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The other side of the coin: IgE deficiency, a susceptibility factor for malignancy occurrence

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ABSTRACT

Since the discovery of IgE, almost all attention was given to conditions with elevated specific or total IgE levels such as atopy, type I hypersensitivity reactions, or parasitic infestations. Recent prospective and retrospective studies show that having very low IgE levels, such as those seen in IgE deficiency (IgE<2.5 kU/L), is not without clinical consequences. Patients with ultra-low IgE levels have an elevated risk of cancer of any type. These results are in agreement with murine models research which demonstrated that grafted tumors grow faster and bigger on an IgE knockout background. The novel finding that IgE deficiency is a susceptibility factor for cancer, fits very well with the AllergoOncology concept. The reports on a beneficial, cytotoxic function of IgE, in cooperation with its high (FcεRI) and low (FcεRII, CD23) affinity IgE receptors resulting in tumor cell phagocytosis, propose a role of IgE in cancer surveillance. It appears that not only deficiency of serum IgE, but also lack of tissue-bound IgE is important in malignancy susceptibility in these patients. As such, IgE deficient individuals with absent serum and cell-bound IgE as suggested by negative type I hypersensitivity skin tests, are at the highest risk for a malignancy diagnosis. In contrast, IgE deficient individuals with cell-bound IgE depicted through positive type I hypersensitivity skin tests, have lower rates of malignancy diagnosis. The present report discusses the evidence and potential role of ultra-low IgE as a novel biomarker for cancer susceptibility.

Keywords: AllergoOncology, Biomarker, IgE deficiency, Cancer, Prognosis

DISCOVERY OF THE IGE MOLECULE AND ITS ROLE IN ALLERGY, PARASITOSIS AND HYPER-IGE SYNDROME

Isolation of the fifth immunoglobulin class, named immunoglobulin E (IgE) has been officially announced in 1968.[1] Two different groups, T. Ishizaka in the United States who first described the existence in low concentration of a factor carrying skin-sensitizing activity,[2] and Johansson and Bennich in Sweden who detected a myeloma protein that could not be identified as any of the 4 known immunoglobulin classes,[3] worked on characterizing this molecule separately. It is known now that elevated IgE levels represent a physiological immune response to helminth infection[4] and that IgE is the key element in type I hypersensitivity reactions.[5] Clinicians use high IgE levels as marker for atopy/allergy, prompting referrals to the Allergy clinics for further evaluation. Soon after isolation, in 1972, extremely high IgE levels were found in 2 children with infections, severe

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chronic dermatitis and coarse facial features. Following this report, elevated IgE levels were also found in the 2 girls from the initial Job's syndrome report in 1966, showing that these children had the same condition, later named hyper-IgE syndrome,[6] a rare genetic, immunodeficiency disorder. Since then, the elevated IgE levels are the focus of thousands of articles in the allergy and immunology literature.

INVERSE ASSOCIATION BETWEEN IGE LEVELS AND CANCER

Interestingly, different epidemiological studies emerged over the years showing an inverse association between elevated IgE levels and malignancy.[7] Specifically, a large Swedish cohort demonstrated an inverse correlation between elevated specific IgE levels and risk for melanoma, and breast and gynecological cancers.[8] Another prospective study found that patients with high total serum IgE levels had lower risk of developing chronic lymphocytic leukemia and multiple myeloma.[9] Similarly, higher pre-diagnostic serum interleukin (IL)-4 levels[10] (IL-4 induces B-cells class switching to the IgE isotype[11]), higher total IgE levels,[12] and respiratory allergen-specific IgE[13] were associated with a lower risk of developing glioma. Moreover, patients diagnosed with glioma and multiple myeloma experienced longer survival if they had high total serum IgE levels (>100 kU/L).[14,15]

WHAT ARE THE MECHANISMS THROUGH WHICH IGE MIGHT PROTECT FROM CANCER?

All these observations naturally bring the question how might IgE protect from cancer? Since middle 1990s, different *in vivo* and *in vitro* studies have demonstrated that IgE antibodies can engage high (FcεRI)- and low (FcεRII, CD23)-affinity IgE receptors to activate different effector cells to kill cancer cells through antibody-dependent cell mediated cytotoxicity (ADCC) and antibody-dependent cell mediated phagocytosis (ADCP).[16–19] In addition, it has been shown that IgE/FcεRI-mediated cross-presentation greatly enhances the ability of dendritic cells to prime $CD8^+$ T cell responses against free soluble antigens, which is crucial for cancer immuno-surveillance.[20] Moreover, *ex vivo* cross-linking of IgE antibodies on the surface of human macrophages through FcεRI promoted macrophage maturation, polarisation, increased production of pro-inflammatory cytokines, and chemoattractant mediators, and resulted in effective antigen presentation. Functional assays in the same study showed that anti-tumor IgE antibodies can engage human macrophages to elicit an efficient effector response against target cancer cells.[21] All these findings provide mechanistic explanation for the epidemiological studies that describe an inverse correlation between elevated IgE levels and cancer.

