Journal of Autoimmunity 54 (2014) 112–117

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

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

ARTICLE INFO

Article history:
Received 17 May 2014
Accepted 19 May 2014
Available online 10 June 2014

Keywords:
Autoimmunity
Inflammation
Tumors
Regulation
Immune homunculus

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.

http://dx.doi.org/10.1016/j.jaut.2014.05.002
0896-8411/

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