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Review

Activation of benign autoimmunity as both tumor and autoimmune disease immunotherapy: A comprehensive review

Irun R. Cohen*

Department of Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel

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ABSTRACT

Here, I consider how benign autoimmunity, the immunological homunculus, can be used to reinstate the healthy regulation of inflammation in both autoimmune diseases and in tumor immunotherapy. Different autoimmune diseases manifest clinically distinct phenotypes, but, in general, they all result from the transition of benign, healthy recognition of key body molecules into a damaging effector reaction. Tumors, in contrast to autoimmune diseases, grow by subverting the immune system into supporting and protecting the growing tumor from immune surveillance. Therefore our therapeutic aim in autoimmune disease is to induce the immune system to down-regulate the specific autoimmune effector reaction that causes the disease; in tumor immunotherapy, on the contrary, we aim to deprive the growing tumor of its illicit activation of immune suppression and to unleash an autoimmune disease targeted to the tumor. The recent success of anti-PD1 and anti-CTLR4 treatments exemplify the reinstatement of tumor autoimmunity subsequent to inhibition of immune suppression. With regard to the therapy of autoimmune diseases, I cite examples of immune system down-regulation of autoimmune diseases by T cell vaccination or HSP60 peptide treatment. Inducing the immune system to regulate itself is safer than global immune suppression and may be more effective in the long run.

1. The nature of inflammation and autoimmune disease

An autoimmune disease can be defined as a clinically distinct illness caused by an immune reaction to an otherwise normal molecule or tissue component of the subject's body. The damage inflicted by most autoimmune diseases is marked by recurrent or chronic forms of noxious inflammation; so autoimmune disease is linked to the regulation of inflammation; the link makes sense because the immune system, in its combined innate and acquired arms, is the orchestrator and manager of inflammation [1]. Inflammation has been defined as a process that is initiated by some injury and proceeds towards healing [2]. Inflammation, in essence, arises from an interaction – better, a two-way dialog – between the immune system and the body in its care [1]. Inflammation is a complex and dynamic process that makes it possible for the multicellular, differentiated organism to repair the blows, insults and infections that visit the body as an inevitable condition of post-developmental life; inflammation, like pre-natal development itself, involves modifications in vascular and connective tissues, the flows of blood and extra-cellular and intra-cellular fluids, programed cell death along with cell proliferation, cell migrations, metabolic adjustments, shifting concentrations and flows of signal molecules and cellular dedifferentiation and differentiation [3]. From this point of view, we can understand how tumors can enhance their growth by stimulating a chronic inflammatory response at the site [4].

The task of managing inflammation is exceedingly complicated because the immune system is also engaged in an ongoing dialog with the symbiotic microbiome and viral inhabitants of the healthy body. Symbiosis complicates the distinction between self and non-self; our symbiotic partners are encoded by DNA that is foreign to our genome, yet our healthy bodies are populated with more prokaryote cells than they are with eukaryote, mammalian cells [5]. Commensal prokaryotes serve important functions: healthy metabolism depends on them [6], they prime our immune systems [7] and an inappropriate immune attack on our symbionts can lead to disaster – witness the quasi-autoimmune condition we call inflammatory bowel disease [8].

The exchange of signals between and among immune cells, body cells and symbionts continues throughout life as the organism responds with appropriate inflammatory responses to its shifting internal states and to its changing environment; a healthy life is

Abbreviation: TCV, T cell vaccination.

* Tel.: +972 8 934 2911.
E-mail address: irun.cohen@weizmann.ac.il.

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accompanied by healing inflammation. In this light, we may view much of the damage inflicted by autoimmune diseases as the result of an *inappropriate orchestration* of the inflammatory response; the components of health-restoring inflammation cause disease when they are exaggerated, misplaced, unnecessarily recurrent or fail to resolve [1]: Properly regulated cell death is needed to maintain health, but inappropriate cell death (for example, in type 1 diabetes or multiple sclerosis) can be fatal; scar tissue is essential to health, but inappropriate scar-tissue formation (for example, in rheumatoid arthritis, atherosclerosis, cirrhosis or scleroderma) can be destructive; inappropriate blood vessel formation (for example, in various eye diseases or in lupus) is damaging; cell activations and migrations are common features in both health and autoimmune disease – the reader can supply his or her own special knowledge about inappropriate inflammation in various autoimmune diseases.

