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Review

Biomarkers, self-antigens and the immunological homunculus

Irun R. Cohen*

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

Abstract

The notion of the immunological homunculus arose from the observations (1) that the healthy adaptive immune system is inclined to respond (T cell reactivity and autoantibodies) to particular sets of body molecules (self-antigens) and (2) that autoimmune diseases are characterized by sets of autoimmune reactivity to some of the very same self-antigens recognized by healthy subjects – with an obvious difference in outcome. I termed this natural autoimmune structuring of the immune system, the immunological homunculus – the immune system's representation of the body. What might be the selective advantage of an immune system expressing patterns of built-in autoimmunity to particular sets of self-molecules? To better characterize the homunculus, we have used informatic tools to study patterns of antibodies to many hundreds of self-molecules arrayed on glass slides – an antigen chip of our design. Results using the antigen chip suggest that the particular self-reactivities comprising the homunculus could serve as a set of biomarkers that help the immune system initiate and regulate the inflammatory processes that maintain the body.

Keywords: Autoimmunity; Immunological homunculus; Heat shock proteins; Inflammation; Disease

1. Biomarkers

A biomarker is a substance or measurement that indicates important facts about a living organism, usually a patient. The Wikipedia defines a biomarker to be

> "a substance used as an indicator of a biologic state …. More specifically, a 'biomarker' indicates a change in expression or state of a protein that correlates with the risk or progression of a disease, or with the susceptibility of the disease to a given treatment. … it can be used … to tailor treatments for the disease in an individual … [and] … may be used as a surrogate for a natural endpoint…" (http://en.wikipedia.org/wiki/Biomarker).

In other words, biomarkers can provide the physician with useful information about:

1. biologic state of an individual;
2. disease risk;
3. disease diagnosis;
4. disease progression;
5. treatments of choice;
6. monitoring responses to treatment; and
7. endpoints for assessing treatment efficacy.

Biomarkers thus allow the physician a preventive or therapeutic jump on the individual's disease process. How can a biomarker provide so much information?

Biomarkers serve because they make life simple. Complexity characterizes biology: the healthy state of a cell, organ, or organism emerges from dazzling amounts of information involving molecules, processes, cells, and organ systems. Disease too is the outcome of a great complexity of factors; so is risk; so is effective treatment. Biomarkers replace with a relatively few simple measurements our need to otherwise detect, collect and judge all the facts of the matter. An effective biomarker, a high concentration of 'bad' cholesterol, for example, can inform us about associated complexities related to genes, heredity, metabolism, diet, blood vessel walls, and the risks of vascular embolism and occlusion [1]. The biomarker, in short, reflects and summarizes all the agents and processes that are needed to produce it – however many and complex these agents and processes may be. A simple biomarker is informative when it faithfully signifies for us the complex factors from which the

* Tel.: +972 8 934 2911; fax: +972 8 934 1 4103.
E-mail address: irun.cohen@weizmann.ac.il

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biomarker emerges. This reduction of biological complexity to one or a few simple biomarkers makes it possible to act quickly without having to wait for real-time events to take place; you can, for example, anticipate, treat and monitor the state of the individual to prevent a future heart attack or stroke. Medical health-maintenance systems do well to prioritize biomarkers.

2. Immune health maintenance

The immune system in both its innate and adaptive arms can be viewed as a type of biological health-maintenance system. In this paper and especially in the accompanying manuscripts to this volume, we attempt to place in perspective in physiological terms, the immune system with respect to the self [2–15].

In physiological terms, we can say that the cells and molecules comprising the immune system act to manage inflammation [16,17]. Inflammation is classically defined as the processes activated by injury that lead to healing [18]. The immune system, by the way it initiates and manages inflammation, maintains health by healing wounds, containing pathogens, organizing the structure of connective tissue, growing (angiogenesis) or destroying blood vessels, triggering regeneration of certain organs, activating the apoptosis of aged, sick or dangerous cells, degrading accumulations of abnormal molecules, disposing of waste, and performing other vital activities [16]. These varied expressions of inflammation maintain the integrity of the organism in response to its relentless post-developmental decomposition caused by environmental injuries and infections, accumulations of metabolic products, waste, and other intoxications, and the inexorable advance of entropy. Well-regulated and timely inflammation maintains health. Hence, to the extent that the immune system initiates and regulates healthy inflammation, the immune system is a health-maintenance system. But, like many other well-intentioned agents, inflammation itself can cause harm; dysregulated or misapplied inflammation produces disease that may require anti-inflammatory therapy [19]. There is considerable discussion on immune regulation in patients with autoimmune disease [20–22]. Let us focus, for now, on the immune regulation of healthy inflammation.

