



Understanding allergy and cancer risk: what are the barriers?

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Evidence suggests that allergic immune responses can protect against some types of cancer. What are the possible underlying mechanisms, and can allergic reactions be harnessed for anticancer therapy?

The major focus of current cancer immunotherapy is to enhance antitumour immunity. Among the most promising approaches are those that inhibit the immune checkpoints that normally maintain self-tolerance: for example, the use of antibodies directed against cytotoxic T lymphocyte-associated antigen 4 (CTLA4) or programmed cell death protein 1 (PD1)¹. In addition, T cells are being genetically engineered to produce chimeric antigen receptors (CARs) that allow them to recognize tumour-specific antigens. Historically, there has been less interest in the potential antitumour effects of mediators of allergic (atopic) disease. Nevertheless, evidence is emerging that allergic responses can have a dual role in protection against pathogens and in tumour surveillance^{2,3}.

Allergic reactions include common conditions such as atopic dermatitis (eczema), allergic rhinitis and asthma. They target tissues that provide a protective interface between our bodies and the environment; namely, skin and mucosal surfaces. The barrier is formed by differentiated cells (keratinocytes) in the outermost layers of multilayered epithelia, which assemble a layer of insoluble, transglutaminase-crosslinked proteins and lipids at the plasma membrane. A deficient epithelial barrier is known to cause atopic diseases; in humans, this is highlighted by the discovery that mutations in the genes encoding the epidermal barrier protein filaggrin predispose individuals to atopic dermatitis and increase asthma severity⁴. In mice, genetic deletion of filaggrin or combined deletion of other barrier proteins leads to characteristics of atopic dermatitis, including epidermal hyperproliferation, dermal accumulation of CD4⁺ T cells and high circulating levels of immunoglobulin E (IgE)⁵.

Allergic immunity is mediated by type 2 immune responses, as it depends on T helper 2 (T_H2) cells, eosinophils, basophils, type 2 innate lymphoid cells, alternatively activated macrophages, and IgE and IgG1 antibodies. When keratinocytes are subjected to mechanical or chemical insults, they express stress-associated proteins, such as the retinoic acid early inducible (RAE1) family

(also known as the NKG2D ligand family), that engage the receptor NKG2D (also known as KLRK1) on cells of the innate and adaptive immune systems, triggering a lymphoid stress-surveillance response⁶. In this situation, keratinocytes also secrete high levels of thymic stromal lymphopoietin (TSLP), which is a potent activator of a wide range of immune cells and epithelial cells⁷. As a result of the immune cell infiltrate, epidermal proliferation is stimulated and the epidermis becomes thickened, which is thought to partially compensate for the barrier defects and can have tumour-suppressive effects⁸.

Direct evidence that allergic responses can be tumour protective has come from chemical carcinogenesis in mice lacking the three barrier proteins envoplakin, periplakin and involucrin (known as EPI^{-/-} mice). When EPI^{-/-} mice are treated with the mutagenic agent DMBA, the epidermal response is normal in terms of the levels of double-stranded DNA breaks and the acquisition of *HRAS* mutations. However, these mice are highly resistant to developing tumours (papillomas) because of their exacerbated atopic response to the tumour promoter TPA. One underlying mechanism is an increased rate of transit of epidermal cells from the basal proliferative layer to the outermost cell layers, which is tumour suppressive in oncogene-driven skin carcinogenesis⁸. Additional mechanisms involve increased expression of TSLP, which is known to be tumour protective in several models of carcinogenesis^{5,9,10}, and upregulation of RAE1, which triggers the immune stress-surveillance response. Interestingly, skin itching — a defence strategy to induce the removal or expulsion of allergens, which prevents them from spreading systemically — is mediated by TSLP and histamine release from degranulating mast cells¹¹. Inhibition of interleukin-4 (IL-4) or CD4 does not prevent the TPA response in EPI^{-/-} mice, indicating that tumour protection in this model is not part of a generalized T_H2-type response⁵.

Although the studies of EPI^{-/-} mice indicate that atopy (a predisposition to allergic hypersensitivity) can be tumour protective, there is so far no evidence that

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individuals lacking filaggrin have an altered predisposition to developing cancer. In addition, several large-scale epidemiological studies of the potential association between allergic diseases and different types of cancer have been largely inconclusive². This could well be because of the pleiotropic nature of allergic immunity. Eosinophils have a broadly tumour-protective function, but positive and negative actions of mast cells on tumorigenesis have been described. Furthermore, T cell receptor- δ -knockout (*Tcrd*^{-/-}) mice lacking functional $\gamma\delta$ T cells develop spontaneous dermatitis and exhibit an increased sensitivity to cutaneous carcinogenesis¹², indicating strong tumour-protective effects of the dendritic epidermal T cells, which are the main immune mediators of the murine lymphoid stress-surveillance response. Stimulation of the NKG2D receptor has pleiotropic effects in cancer¹³. In addition, IL-4, IL-13 and IL-33 have marked effects on carcinogenesis, and both antitumour and protumour activities have been reported.

Although these observations indicate that a generalized allergic reaction is not consistently tumour protective, there is promising evidence that IgE-mediated immunotherapeutic approaches could be beneficial¹⁴. The potent capability of IgE and IgG1 to kill tumour cells via antibody-dependent cellular cytotoxicity, or to act as an adjuvant in antitumorigenic events, has been demonstrated in various mouse tumour models¹⁴. These observations are not directly applicable to patients because of species-specific differences in the expression of the Fc receptor for IgE (Fc ϵ RI); this receptor is found only on basophils and mast cells in mice, but is expressed by a broad range of immune cells in humans. Nevertheless, clinical studies are being initiated to test the efficacy of mouse-human chimeric IgE antibodies against solid tumours¹⁵.

Finally, it is important to draw a distinction between the potentially beneficial effects of atopy and the well-established positive correlation between chronic inflammation, tissue damage and cancer. In the gut, specific intestinal microbes can have dramatic impacts on inflammatory bowel disease and the development of colorectal cancer. Recently, it has been shown that flagellated bacteria, which are present in wounds resulting from an acute breach in the epidermal barrier, can promote skin tumour formation in mice¹⁶. Patients with the skin blistering disorder recessive dystrophic epidermolysis bullosa, in which repetitive cycles of wounding and repair predispose the skin to developing squamous cell

carcinomas, have high levels of high mobility group box 1 protein (HMGB1), a danger-associated molecular pattern (DAMP). In a mouse model of wound-induced skin cancer, induction of HMGB1 can be reduced by ablation of Toll-like receptor 5 (TLR5), the flagellin receptor, in leukocytes¹⁶. These studies point, for the first time, to a role for skin commensal bacteria in cancer.

In conclusion, although atopy is undoubtedly a complex immune response to a defective epithelial barrier, there is enough evidence to suggest that harnessing specific aspects of that response could be a valuable adjunct to current cancer immunotherapies.

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Competing interests statement

The authors declare no competing interests.