Of course there are autoimmune diseases like hemolytic anemia or thrombocytopenia where inappropriate cell death is triggered by the inappropriate production of autoantibodies, but inflammatory phagocytosis also plays a part in these processes [9]. Special cases of autoimmune diseases may involve autoantibodies that act as agonists or blockers of receptor signaling – a possible example is schizophrenia, but even here there are signs of inappropriate inflammation [10].

2. The causes of autoimmune disease

What are the inciting causes of immune mismanagement leading to autoimmune diseases? Causality in biology can usually be parsed into genes or environment, or to a combination of the two. Except for a few, relatively rare conditions such as APS-1 due to the *AIRE* mutation [11], autoimmune diseases arise on a background of a collective of genetic susceptibilities, each contributing relatively low risk [12]; indeed, one's genome does not sentence one irrevocably to an autoimmune disease – even monozygotic twins are often discordant for developing an autoimmune disease [13]. The vast majority of people who harbor autoimmune disease susceptibility genes will never develop the clinical disease – in fact, autoimmune-disease susceptibility alleles are quite prevalent and some of these alleles appear to be advantageous in fighting infections [14]. Thus, the environment would have to be a major factor, if not the major factor in the induction of autoimmune disease; if so, what aspect of the environment is to blame? The simplest answer would be to say that an autoimmune disease arising in different people is likely to arise through different inciting factors in each patient; indeed, any factor that activates inflammation (or immune activation) could lead to an autoimmune disease, *whenever* immune regulation of the inflammatory response fails to manage the situation appropriately. Such inciting factors include infections, trauma, environmental pollution, unhealthy nutrition and even psychic stress. Thus, the root cause of most autoimmune diseases is the failure of the subject's immune-body dialog to orchestrate the dynamics or magnitude of an inflammatory response, limit it to a relevant body site, and terminate it at the appropriate time [1] – ripeness is all. A key issue for our understanding and management of autoimmunity is to learn how the immune system manages inflammation; if in the context of disease we succeed to reinstate the physiologic regulation of inflammation, we may reinstate health.

3. Physiological self-reactivity and the immunological homunculus

The tri-partite dialog of the immune system with our body and with our symbiotic residents requires the transmission and reception of signals between the participants: dialogs depend on understandable languages – be they molecular or verbal. It is clear that signaling by way of cytokines, chemokines, and toll-like and other innate receptors and their ligands form regulatory networks between the immune system, the body and the microbiome. In addition to these communication networks based on innate signals, I have proposed that the autoantibodies and auto-reactive B cells and T cells that are demonstrable in healthy immune repertoires also participate in the ongoing immune-body dialog; benign autoimmunity, by sensing key biomarker antigens expressed by the tissues, can help manage healing inflammation [15]. These auto-reactive repertoires, in effect, form a picture of informative body molecules that can help disclose the state of the body to the immune system – fine-tuning the inflammatory process is enhanced by reliable self-antigen signaling. The immunological homunculus theory proposes that healthy autoimmune repertoires contribute to healthy immune management of inflammation. Autoantibodies have been noted to enhance wound healing [16] and auto-reactive T cells have been reported to exert a protective function in the central nervous system [17]. Some contribution of benign autoimmunity to health is supported by the fact that healthy human babies are born with a shared repertoire of IgM and IgA autoantibodies produced by the developing fetus in utero and directed to a defined set of homuncular self-antigens; babies also receive a repertoire of IgG autoantibodies transferred from mother [18]. It is reasonable to suppose that if every human is born with a shared autoantibody repertoire, such autoimmunity must be doing some good, must bear some selective advantage [19–21].