3. Immune computation for health maintenance

Health maintenance performed by the immune system, like health-maintenance systems devised by humans, requires that the systems have access to information regarding biologic state (is something wrong?) and information regarding disease process and choice of therapy – how the problem can best be handled (choice of inflammatory response type: Th1 or Th2; induce cell growth or apoptosis; and so forth). Moreover, the inflammatory process has to be adjusted dynamically as healing progresses and terminated when repair is achieved. It may be said that the healthy immune system functions to translate the dynamic state of the body into the dynamic state of the immune response (Fig. 1). Elsewhere I have proposed that the translation of body state into a fitting immune response state

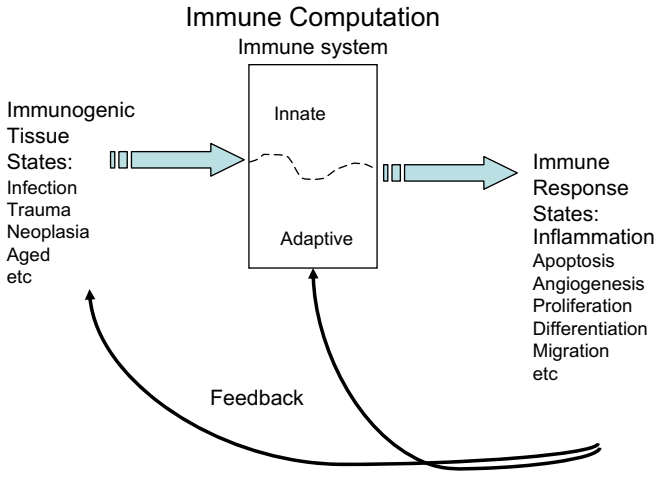

Fig. 1. Immune computation. The immune system in both its innate and adaptive arms is affected by signals that reflect the immunogenic states of body tissues; these signals are molecular patterns generated by infection, neoplasia, trauma, aging, and so forth. The immune system transforms these signals into varieties of immune response – immune response states – leading to a variety of inflammatory effects: apoptosis, angiogenesis, etc. The transformation of immunogenic tissue states into immune response states constitutes computation [23]. The immune response feeds back to affect the state of the tissues – usually to induce healing. Note that the immune system itself is influenced by feedback from its own reactions; in this way, the immune system is self-organizing [16].

can be termed immune computation [23,24]. Successful immune computation is a boon; immune miscalculation is a misfortune. How can the immune system manage inflammation properly given the complexity of the organism?

4. Biomarkers for immune health maintenance

Complexity reduction is key; living systems are just too complex to control without reducing the information to manageably small pieces [25]. It is impossible to measure every factor relevant to the state of any living organism; indeed, even a sample of the information, if too large, can be confusing if not paralyzing. The immune system, like any good physician, has to focus on essentials; to function, the immune system needs to attend to a relatively few, but informative signals. The immune system, like health-maintenance systems generally, needs biomarkers. I propose that an important function of the immunological homunculus is to create and detect biomarkers (Fig. 2).

5. Innate-ligand and self-antigen biomarkers

The classical formulation of the clonal selection theory proposed that the healthy immune system must be blinded to body molecules by the deletion of self-reactive lymphocytes during development [26]. Neo-clonal selection theories continue to teach that the healthy immune system must not respond to self-molecules, but add ignorance [27] and/or active regulation [28] to clonal deletion to annul autoimmunity. To regulate healthy inflammation, however, the immune system must be

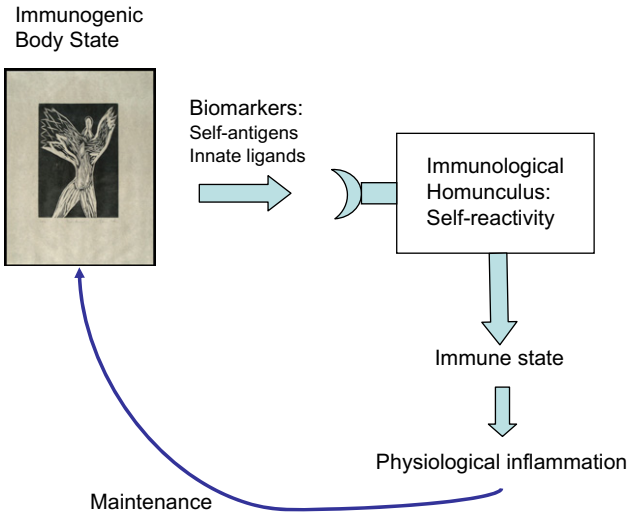

Fig. 2. Immune biomarkers. The self-antigens and innate ligands that transmit the states of the body to the immune system can be viewed as biomarkers. These biomarkers are detected by natural autoimmunity – the immunological homunculus – leading to immune response states that initiate and regulate inflammation. Physiological inflammation maintains the health of the body.

sensitive to the state of the body and intimately responsive to it; autoimmunity, rather than shunned, has to be built into the system; a degree of autoimmunity must be physiological.