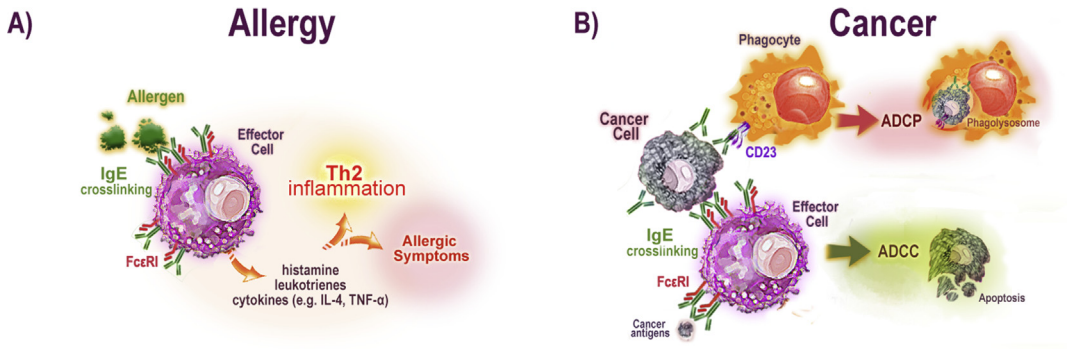

Fig. 1 A) For allergists, all allergic symptoms are centered around IgE antibodies. Its fixation via IgE receptors on effector cells means that an allergic person is sensitized. Upon subsequent allergen contact, the IgE gets crosslinked and mediators are released from the activated mast cells, causing inflammation and typical allergic symptoms. The mast cell mediators best known are tryptase, histamine, and leukotrienes, but also different cytokines, including tumor necrosis factor-alpha (TNF-α). B) Tumor cells do overexpress numerous antigens at a higher density and distinct composition than healthy cells. IgE bound to FcεRI can be crosslinked by overexpressed tumor antigens on malignant cells, resulting in activation of the effector cells, release of cytotoxic mediators and cytokines like TNF-α, and subsequent antibody-dependent cell mediated cytotoxicity (ADCC). Similarly, IgE via FcεRII (CD23) is involved in killing the tumor cells through antibody-dependent cell mediated phagocytosis (ADCP). It is possible that these mechanisms play an important role in cancer surveillance when the number of aberrant cells is still low. Consequently, a state of IgE deficiency is a risk for failure of this surveillance machinery.

What we know about IgE deficiency	
Patients might have no associated symptoms	• First case of IgE deficiency with no associated symptoms was described in 1970.[33]
May be associated with other immunodeficiencies	• Ataxia telangiectasia,[31] Common Variable Immunodeficiency (CVID),[38] IgA deficiency,[39] IgG subclass deficiency.[40] • When all other immunoglobulins are normal, the condition is called "Selective IgE deficiency".
Patients might have environmental allergy-like symptoms	• Environmental allergy-like symptoms (e.g. asthma, rhinosinusitis), were described in different populations[28,29,36,38,46] • Some of these patients have positive type I hypersensitivity reaction skin tests to environmental allergens, despite absent serum IgE levels.[47]
Patients might have non-specific manifestations	• Fatigue, joints pain[28]
IgE deficient patients have higher rates and risk of malignancy	• Patients with IgE deficiency have higher rates and risk to develop malignancy, compared with non-IgE deficient individuals.[29,34,36,37] • Those with absent serum IgE and absent cell-bound IgE (negative type I hypersensitivity skin tests) appear to have the highest risk for associated malignancy[47] • New IgE therapies for cancer are under development[49]

Table 1. What we know about IgE deficiency.

While we are only at the beginning of understanding the complex mechanisms through which IgE is involved in fighting against malignancy, a new role of IgE in anti-tumor surveillance has emerged for the past 2 decades (Fig. 1). The field of AllergoOncology appeared in 2008 as a need to elucidate the exact relationship between IgE, different effector cells, key molecules or types of signals which result in recognition and destruction of tumoral cells.[16,22,23] In this regard, recent murine studies show that tumor growth was inhibited in high-IgE KN1 mice, which have 4 to 6-times higher serum IgE levels compared to wild type mice.[24,25] On the other hand, engineered mice with very low or absent IgE levels were more susceptible to tumor growth.[25,26]