4. Pathologic self-reactivity

In contrast to the possible contribution of benign autoimmunity to health, the pathogenic roles of autoimmune reactions in autoimmune disease are uncontestable; my colleagues and I were among the first to demonstrate that a single clone of activated, auto-reactive T cells could mediate an experimental autoimmune disease in rodents [22]; auto-reactive T cells even fulfill Koch's postulates as etiologic agents of disease [23]; clinically, specific autoantibodies and auto-reactive T cells are the hallmarks of human autoimmune diseases [1]. The problem is to resolve the paradox of benign autoimmunity as a component of a healthy immune system and pernicious autoimmunity as agents of autoimmune disease. The observation that identical target antigens have been identified in both types of autoimmunity suggests that autoimmune disease involves a transition from benign autoimmunity to pernicious autoimmunity [24]; conversely, one could imagine that a pernicious autoimmune disease might be reversed by inducing a transition from pernicious autoimmunity back to benign autoimmunity. I shall provide two examples below.

5. Autoimmune cancer immunotherapy

In recent years it has become clear that clinically important tumors thrive by inducing the patient's cells in the tumor microenvironment to supply the growing tumor with new blood vessels and growth factors; the tumor also induces Tregs and other endogenous immune cells to suppress the ability of the immune system to attack the tumor (Fig. 1). The clinical benefit of healthy autoimmunity can be inferred by the finding that the administration to cancer patients of antibodies to immune suppressor molecules can unleash an autoimmune attack on the patient's tumor (Fig. 2), leading in some cases to its eradication [25,26]. The molecules PD-1 and CTLA-4 expressed on T cells and other cells were discovered to act in suppressor pathways that down-regulate immune effector activity; hence, treatment of cancer patients with anti-PD-1, anti-PD-1 Ligand, or anti-CTLA-4 antibodies, by blocking

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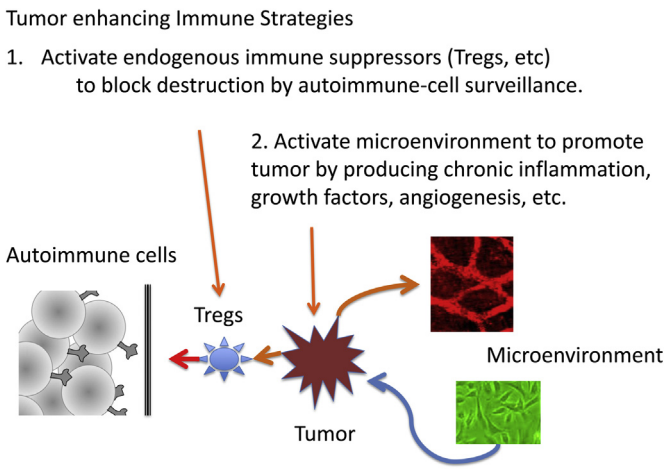

Fig. 1. Growing tumors exploit the microenvironment to obtain blood flow and growth factors and activate immune suppressors to block autoimmune rejection.

these pathways, seems to empower the patient's immune system to penetrate the wall of tumor-induced suppression and attack the tumor [25,26].

Note that anti-suppressor antibody treatment does not actively immunize the patient against tumor-associated antigens; rather anti-suppressor antibody treatment appears to enable latent anti-tumor autoimmunity to assert itself. The anti-suppressor treatments unleash, as it were, an "autoimmune disease" targeted preferentially to the tumor. Except for specific tumors caused by oncogenic viruses, most tumor-associated antigens are self-antigens expressed in healthy cells; anti-suppressor immunotherapy relies on healthy autoimmunity to target the tumor. Indeed, the natural history of a transplantable syngeneic tumor in mice is marked by changes in the autoantibody repertoire; tumors of different virulence and metastatic states are accompanied by varying autoantibody repertoires [27]. What is the origin of tumor-associated autoimmunity?

6. Anti-tumor autoimmunity to tumor-associated self-antigens

Autoimmunity to tumor-associated molecules is expressed in healthy humans from the time of birth: we have found that many of the most prevalent and abundant autoantibodies in the benign auto-reactive repertoires present in healthy newborns and their mothers bind to known tumor-associated self-antigens [18,28]; thus neonates, who are likely to be born free of tumors, already express tumor-associated autoimmunity in preparation, as it were, for neoplastic accidents. The immune system of the developing fetus is exposed to differentiation molecules that become down-regulated as development progresses; but later in life these molecules can become over-expressed by dedifferentiating tumor cells [4,27]. Thus, one may speculate that prenatal exposure to differentiation molecules may prime the human for tumor-associated immune reactivity that can be induced to attack potential tumors when neoplastic dedifferentiation does occur later in life. The idea is that such potential tumor-associated autoimmune reactivity is encoded in the healthy immunological homunculus. We do not as yet know whether latent anti-tumor homuncular autoimmunity (both T cell and B cell) is essential to effective anti-PD1 or anti-CTLR4 antibody therapy [25,26], but this is not an unreasonable working hypothesis.