Indeed, the immune system appears to scan and respond to body molecules by way of several sets of receptors. Innate receptors belonging to the Toll-like receptor family respond to both foreign and self-molecules [29]; innate receptors for cytokines, chemokines and other molecules allow immune cells to detect and respond to molecules produced by body cells [30]. The classical clonal selection theory did not view innate receptors as 'real' immune receptors; 'real' receptors were limited to adaptive antigen receptors [26]. Now, however, it is clear to immunology that the innate and adaptive classes of immune receptors are functionally integrated into a single immune system [16,23]. The immune system inspects the body using both its innate and adaptive receptors. Which body molecules are recognized by adaptive antigen receptors?

6. Homuncular biomarkers

We recently studied the autoantibodies present at birth in human cord blood – the congenital immunological homunculus – using an antigen microarray chip [31]. We surveyed IgG, IgA and IgM antibodies binding to about 300 self-antigens. IgG antibodies are actively transported from the mother to her developing fetus, so the repertoire of IgG autoantibodies in cord blood represents primarily the homunculus repertoire developed by the mother. The cord blood IgA and IgM antibodies, which do not cross the placenta, were produced by the babies in utero. Although the 300 self-molecules spotted on the microarray are likely to be a relatively small selection of homunculus reactivities, the set of self-antigens bound by the congenital repertoire of homuncular autoantibodies is informative: The self-molecules included tissue antigens (glutamic acid decarboxylase, myelin oligodendrocyte glycoprotein, myosin, collagen 1, thyroglobulin), immune modulator molecules (gelectins, ubiquitin, gelsolin, interleukins), and stress proteins (HSP40, HSP47, HSP60 peptides, HSP70 peptides) [31]. It seems reasonable to suspect that these self-molecules can provide the immune system with just the right kinds of biomarker information about body state needed to manage a healthy inflammatory program (Fig. 2). Tissue-associated antigens can mark the address – the site where immune intervention is needed; stress-associated molecules can mark the nature of the insult and its progression. Indeed, the immune system – by anti-ergotypic T cells and antibodies, cytokine networks and immune memory – is able to monitor its own state in the course of the immune response [16,23,24,30].

7. Advantages of the immunological homunculus

Many of the self-antigens implicated in autoimmune diseases are recognized by autoimmune T cells and B cells present in the healthy immunological homunculus from birth [31]. Thus it is reasonable to conclude that the structuring of autoimmune reactivity encoded in the homunculus in health probably plays a role in the pathophysiology of autoimmune disease; disease-causing T cells and autoantibodies could arise from the pathogenic activation of autoimmune progenitor clones resident within the homunculus set of natural autoreactivities [16]. Hence, the immunological homunculus, from an evolutionary perspective, is costly to maintain. The fact that the homunculus exists implies that the occasional cost in disease must be offset by a general benefit of natural autoimmunity to health. What are the advantages of having natural autoimmunity built into the immune system?

It has been proposed that natural autoimmunity could help rid the body of troublesome waste molecules and cells [32]. Natural autoimmune T cells and B cells and autoantibodies, in addition, could provide an early immune response to pathogens expressing molecules that are cross-reactive with particular self-antigens [33]; an example is the response to bacterial heat shock proteins and other molecules that are highly conserved and cross-reactive with self [34]. Natural autoimmunity has also been proposed to prevent pathogenic autoimmunity by generating regulatory circuits [35,36] or by blocking the access of potentially pathogenic agents to key self-antigens [37]. Note that these proposed health-promoting attributes of natural autoimmunity are not mutually exclusive; the immunological homunculus might help maintain health in a variety of ways. Here I suggest we might add to the list of benefits the idea that the self-antigens recognized by homuncular agents can also serve as biomarkers that inform the immune system of the state of the body, both locally and globally. If this is true, then we might be able to gain some insight into states of health and disease by studying an individual's patterns of autoimmunity [23]. The immunological homunculus, as a natural biomarker system for immune health-maintenance, might be enlisted to serve our medical health-maintenance system. It might also help us choose the correct medication for patients

[38]. We just have to listen to what the immunological homunculus can tell us [39,40].

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