Why could passive Immunoglobulin E antibody therapy be safe in clinical oncology?

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Passive immunotherapy with antibodies belongs to the state of the art treatment not only in allergy, but also in rheumatology and, especially successful in oncology. These therapies are based on the concept of monoclonal antibodies and exploit (1) the epitope-specific effects of an antibody as well as (2) the effects determined by the constant domain of the immunoglobulin isotype. Thereby, monoclonal antibody therapies have the capacity to modulate biological processes. For instance omalizumab (Xolair®, Novartis, Basel, Switzerland), via binding to the Fcε3 domain of IgE [1], interferes with FcεRI binding and thus hinders allergic reactivity [2]; infliximab (Remicade®, Centocor, Ortho Biotech Inc, Malvern, PA, USA) binds tumour necrosis factor-α (TNF-α) and as a consequence dampens inflammation [3]; therapies like the anti IL-12/IL-23 antibody ustekinumab (Stelara®, Centocor) being recently FDA approved for the treatment of psoriasis, promise cure for multiple skin diseases dependent on this pro-inflammatory pathway [4].

In clinical oncology often both mechanistic aspects of monoclonal antibodies are important. For example, one growth inhibitory aspect of the FDA approved human epidermal growth factor receptor (EGFR, HER-1) monoclonal antibodies cetuximab (Erbitux®, MerckKGaA, Darmstadt, Germany) and panitumumab (Vectibix®, Amgen Inc, Thousand Oaks, CA, USA) [5] as used, for example, in colon cancer, is to interfere in an epitope-specific manner with receptor configuration and thus binding of its ligand EGF (epidermal growth factor) [6, 7]. The anti-HER-2 monoclonal antibody trastuzumab (Herceptin®, Roche, Hertfordshire, UK) which is applied in metastatic breast cancer and other HER-2 overexpressing cancer entities [8], has anti-proliferative actions because it inhibits hetero- and homodimerization of the EGFR family member HER-2 [9]. However, antibody therapies used in oncology including the examples mentioned above, also exploit immunological effector functions and stimulate immune attack specifically against the targeted cancer cells [10]. The efficacy of antibody-dependent cell-mediated cytotoxicity (ADCC) is dependent on the affinity to the antigen and its overexpression level [11]. The interaction of applied antibodies and effector cells is mediated by their Fc domains that determine not only the binding to complement, but also binding to their relevant Fc receptors. Therefore, the class or subclass of an antibody critically determines its effector function. All presently approved immunoglobulins belong to the IgG class, whereas intensive research on IgA is ongoing [12-14]. Therefore,
the today most important Ig receptors are FcγRI-III (and much less FcαRI). FcγR equipped effector cells are predominantly constituted by NK cells, macrophages, neutrophils and eosinophils, which accomplish antibody-dependent cytotoxicity (ADCC) and -phagocytosis of the tumour cell. For some monoclonal antibody therapies also complement-dependent cytotoxicity plays a role in their anti-cancer efficacy [15]. To this end, IgG antibody therapies are therefore among the most successful immunological therapies today. Needless to say that simultaneously, four of the five human immunoglobulin classes are more or less ignored. It can be anticipated that thereby, modern medicine might miss important therapy options.

The recently introduced concept of AllergoOncology [16] deals with exactly this problem and aims to address the opportunities vs. possible pitfalls of IgE-mediated and Th2-biased cellular responses in malignant diseases. Previous pioneer studies and current work have collected in vitro and in vivo evidence that engineered anti-cancer IgE antibodies may be comparable, or even superior to their IgG counterparts [17-22]. In these studies IgG and IgE with exactly the same variable domains and antigen affinity, but with either γ or ε constant domains, have been compared head-to-head in functional assays, which combine oncologic and allergologic readouts. For instance, effector cells such as mast cells or macrophages, which express both FcγRI and FcεRI, can be sensitized with anti-tumour-specific IgG or IgE. Bound to these effector cells they could be shuttled into the tissue site. Consequently, instead of a soluble antigen or allergen, a tumour cell overexpressing the specific epitope of the antibody can be used as the target. The released mediators are further tested for their tumoricidal effects. For instance, TNF-α has been early proposed to lyse tumour cells upon ADCC [23]. As can be seen from the name, TNF-α had been originally identified in necrotic tumour tissue before its pathophysiological role in inflammation including allergy was recognized [24].

In spite of numerous elegant studies and the accumulating evidence that IgE could have beneficial roles in clinical oncology, studies with IgE anti-tumour antigen antibodies have so far not risen above preclinical proof of concept studies. This might be due to serious concerns in respect to the role of IgE antibodies in anaphylaxis. In sensitized organisms minute levels of allergen may be sufficient to trigger IgE-armed allergy effector cells, and lead to potentially deleterious systemic hypersensitivity reactions. In this context it is worth mentioning that anaphylactic reactions are well known in routine clinical oncology, because allergic reactions to biologicals [25] or chemotherapy are relatively common side-effects [26]. Oncologists try to prevent them by pre-medication with anti-allergic drugs.

