding proteins.

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The human immune system not only fights but also memorizes encounters with infectious pathogens. During the course of an initial infection, naive T cells become exposed to a pathogen's antigens as presented by the innate arm of immunity. As soon as their T cell antigen receptors (TCRs) become educated to the pathogen and transmit their signal, these 'effector' T cells respond by secreting inflammatory cytokines and other toxic molecules. In doing so, they orchestrate a theater of operations for rapid clearance of the pathogen. In parallel, some of these antigen-experienced T cells commit to an alternative fate; instead of engaging the pathogen, they alter their original identity by epigenetic means to differentiate into long-lived, heterogeneous, populations¹. These 'memory' T cells circulate or reside within tissues and scout for potential re-appearance of the pathogen²; if this happens, they release their inflammatory protein cargo at unprecedented speed and quantity. In the interim, however, these cells remain in a state of dormant awareness and utilize checkpoint mechanisms to restrict their toxic cargo from being unnecessarily produced, which would harm the body. Such checkpoints include on-off switches at the level of the transcription

of cytokine-encoding genes that should respond only when TCR signals trigger production of the corresponding mRNAs¹. In this issue of *Nature Immunology*, Salerno et al. argue that transcriptional inhibition is not the main mechanism that restricts the release of cytokines by memory T cells³.

Salerno et al. build on the published observation that memory T cells contain large quantities of specific cytokine-encoding mRNAs but do not produce the corresponding proteins in the absence of antigen⁴. IFN- γ , which is an essential cytokine for immunity to intracellular pathogens and tumors, is one such example. Naive T lymphocytes do not produce large amounts of IFN- γ , but after stimulation via the TCR, the expression of IFN- γ -encoding mRNA (*Ifng* mRNA) progressively increases, particularly during differentiation into memory cells. However, memory T cells are able to produce very large amounts of this cytokine only when re-activated. Salerno et al. provide proof that such restriction of the functional memory response lies in a specific form of post-transcriptional control of RNA³.

Post-transcriptional regulation involves a variety of mechanisms that help an mRNA mature and become functional and subsequently control its fate via protein

synthesis or destruction. For many mRNAs encoding immunological molecules, these steps do not occur automatically but are under cell- and signal-induced checkpoints⁵. The specificity of the post-transcriptional machinery engaged in these controls is instructed by regulatory RNA structures that are located in the mRNAs and are targeted by regulatory RNA-binding proteins. Several such post-transcriptional checkpoints that control the reactivity of cells of the immune system have been identified^{5,6}. One of the most widely studied families of regulatory RNA structures is rich in adenyl and uracyl nucleotides (commonly referred to as an 'AU-rich element' (ARE)) and is located mainly in the 3' untranslated regions of many potent cytokine-encoding mRNAs, including *Ifng* mRNA. Salerno et al. investigate if and how the ARE can suppress the release of IFN- γ protein from resting memory T cells³. They use an elegant strategy to monitor the effects of this RNA element in controlling the expression of *Ifng* mRNA in antigen-experienced mouse CD8⁺ T cells. They further reveal that when this ARE is mutated, memory T cells secrete substantial amounts of IFN- γ protein in the resting state and produce larger amounts of IFN- γ than usual during a recall response.