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# Autoimmunization to Epidermal Growth Factor, a component of the immunological homunculus

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## Abstract

Epidermal growth factor (EGF) is being tried as a vaccine in cancer immunotherapy with the aim of inducing neutralizing antibodies that might affect EGF-dependent tumors. Here we summarize our experience using the EGF self-molecule as an autoimmunigen. We report here that IgG anti-EGF antibodies are prevalent in healthy people and that augmentation of the response to EGF requires conjugation to an effective carrier and an adjuvant. Paradoxically, the response to EGF immunization could be enhanced by an ‘immunosuppressive’ treatment with cyclophosphamide, most probably by suppressing active control mechanisms. EGF is expressed in the thymus. Thus, EGF may be added to the immunological homunculus, the class of self-antigens to which there is both natural autoimmunity and natural regulation of the autoimmunity. The results using EGF as a vaccine can teach us about the homunculus and how to activate it. © 2002 Elsevier Science B.V. All rights reserved.

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## Take-home messages

- Immunogenic cancer vaccines can be created using homuncular self-antigens and not only by using cancer-specific neoantigens. This conclusion is reasonable. Autoimmunity to homuncular self-antigens is built into the system through a relatively high frequency of specifically reactive T cells and B cells; fewer precursor cells are likely to exist with receptors for neoantigens. Thus homuncular self-antigens are likely to be more immunogenic than are the rare antigens specific to a tumor. In fact, oncologists have discovered that immune responses to cellular melanoma vaccines are mostly directed to conserved self-antigens rather than to neoantigens [29,30].
- To be effective, cancer vaccines should include adjuvants, strong pro-inflammatory signals.
- Cryptic self epitopes might be more effective than are dominant epitopes. This notion, however, needs more conformation.
- High dose, frequent and repeated vaccination might be required to overcome the natural down-regulation that controls homuncular autoimmunity.

**Abbreviations:** mu-, mouse; hu-, human; EGF, Epidermal Growth Factor; mAb, monoclonal antibody; CFA, Complete Freund’s Adjuvant; IFA, Incomplete Freund’s Adjuvant

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- To further overcome natural down-regulation, some form of immunosuppressive treatment should be considered in the vaccination protocol.
- The risk of autoimmunity, as a side effect of the homuncular immunotherapy, remains to be established. For reasons that are not entirely clear, autoimmunity rarely leads to autoimmune disease. It seems that tissue signals are important in regulating the outcome of immune attack [31] and it is possible that a tumor might be more susceptible to autoimmune damage than is healthy tissue.

## 1. Introduction

Immunology, born a century ago as a branch of microbiology, has built most of its experimental basis on immunization to foreign antigens. Much less information has been gathered about the reactivity of the immune system to self-molecules and most autoimmunization experiments have been limited to animal models involving a handful of experimental autoimmune diseases. Nevertheless, the detection of natural autoantibodies [1] and self-reactive T cells in healthy subjects [2], the discovery of the role of positive selection of the T-cell repertoire by self-peptides in the thymus [3], and the existence of a functional immune system in antigen-free animals [4] indicate that there naturally exists a background of immune reactivity towards self molecules.

It has been noted that natural autoimmunity is not random, but seems to be directed towards a particular subset of self-antigens. The immunological homunculus is the term that has been applied to the natural autoimmune repertoire directed to these dominant self-antigens [5,6]. The immunological homunculus can be viewed as an internal representation of certain self-molecules, analogous to the neurological homunculus, the nervous system's functional picture of the individual's body imprinted in the sensory and motor cortices. The neurological homunculus is composed of networks of connected neurons. The immunological homunculus, in contrast, is composed of T and B cells that recognize dominant epitopes of the self and these autoimmune cells, like neurons, are regulated by cellular networks, which include here idiotype–anti-idiotype interactions.

Which self-antigens are included in the homuncular set? T-cells recognizing self heat shock proteins [7], myelin [8], insulin [9] thyroglobulin [10] acetylcholine receptor and myelin oligodendrocyte glycoprotein (MOG) [11] have been described in the natural repertoire, suggesting that these pro-

teins are target antigens. Coutinho and his colleagues, using an immunoblotting technique [12], have detected stable patterns of natural autoantibodies that recognize a restricted set of self proteins; these patterns are highly conserved from one individual to another, thus creating the B cell immunological homunculus, in both experimental animals [13] and human subjects [14]. These and other experimental observations support the view that not all self-molecules are equal in the immune system; a privileged subset of self molecules exist, for which the immune system has built a complex fail-safe regulation [15]. These observations, however, are only the beginning of the story; the immunological homunculus requires a more precise characterization of its component parts, their molecular connections, the ontology of its development and its physiological and pathological behaviors. In this article we draw some general conclusions about the immunological homunculus based on investigation of the autoimmunology of what appears to be a new member of the homuncular set, Epidermal Growth Factor (EGF).