Speculation aside, conceptually we may link homuncular autoimmunity to both tumor immunotherapy and to autoimmune disease immunotherapy: tumor immunotherapy can be achieved by depriving the tumor of its "protective" immune down-regulation; conversely, autoimmune disease immunotherapy might be achieved by reinstating "protective", self-antigen-specific immune down-regulation; in tumor immunotherapy we want to activate an autoimmune reaction; in autoimmune disease immunotherapy we want to do the opposite and up-regulate autoimmune suppression (Fig. 3). Below, I shall cite two examples of autoimmune down-regulation that were discovered in my laboratory and have made it to successful clinical trials: T-cell vaccination and HSP60 peptide treatment of new-onset type 1 diabetes.

7. T-cell vaccination (TCV)

TCV is a type of autologous, personalized cell-based therapy in which a sample of a subject's autoimmune T cells are expanded and activated *ex vivo;* aliquots of the activated T cells are then attenuated by irradiation and injected subcutaneously back into the subject as a therapeutic vaccine (Fig. 4). The subject responds to his or her own vaccine T cells by activating regulatory networks of T

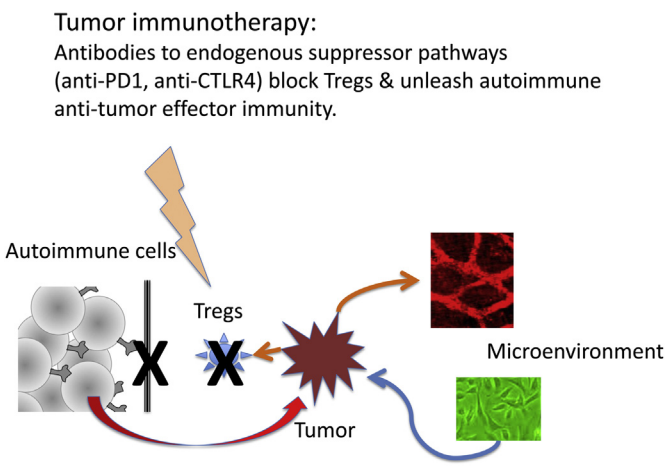

Fig. 2. Tumor immunotherapy: antibodies to endogenous immune suppressor pathways block Tregs and unleash autoimmune cells to attack the tumor. Other tumor-supporting factors in the tumor microenvironment may still operate.

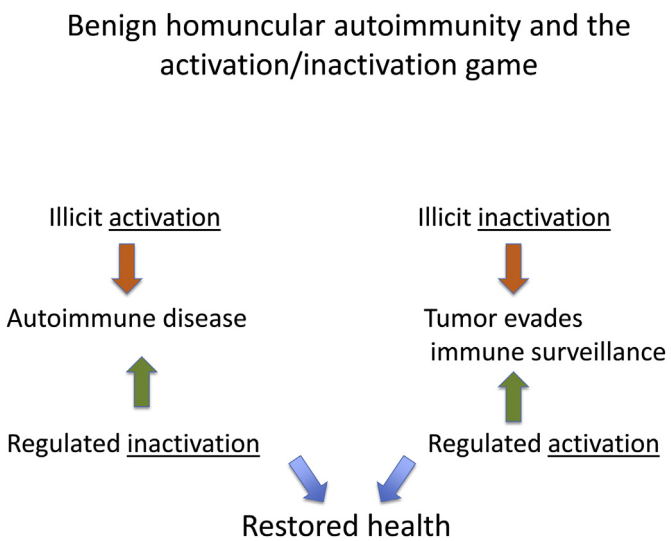

Fig. 3. Homuncular autoimmunity in autoimmune disease and tumor pathogenesis and therapy. The illicit activation of homuncular autoimmunity in autoimmune disease needs to be countered by regulated inactivation, and the illicit inactivation of homuncular autoimmunity by a tumor needs to be countered by regulated activation.