IGE DEFICIENCY PREDISPOSES TO MALIGNANCY

The results discussed above bring up the next question: what happens with patients who are deficient in IgE–are they at higher risk of developing malignancy? Surprisingly, although hyper-IgE syndrome and IgE mediated disorders represented the focus of multiple basic and clinical research investigations, IgE deficiency has received relatively little study. This has happened in part because high IgE levels tend to be more dramatic and for most laboratories lower or absent serum IgE levels are usually reported to be within normal limits. Total serum IgE of 100–120 kU/L is typically considered the normal upper limit in adults,[27] while atopic patients present usually with elevated IgE levels.[5] In contrast, IgE deficiency is defined as IgE<2.5 kU/L[28] or IgE<2 kU/L.[29,30]

Soon after IgE was isolated, case series of IgE deficient individuals with associated ataxia telangiectasia[31] were reported, as well as description of familial IgE deficiency in 3 generations of relatives of 58-year old twins with chronic bronchitis and fibrotic lung disease.[32] On the other hand, the first report of a healthy IgE deficiency individual raised

What we don't know about IgE deficiency:

- It is unclear how many IgE deficient individuals have truly absent IgE in the serum, compared with those who have very low IgE levels, but close to the limits of IgE detection in the blood.
- There is, therefore, a need to introduce more precise IgE measurements in the clinical practice, at levels <2 kU/L.
- If so, what exactly is the genetic defect resulting in IgE deficiency?
- Consequently, is there a familial component of IgE deficiency?
- At what point in lifetime might individuals become IgE deficient, and how is this related to cancer occurrence?
- What are the full clinical characteristics of patients with IgE deficiency ?

What we don't know about IgE deficiency and cancer:

- Is cancer causative to IgE deficiency, or vice versa: Does IgE deficiency reflect an immunomodulatory response resulting in cancer?
- Would it be useful to introduce evaluation for IgE deficiency as a routine test in clinical practice?
- What would be the ethical implications of predicting the cancer risk in patients who have their IgE levels checked for allergy diagnosis?
- Is there any role for performing allergy skin tests as part of the oncology screening in IgE deficient individuals?
- Many of these questions could be answered by multicenter longitudinal studies following the IgE levels and cancer prevalence/progression

Table 2. Questions left unanswered about IgE deficiency.

the possibility that very low IgE levels might not necessarily have any clinical significance.[33] The first evidence of higher rates of malignancy diagnosis in patients with IgE deficiency appeared only after 2014.[29,34,35] While patient populations included in these retrospective studies had IgE levels performed for various medical reasons, a subsequent study performed on 2005–2006 NHANES (National Health and Nutrition Examination Survey) database where IgE levels were measured without any relation to the medical status of these individuals, found also higher rates of malignancy diagnosis in IgE deficient patients (12%) compared to those with high (100 $\leq$ IgE>1000 kU/L) (6.7%, OR = 1.86, 95% CI: 1.02–3.4, p = 0.04) and very high (IgE$\geq$1000 kU/L) (5.3%, OR = 3.07, 95% CI: 1.03–9.1, p = 0.04) IgE levels.[36] However, the retrospective nature of these studies brought into question whether the malignancy itself or the treatment received for cancer resulted in very low serum IgE levels. Recently, the first prospective study showed that after a median of 43.5-month follow up from the IgE collection time, IgE deficient patients had significantly higher rates and risk of developing new malignancy (17.65%) compared with non-IgE deficient individuals (3.8%, OR = 5.4, CI 95%: 1.3–22.9, p = 0.01).[37] Table 1 shows what we know about the array of clinical presentations of patients with IgE deficiency, whereas in Table 2, we highlight the questions left unanswered about this condition.

At this time, we do not know if the ultra-low IgE levels are caused by the malignant process and possibly they are detected before the cancer becomes clinically apparent, or if the IgE deficiency is part of an immunomodulatory response associated with increased malignancy susceptibility. To answer these questions, the cause of IgE deficiency needs to be elucidated. Existent data describe 2 categories of patients with IgE deficiency: those with selective IgE deficiency when all other immunoglobulins are normal, and those with an associated humoral immunodeficiency, such as

common variable immunodeficiency (CVID),[38] IgA deficiency,[39] or IgG subclass deficiency[40] (Table 1). Interestingly, although malignancy is common in CVID patients, the higher rate of cancer in IgE deficient individuals was unrelated to the CVID diagnosis.[34] Evaluating for any abnormalities in the pathway involved in the IgE synthesis and secretion, is mandatory. Sequencing analysis of the gene encoding activation-induced cytidine deaminase (AID), the enzyme required for immunoglobulin class switch recombination, did not reveal a mutation that might explain the selective IgE deficiency.[41] Further research is needed in this area, such as consequent screening for AID mutations in a larger population of patients with IgE deficiency, as well as evaluating for possible mutations in genes encoding other molecules involved in the IgE production pathway, or by assessing for any defects in the survival of IgE-producing B cells. It is important to note that AID may also target non-immunoglobulin genes and control oncogenes versus tumor suppressor genes, and its aberrant expression may have impact in Th2-driven inflammation.[42] The AID/APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like) network has also implications for pathways associated with ovarian cancer survival,[43] pointing out how complex, intricated, and not fully known the relationship between the IgE, Th2 state, and the overall anti-tumoral effect is.