Interestingly, clinical and immunohistochemical studies have shown that IgE specific to tumour antigens and with tumoricidic properties can be found in tumour patients in the circulation and the tumour tissue [27, 28]. In a recent diagnostic study we compared the IgE levels in 96 serum samples from oncology patients to those in 688 samples from allergic subjects. The comparative prevalence of IgE levels for instance for EGFR was four times higher in cancer patients [29]. However, anaphylaxis has not been observed in any of the above mentioned studies on naturally occurring IgE antibodies in head and neck cancers, pancreatic, ovary, breast or colon cancers. The question arises how tumour-specific IgE may
be beneficial without increasing the anaphylactic risk. This knowledge could be exploited for the design of IgE-based cancer immunotherapeutics.

The most important basic principle in Type I allergy is that only allergens which are able to target more than one IgE bound to FcεRI on effector cells will lead to productive crosslinking and mediator release [30]. According to that principle, IgE towards tumour antigens also need to be cross-linked by tumour antigens to be tumoricidal. When comparing thus the requirements of an allergen to those needed for an overexpressed tumour antigen, the critical point seems to be epitope-spacing and -rigidity. More than any other immunoglobulin class IgE antibodies are tightly fixed to their receptor in a bent form [31]. This geometry determines the minimal requirements for epitope spacing on the triggering antigen for successful IgE bridging. More than at least two epitopes have to be minimally 40Å and maximally 240Å apart, and they have to be displayed rather rigidly [32]. These requirements are excellently fulfilled by most potent allergens forming covalent multimers, but may also be achieved by non-covalent complexing of molecules by aggregation. The capacity of cellular antigens to bridge cytophilic IgE has thus to follow strict geometrical rules and in principle, two different scenarios can be considered: (i) at low-level antigen expression, for instance such as levels of growth factor receptors on healthy cells, IgE bridging cannot be achieved; (ii) in contrast, overexpressed tumour antigens, tightly packed on the whole cell membrane or packed in lipid rafts, obviously may achieve bridging requirements because they form tumour-associated molecular patterns [32]. This implicates that at the site of the tumour, IgE may fully exert all effector functions via FcεRI on shuttle cells, such as macrophages, mast cells and eosinophils. All these cell types have been observed previously in tumour tissues [33, 34].

Ideally, an engineered tumour-specific IgE antibody may, like natural anti-tumour IgE, exploit the specific effector mechanisms at the site of the tumour where the highest target antigen expression is found, but not systemically.

There is, however, a last concern before clinical studies with therapeutic IgE can be initiated: The possible crosslinking capacity of soluble forms of tumour antigens. This important concern is carefully addressed by Rudman and co-workers in this issue [35]. For most tumours, antigen shedding is a well-known mechanism as a sign of immunological escape [36]; moreover some soluble tumour antigens may regulate tumour growth for instance by modulating angiogenesis or lymphangiogenesis [37], or by interaction with specific receptors [38]. Alternatively metalloproteinases like ADAM15 may shed functional ectodomains of membrane antigens that stabilize heterodimerization and, as a result lead to receptor activation [39]. Therefore, soluble tumour antigens in the circulation may potentially trigger anaphylactic effector cells via tumour-specific IgE before it has been shuttled to the cancer tissue, if it has capacity to crosslink IgE.

In line with their previous fundamental work on anticancer IgE in this issue Rudman et al. tackle this question by a series of elegant \textit{in vitro} assays. Their work is the logical consequence of a series of studies, in which they repeatedly could demonstrate the superior \textit{in vitro} and \textit{in vivo} efficacy of a recombinant anti-folate receptor α (FRα) IgE antibody Mov18 [17-20]. FRα is very specifically overexpressed in ovarian cancer and represents...
therefore an interesting target [40], but it is also found in a monomeric form in the circulation. The potential IgE crosslinking capacity of soluble FRα represents thus an important safety aspect that needs to be answered in readiness for clinical application of IgE for cancer treatment.

Indeed, the authors add convincing evidence for safety of a humanized IgE-anti-tumour antibody: In line with the in silico stereometric arguments above, they demonstrate that FRα overexpressed on tumour cells, but not soluble FRα is able to crosslink the engineered anti-FRα IgE antibody when fixed to effector cells. This effect could be reproduced using a rat basophil leukaemia cell line transfected with human FcεRI [41]. More close to the clinical setting, the effects could be reproduced with patients’ primary human basophils either isolated or within whole blood which also did not get activated by Mov18 IgE in context with monomeric soluble FRα. This observation held true although levels of soluble FRα were significantly elevated in ovarian cancer patients’ sera as compared to healthy controls. Their data suggest that the extent of FRα overexpression on the tumour cells and the density of tumour cells determine the IgE-crosslinking capacity. Therefore, circulating tumour cells will most likely not be able to trigger mediator release. The truly innovative aspect of this highly interdisciplinary work is that not only assays are used which support a research hypothesis, but also material from cancer patients suffering from ovarian cancer of various stages which supports the clinical relevance of the observations.

The work by Rudman et al. [35] may open up avenues to novel anti-cancer therapeutics based on IgE antibodies in clinical oncology. For the allergy field, studies on this specific topic may contribute to the basic understanding of IgE biology possibly offering a rationale for the survival of IgE immunoglobulins.

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References