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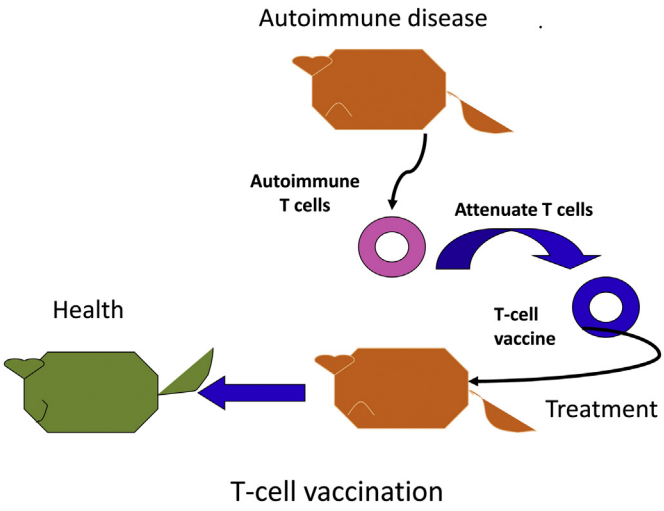

Fig. 4. T cell vaccination. Pathogenic autoimmune T cells are activated and attenuated *ex vivo* to produce a T cell vaccine. The vaccinated subject activates endogenous regulatory networks to down-regulate the inappropriate inflammation that causes the disease.

cells that, in turn, arrest the damaging inflammation that causes the autoimmune disease [29–31].

Note that the regulatory T cells induced by TCV are essentially autoimmune in that they recognize epitopes in the disease-causing T-cell receptors – an example is anti-idiotypic autoimmune regulation [30,31]. Other self-antigen targets presented to T-regulators by activated effector T cells have been identified as "ergotopes" – biomarkers of the state of activation of the disease-causing T cells [32,33]. Thus, TCV can be considered metaphorically to enlist healthy autoimmunity to fight pernicious autoimmunity. The regulatory networks activated by TCV are complex [34,35] and much remains to be studied in the therapeutic process. Nevertheless, TCV has shown safety and effectiveness in various open clinical trials, mostly in multiple sclerosis [36] but also in rheumatoid arthritis [37]. A small, but blinded, randomized and controlled study of TCV in multiple sclerosis has been recently reported to be successful [38]. Unfortunately, TCV has been ignored in the past by standard pharmaceutical avoidance of cell-based, individualized treatments, but cell therapy appears to be coming of age and TCV has been granted fast-track status by the FDA for the treatment of some types of multiple sclerosis [39]. TCV could certainly be considered as a therapeutic option for patients suffering from the less prevalent autoimmune diseases for which there are no specific therapies in existence or being developed.

Note that resistance to an autoimmune disease induced by TCV, at least in experimental animals, is not the result of "clonal deletion" or "non-reactivity" of the autoimmune response to the target antigen; the resistant subject can still respond to the self-antigen that previously induced the disease and the subject continues to harbor potentially pathogenic autoimmune effector T cells [23]; the clinical disease is aborted by termination of the noxious inflammation induced by the benign TCV autoimmune reaction. The ability to recognize the relevant self-antigens persists, only the inflammatory outcome is modulated by the therapy. TCV is a proof of the principle that a pernicious autoimmune disease can be redeemed by healthy autoimmunity.

8. HSP60 peptide therapy of type 1 diabetes (T1D)

HSP60 is a homuncular self-antigen; healthy humans are born with autoantibodies that bind HSP60 [18], and cord blood contains a high frequency of HSP60-reactive T cells [40]. We found that the onset of type 1 diabetes (T1D) in both NOD mice and in humans is associated with up-regulation of anti-HSP60 autoantibodies and T cells [41]. A clone of anti-HSP60 T cells bearing a T-cell receptor sequence shared by different NOD mice [42] identified a peptide segment of HSP60 we termed peptide p277 (positions 437–460 in the HSP60 human sequence); subcutaneous administration of a single dose of 100 μg of p277 arrested the destruction of pancreatic beta cells, even in mice that were already clinically diabetic [43]. The finding that humans with new onset T1D also manifested autoimmune responses to HSP60 and p277 prompted us to explore the possible clinical usefulness of p277 peptide therapy; the peptide was slightly modified to enhance stability and was administered subcutaneously in an emulsion of a digestible lipid vehicle—the combination of p277 and vehicle is termed DiaPep277 [44]. A phase I clinical trial showed no toxicity and phase II trials demonstrated clinical effectiveness and no significant toxicity [45]; most recently, a phase III clinical trial involving over 450 subjects in 40 centers confirmed clinical effectiveness and safety [46], and a confirmatory phase III trial will soon be completed.