It is known that the IgE levels correlate with the IgE receptor expression.[44] For example, in IgE-deficient mice, the expression of FcεRI on mast cells is only 20% of normal.[45] For the ADCC and ADCP to take place against tumor cells, the existence of IgE receptors on the effector cells is crucial.[16] It is therefore possible that very low serum IgE levels in humans may similarly result in downregulation of the high affinity IgE receptors, with consequences on the ability to recognize and kill the tumor cells.

IGE DEFICIENT INDIVIDUALS WITH ABSENT SERUM AND ABSENT CELL-BOUND IGE MIGHT HAVE THE HIGHER RISK TO DEVELOP CANCER

There are also many unanswered clinical questions about the relationship between IgE deficiency and risk of developing malignancy (Table 2). For example, should we check serum total IgE levels in all individuals? At this time, patients with IgE deficiency are diagnosed in general by Allergists during the work-up for evaluation of chronic allergy-like respiratory symptoms. Low IgE may emerge as a novel, unrecognized and unexpected biomarker for cancer development, as we recently highlighted in a position paper of the European Academy of Allergy and Clinical Immunology (EAACI).[30] However, substantial effort and interactive research are needed to further determine this aspect. Another important question is which IgE deficient patients have the highest risk for developing malignancy. The first clue appears to come from evaluation of their chronic respiratory symptoms. Interestingly, although IgE deficient patients have very low or absent serum IgE levels, they can still develop chronic environmental allergy-like symptoms, and 3%–73% of these patients have associated diagnoses of asthma and/or rhinosinusitis.[28,29,36,38,46] Despite very low serum IgE levels, some of the IgE deficient patients have positive skin tests to specific environmental allergens, suggesting existence of tissue bound-IgE in certain individuals with IgE deficiency.[47] When the IgE levels in 21 pregnant women with IgE deficiency (IgE<2 IU/mL) were assayed again using a lower detection limit of 0.02 IU/mL, 20/21 had detected levels ranging between 0.5 and 2.1 IU/mL.[46] Therefore, it appears that some IgE deficient patients produce enough IgE to prime mast cells, whereas others either produce no IgE at all or produce IgE in very small amounts that cannot stimulate the mast cells during the skin tests placement.

Interestingly, those IgE deficient patients with absent cell-bound IgE (negative type I hypersensitivity skin tests) had the highest likelihood to have an associated malignancy diagnosis compared with IgE deficient individuals with evidence of mast-cell-bound IgE (positive skin tests) (rate of malignancy diagnosis of 42.9% vs 6.1%, OR = 34.86, 95% CI: 2.67–453.6, p = 0.007).[47] These results add to the existent data that tissue-bound IgE is involved in local anti-tumoral activity. Prior studies showed that IgE molecules were the most abundant immunoglobulin isotype in

head and neck cancer tissues,[48] while in mice, IgE transcripts were detected at the site of squamous skin cancer, promoting a unique tumor-protective IgE response.[26] Signaling through IgE/FcεRI can lead to ADCC, while the IgE/FcεRII-mediated pathway results in ADCP of tumor cells and subsequent cross presentation to cytotoxic T lymphocytes. IgE thus initiates and concerts numerous anti-tumor mechanisms. Therefore, performing type I hypersensitivity skin tests to environmental allergens to assess for the existence or absence of cell bound-IgE in IgE deficient patients, may be useful to possibly predict which individuals might have the highest risk to develop malignancy. The introduction of skin tests and serum specific IgE to tumor antigens, may be an interesting option in the future. How exactly to monitor or screen these individuals for cancer occurrence, and with which other tumor markers and scanning methods and in which time intervals, is another area of research in the context of clinical oncology.

CONCLUSIONS

Over the years, the clinical significance of IgE deficiency has not been very well established. However, recent data show that certain IgE deficient individuals have higher risk to develop cancer. Although there is a long way to fully understand the mechanisms behind this association, anti-IgE therapies as treatment for solid tumors are already under development.[49] All these findings bring to light the new anti-tumor role of IgE, a field completely novel to us Allergists.

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