For the past 8 years, the staff at the Center of Molecular Immunology in Havana has been studying active immunization to diverse formulations of EGF both in experimental animals and in human cancer patients. The ultimate goal has been to exploit autoantibodies as a way to remove or inactivate EGF, aimed at reducing the growth rate of human EGF-dependant tumors [16,17]. EGF vaccination is currently in clinical trials as a cancer vaccine [18]. Dozens of experiments in mice, rats and monkeys have been carried out, and more than 60 human cancer patients have been vaccinated. Irrespective of the clinical success of these trials, this work has provided a rare insight into human autoimmunity based on deliberate immunization to an autologous growth factor; this novel insight into autoimmunity may help us better define and characterize aspects of the hypothesis of the immunological homunculus.

### 1.1. Natural IgG antibodies against self-EGF

The study of EGF autoimmunity in humans led to a surprising finding; significant IgG anti-EGF antibody titers were present in many subjects even before the initiation of active vaccination. This observation obliged us to study natural autoimmunity to EGF in more detail.

Sera from 61 healthy blood donors were collected and natural anti-EGF antibodies were measured using an ELISA test. Natural antibodies to human serum albumin (HSA) and insulin were measured as specificity controls. Positive sera were defined as those that manifested an ELISA OD 405 reading that was at least 5 standard deviations greater than the mean OD obtained in wells that contained fetal calf serum instead of the patients' sera. We found that 79% of 61 healthy individuals had measurable anti-EGF antibody titers at a serum dilution of 1:500; this prevalence of positive anti-EGF antibody was significantly higher than that of antibodies to HSA (2%) and insulin (17%). The natural IgG antibodies were specific; the binding could be inhibited by adding an excess of EGF to the ELISA well. Sera from cancer patients also were found to contain natural anti-EGF antibodies, but the frequency of these antibodies was not greater than that found in sera from healthy subjects. Natural antibodies to EGF were not related to gender. In mice, the prevalence of sera with natural anti-EGF antibodies was 20% for the BALB/c strain and 25% for the NMRI outbred strain, at a dilution of 1:100.

## 2. Adjuvants and molecular alterations influence immunization to self-EGF

Active subcutaneous immunization against self-EGF was done in mice using mouse EGF (mu-EGF) in Complete Freund's Adjuvant (CFA). We found that BALB/c mice did not produce antibodies against mu-EGF unless the antigen was chemically linked to carrier proteins (Tetanus Toxoid or Cholera toxin B-chain). In this case, antibody responses were obtained up to titers of 1:1000 in all of the immunized animals. However, the need for a foreign carrier molecule could be overcome if the BALB/c mice were immunized with human

recombinant EGF (hu-EGF). The resulting antibodies recognized mu-EGF. Hu-EGF and mu-EGF differ by 16 of the 53 amino acids constituting the molecule [19] and this difference apparently suffices to circumvent the natural down-regulation of the response to immunization to self-EGF epitopes. In contrast to the BALB/c mice, only 20% of the outbred NMRI strain made antibodies to mu-EGF when immunized with hu-EGF, but that response could be raised to 100% if the hu-EGF was linked to a carrier protein. Thus, it appears that genetic differences between mice can influence the nature of the response to self-EGF epitopes. The antibodies elicited in response to EGF immunizations were of the IgG isotype. This indicates that the response was T-cell dependent.

Autoantibodies to EGF could also be elicited in three different species of non-human primates (green monkeys, rhesus monkeys and chimpanzees). Like the immunized mice, the immunized primates made no antibody in response to self-EGF (hu-EGF) administered in Alum adjuvant. But an anti-self-EGF antibody response could be induced by immunizing them with hu-EGF linked to a carrier protein.

Clinical trials in humans have demonstrated that an IgG autoantibody response to hu-EGF can be elicited by immunization with hu-EGF linked to a carrier protein (Tetanus Toxoid or the P64K recombinant protein from *Neisseria meningitides*), administered either in Alum or Montanide ISA 51 as adjuvant.