Relevant to the present discussion, we should note that a dose of only 1 mg of DiaPep277 given once in three months sufficed to significantly down-regulate beta cell destruction and enhanced significantly metabolic control in the peptide-treated subjects compared to placebo-treated controls [46]. Like most peptides, the half-life of p277 in plasma is short, so the effects of treatment are most probably the result of the induction of an active immune regulatory network [47]. A full description of the immune effects of p277 in mice and humans is beyond the scope of the present discussion, but the main points can be summarized thusly [44]:

Peptide p277 is both an antigen for T cells and B cells and a ligand for the innate toll-like receptor (TLR)-2 on various functional classes of T cells, including Tregs; p277 acts as a co-activator for the suppressive effects of Tregs on T effectors; and p277 is also an antigen for specific T-cell receptors on certain clones of regulatory T cells – the same type of T regulators activated by TCV. In short, peptide p277 is a component of an immune regulatory network. The net effects of p277 treatment, studied mostly in experimental mice, show that effector T cells and autoantibodies to other self-antigens (such as GAD and insulin) are also modulated, but immune reactivity to foreign, bacterial antigens is not affected. Moreover, p277 treatment shows anatomic specificity: T cells recovered from the pancreatic islets of treated mice do not produce the cytokine IFNγ in response to mitogenic anti-CD3, but T cells from the spleens of the same mice respond normally. Spontaneous antibodies to peptide p277 and other HSP60 epitopes appear to be biomarkers indicating natural resistance to the induction of T1D in male NOD mice.

In view of the above effects of peptide p277 treatment, I would like to propose that our successful clinical experience is a demonstration of the ability of a single self-antigen, a component of benign, homuncular autoimmunity, to redeem, at least to some significant degree, the pernicious autoimmunity involved in the inflammatory destruction of beta cells in T1D. Benign autoimmunity can be used to modulate an inflammatory autoimmune disease; peptide p277 is a realization of the immunological homunculus idea.

9. Treating autoimmune disease: to suppress or to activate?

At the present time, clinical therapy for autoimmune diseases is dominated by the use of powerful agents, chemical or biological, that suppress the immune system globally. Such suppressive treatments are costly in undesirable side effects and are not effective in many patients. It is true that artificially suppressing the immune system can arrest the noxious inflammation that causes

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the disease, but global suppression of the immune system over time is likely to neutralize the possibility of reinstating healthy immune regulation; the suppressed subject gets hooked on continuous suppression.

The use of benign autoimmune agents such as TCV and self-peptides contrast greatly with blanket immune suppression; in this case, we don't suppress the immune system globally, rather we attempt to stimulate endogenous immune regulatory mechanisms and thereby enlist the immune system to manage the inflammatory reaction properly (Fig. 5). I would hope that continued clinical successes of TCV and peptide p277 treatments will help strengthen the position of colleagues who have approached therapy of autoimmune inflammatory diseases by activating the immune system to correct itself – examples of this approach are oral tolerance [48], the use of plasmid DNA encoding specific self-antigens [49], or the direct administration of self-antigens [50]. It is certainly safer and more effective in the long run to reason with the immune system than it is to punish it.

10. To summarize

The healthy body from birth is outfitted with a shared set of autoimmune reactivities, both innate and adaptive, aimed at a defined set of informative body molecules – the *autoimmune homunculus*. Fig. 6 summarizes this review. The autoimmune homunculus features, metaphorically like Janus, two functional faces: an aggressive, *war-like* face that generates effector inflammation; and a benign, *peaceful* face that generates healing inflammation. Both types of inflammation are needed to maintain and protect the body.

Autoimmune diseases arise by an illicit autoimmune war on otherwise normal body cells and tissues.