## 3. Repeated immunizations maintain titers of human anti-EGF.

The protocol for vaccination of human subjects included five weekly doses of 50 µg of hu-EGF, followed by 50 µg given a month later; the adjuvants were either Alum or Montanide ISA 51. The anti-EGF antibody titers reached levels ranging between 1:2000–1:32 000 in 60% of the immunized subjects. These anti-EGF titers declined spontaneously after 6 months. Upon re-immunization with a single injection, antibody titers rose, but only to the levels reached in the first round of immunization. The titers dropped after 2–4 months. Repeated immunizations were

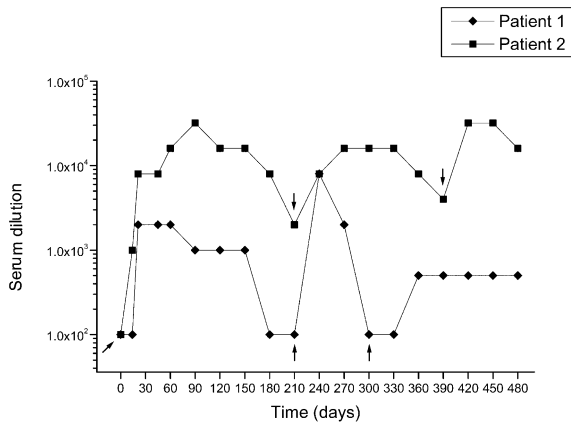


Fig. 1. Time course of anti-EGF antibody titers in two patients. The arrows indicate the time of immunizations. Primary immunization was a course of 5 weekly subcutaneous injections of 50  $\mu$ g. At various times, serum samples were taken and antibodies against hu-EGF were measured using an ELISA test, as described [17].

needed to maintain a high level of anti-EGF antibodies (Fig. 1).

Tetanus Toxoid was found to be an effective carrier in humans; a high memory antibody response (up to 1:800 000 dilution) to EGF was obtained, probably because all patients had previously received anti-tetanus vaccinations.

#### 4. Immunosuppression increases the anti-EGF antibody response

The theory of the immunological homunculus proposes that immune responses to homuncular antigens are naturally controlled by active immune down-regulation [5]. If this were true, then the response to immunization with homuncular self-antigens might be amplified by suppressing the proposed regulatory mechanisms. To test this notion, BALB/c mice were immunized using a combined protocol: the mice were injected subcutaneously with 2 doses of hu-EGF in CFA, 10  $\mu$ g each dose. A group of animals were treated with Cyclophosphamide 3 days before the first immunization, receiving 100 mg/kg body wt.

We found that Cyclophosphamide pretreatment favored the induction of the antibody response to EGF. At day 81, the geometric mean titre of the

group immunized with hu-EGF alone was  $400 \pm 20$ , while that of the group pre-treated with cyclophosphamide was  $2250 \pm 40$  ( $<0.01$ ).

To evaluate the contribution of T cell subpopulations to this effect, we immunized BALB/c mice subcutaneously with hu-EGF in CFA (50  $\mu$ g), and 2 weeks later treated them intravenously with a single depleting dose of either anti-CD4 or anti-CD8 antibodies. Five days later, the immunized mice were boosted subcutaneously by a second dose of hu-EGF in IFA (50  $\mu$ g). Fig. 2 shows that both the anti-CD4 and the anti-CD8 antibodies acted to enhance the IgG antibody response to EGF, which was significantly higher than the response of the mice immunized twice with hu-EGF and treated with control saline. Thus, 'immunosuppressive' antibody treatments did indeed act to amplify the autoimmune IgG response to EGF.

To evaluate the clinical relevance of this notion, 20 lung cancer patients were immunized with 5 doses of the EGF vaccine, 50  $\mu$ g each dose. Patients received Alum or Montanide ISA 51 as adjuvant. Another group of 20 patients received a similar schedule of immunization, but were treated with Cyclophosphamide at 100 mg/kg per body wt., 3 days before the first immunization. Cyclophosphamide pretreatment consistently enhanced

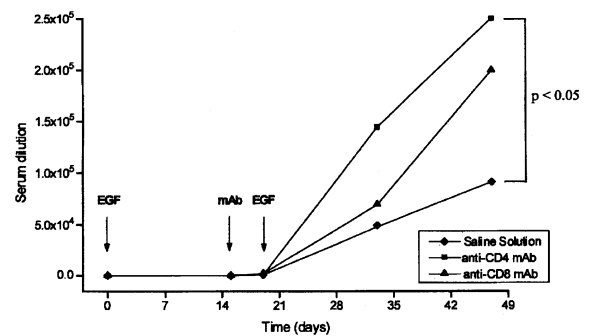


Fig. 2. Immunosuppressive monoclonal antibodies, anti-CD4 or anti-CD8, enhance the anti-EGF antibody response. BALB/c mice (5 in each group) were immunized with hu-EGF (50  $\mu$ g, subcutaneously, in CFA) at days 0 and 19 (IFA was used as adjuvant in the second immunization). Between both immunizations, a single dose of either anti-CD4 or anti-CD8 monoclonal antibodies (0.5 mg, intravenously) was given on day 14. Geometric means of anti-EGF antibody titers measured in sera taken at days 0, 19, 33 and 47 are shown.