The *tumor state*, in contrast, is marked by peaceful suppression of what should have been an aggressive autoimmune war on the tumor cells.

Ideal therapy of an autoimmune disease will result by reinstating *regulated inactivation* of the state of *war* and reemergence of a state of homuncular *peace*.

Ideal immune therapy of a tumor will result from *regulated activation* of a state of autoimmune homuncular war targeted against the tumor.

11. In honor of Michael Sela and Ruth Arnon

This issue of the Journal of Autoimmunity is dedicated to the honor of Michael Sela and Ruth Arnon. The Journal of

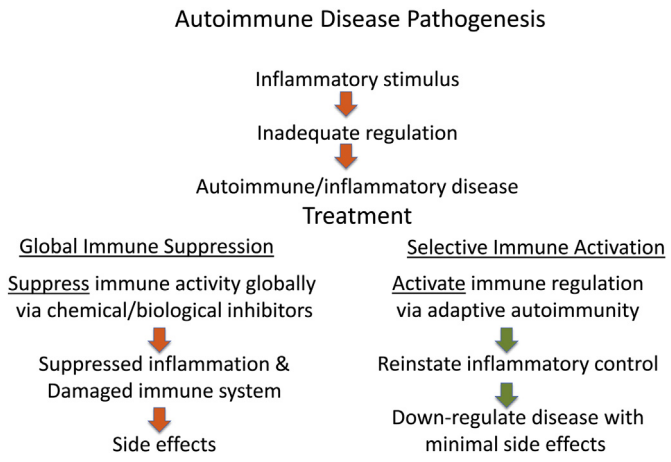

Fig. 5. Autoimmune disease therapy: selective immune system activation contrasts with global immune suppression.

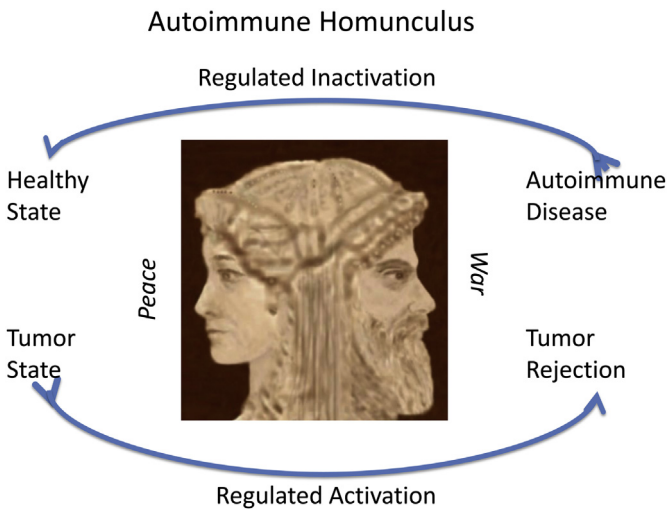

Fig. 6. The two faces of the autoimmune homunculus, and the transitions from states of disease to a state of health – see text.

Autoimmunity has honored distinguished immunologists as well as published dedicated themes on subjects of critical importance, including, for example, recognition of Abul Abbas, Noel Rose and Ian Mackay, and themes focused on the liver as a victim of autoimmunity [51–54]. All immunologists and many hundreds of thousands of patients owe thanks and approbation to Michael and Ruth for their pioneering work on the chemical basis of antigenicity and immunogenicity (the latter term coined by Michael Sela) and for their fundamental discoveries, together with the late Dvora Teitelbaum, leading to their development of an important therapy for multiple sclerosis – glatiramer acetate (Copaxone) [55]. Their translational work on tumor immunotherapy [56] and on vaccine development [57] are a matter of public record. But for me personally, Michael and Ruth together created the infrastructure of people, discovery, thinking, and translational research that has made it possible for me to do the immunology that I have done at the Weizmann Institute – I don't believe I could have thrived so well in any other scientific environment. In fact, Ruth Arnon and Dvora Teitelbaum taught me the basics of experimental autoimmune disease models. Michael Sela for me has been a role model of curiosity about people and the world, of the importance of music, art, literature and dance in the formation of creative thinking, and, above all, of the nobility of being a mensch, a person who forever strives to do the right thing.

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