Name	Sequence
hu-EGF	MNSDSECPLSHDGYCLHDGVCMYIEALDKYACNCVVG YIGERCQYRDLKWWELR
P 1-14	MNSDSECPLSHDGY
P 7-21	CPLSHDGYILHDGVC
P 15-33	CLHDGVSMYIEALDKYACN
P 34-54	CVVG YIGERCQYRDLKWWELR
P 34-46	CVVG YIGERCQYR
P 44-54	QYRDLKWWELR

Fig. 3. Sequences of EGF peptides used in epitope mapping.

the antibody response to EGF with either of these adjuvants, to a somewhat greater degree with Montanide ISA 51. This result confirms previous observations that Cyclophosphamide pre-treatment can enhance specific immunity against selected cancer vaccine antigens [20].

### 5. Shifts in epitope dominance during EGF vaccination

To map the epitopes of EGF recognized by anti-EGF antibodies, we prepared 6 peptides, synthesized to cover different zones of the EGF molecule (Fig. 3). Sera of the patients included in the EGF-vaccine trials were tested for antibodies against the various peptides, both before and after vaccination.

All 6 peptides were recognized with diverse intensities by antibodies in pre- and post-vaccination sera, at dilutions of 1:100. However, the amino-terminal peptides 1–14 and 7–21 were preferentially recognized by natural antibodies present before vaccination, whereas the central peptide 15–33 and the carboxy-terminal peptide 34–54 were better recognized by sera obtained after vaccination. These two last peptides include disulfide bridges, which define the two carboxy-terminal loops of the EGF molecule. The central loop peptide 15–33 was dominant in the post-vaccination response even in patients treated with the immunosuppressive agent Cyclophosphamide before vaccination, in whom antibodies against the other peptides disappeared. Thus, vaccination with self-EGF appears to shift the antibody response away from epitopes recognized by natural autoantibodies.

### 6. EGF expression in the thymus

Homunculus theory proposes that the structure of natural autoimmunity and its connectivity to dominant self epitopes is a germ-line property, which has evolved through the experience of the species. But how can germ-line experience influence the structure of the antigen-receptor repertoire which is somatically selected? Quite simply, the germ-line encoded expression of particular self-antigens in the thymus (and elsewhere) early in T-cell ontogeny could, by positive selection, determine the emerging repertoires of immune receptors in favor of homuncular antigens [15]. Is EGF a candidate homuncular antigen, expressed in the thymus?

It has been reported that thymus epithelial cells contain EGF-receptors and can be stimulated by EGF to proliferate [21]. The treatment of thymus epithelial cells with EGF or TGF-alpha increases IL-1 and IL-6 production, thus establishing a link between epithelial cell growth factors and the cytokines of the immune system [22]. Indeed, fetal organ cultures express both functional EGF receptors and the EGF molecule itself [23]. There is also a high-molecular weight EGF-like molecule present in the membranes of fetal thymocytes [24]. In fact, the submandibular gland, the main source of EGF in vivo, has been claimed to be a key organ in the neuro-immunoregulatory network [25]. EGF is thus expressed in the thymus and elsewhere in a way that conceivably could very well influence positive selection of the T-cell repertoire. It is presently unknown how EGF and other homuncular self-antigens avoid negative selection.

## 7. Towards an operational definition of homuncular self-antigens

The studies of autoimmunity to self-EGF described here lead us to a functional definition of a homuncular antigen. A homuncular self-antigen is one that:

1. is recognized by natural autoantibodies and T-cells in healthy subjects;
2. is expressed in the thymus;
3. activates an immune response more effectively when accompanied by accessory signals — adjuvants, carrier epitopes or carrier molecules;
4. the immune response to the antigen can be enhanced by suppressing immune regulation; and
5. the antigen can be a target molecule in an autoimmune disease.

Up to now, no autoimmune disease has been described in which EGF is the target, but it has been reported that patients with systemic lupus erythematosus have circulating autoantibodies directed against a region of thrombomodulin containing EGF-domains and that these antibodies could be a risk factor for the occurrence of thrombosis [26].

In our experiments, the novel finding has been that the immune response to EGF can be enhanced by immunosuppressive treatment using anti-CD4 or anti-CD8 monoclonal antibodies combined with immunization. This finding is compatible with the concept of dominant tolerance mediated by T cells. Sakaguchi and colleagues have demonstrated that autoimmune disease can be induced by immunosuppression [27]. Regulatory T cells normally limit the expression of immunity to homuncular antigens as part of the tight control exerted by the immune system itself on its own autoimmune repertoire [28].

Although many of these conclusions diverge from currently accepted vaccination practices, the experience with EGF auto-vaccination suggest their consideration. The more classical approaches, as is clear to all, need renovation [15].

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