INVITED ARTICLE

The immune system, natural autoantibodies and general homeostasis in health and disease

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"…We have met with a paradox.
Now we have some hope of making progress…"
Niels Bohr

Abstract
It is generally accepted that the destination of the immune system is not only to discriminate between self and non-self but also to mount responses against non-self. During the last decades, it became evident that weak self-reactivity is a necessary condition for immune homeostasis. Natural self reactivity and the internal image created by autoantibodies, participate greatly to the maintenance of homeostasis. Under conditions of increased or altered antigenic pressure, the homeostatic status is disrupted and the organism becomes vulnerable to the emergence of diseases.
"Immunculus" is the self-reactive and interconnected entity of the immune system, provided by a complicated network of natural autoantibobies of different specificity, as a mosaic picture. Quantitative changes in each part of the image are related to variations of expression of relative antigens. The immune system takes in account image information from the continuous screening of the antigenic status and compares between presented state and the desired (optimal) one. Substantial and prolonged deviations from the optimal state, triggers the induction of compensatory and reparative processes, aiming to restore molecular and functional homeostasis.
So, natural autoimmunity through the ability of natural a-Abs to induce mechanisms of natural and acquired immunity, aims to prevent pathogenic processes and maintain or restore health status. Hippokratia 2011; 15 (4): 295-298

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Natural autoantibodies and the health state of the human organism

The last twenty years of clinical immunology research, scientists faced the emerge of paradoxes *sui generis* contradicting adopted positions on the function of the immune system. As an example, the role of natural serum autoantibodies (a-Abs) in health and disease may be noted. The generation of a-Abs against self-antigens is a common phenomenon in humans. Earlier, elevated levels of a-Abs had been exclusively associated with the pathogenesis of autoimmune diseases. Now, it is a common place that the rise of serum content of many a-Abs also occur in the context of other diseases, not belonging to the spectrum of autoimmune diseases, including stroke[1], cancer[2], or complicated pregnancy[1]. Moreover, it was clearly demonstrated that natural a-Abs of IgG, and IgM classes against very different self-antigens are permanently present in the serum of healthy individuals[3]. Experimental data indicates a roughly equal serum content of a-Abs of the same specificity in the vast majority of healthy individuals[3]. Conversely, notable deviations in the production and serum content of particular a-Abs are related to primary molecular changes in certain cell populations, in different tissues and organs, accompanying a plurality of diseases[4]. It seems that production and secretion of natural a-Abs are regulated directly by the quantity/availability of respective antigens (by feed-back principle[5]). Since expression/degradation rates of any cytoplasmic, membrane, or nuclear antigen in any specialized cell is nearly the same in any healthy person (they vary only slightly between individuals), minor variability

in serum content of a-Abs with different specificities, is typical for humans in the normal (healthy) state, but not for cases of pathology.

Plurality of very different chronic diseases has been connected to the steady abnormal changes in the rates of apoptotic, necroptotic, or necrotic events, as well as to the abnormalities in expression/secretion of multiple autoantigens. Such events lead inevitably to changes in the serum content of a-Abs with respective specificity (feedback principle).

In spite of former ideas about immanent aggressiveness of any form of autoimmunity *("horror autotoxicus"),* secondary elevation of natural a-Abs does not reveal to, and not reflect the self-destructive activity of the immune system[1]. Immune recognition of different malignant tumors[2,6] is completely analogous to the immune recognition of any foci of non-malignant pathology in any organ and is reflected in secondary changes in the production of a-Abs against antigens of affected cell populations[4]. Accordingly, quantitative changes in serum contents of a-Abs directed to multiple malignant cell-associated antigens, could be considered as indicators of active immune recognition of tumors, just as in any other form of chronic pathology. On these grounds, an explanation might be given on the paradox: why the immune system can actively "see" growing tumor but not destroy it? What is the biological meaning of activation of the natural autoimmune processes reflected by the elevated production and serum content of according natural a-Abs, which do not aim to the destruction of the recognized target?

Nearly half a century ago, Pierre Grabar and later Stratis Avrameas proposed a homeostatic function of the immune system mediated by the natural a-Abs[7,8]. Earlier, in thirties, an idea of the regulatory a-Abs was mentioned by Karl Landsteiner[9]. However, the prophet of these new immunological views was Elia Metchnikoff, who claimed that it would be wrong to consider immunity mainly as a gendarme of an organism in the constant Host-against-Parasite struggle. The immune system has a much more wide biological predestination – the dynamic participation in self-homeostasis, self-reparation, self-optimization, and maintenance of a harmony state, under the constant pressure of the environment[10]. Metchnikoff's conception was too ahead of his time.

Nowadays, scientific community admits his staggering intuition: the global function of the immune system is the maintenance and regulation of an optimal molecular homeostasis of the body, including struggle against hazard microbes[11-13].

Natural a-Abs and maintenance of homeostasis

Regulatory-and-control function of any system can provide regulation of the system functions only based upon the operation of an internal "image" -model of the whole system, by using multiple and effective feed-backs – for the reflection of the present situation in the system in each period of time, its comparison to the desired one, and its correction in case of necessity – this trivial basics of cybernetic is well-known from the times of Norbert Wiener[14].

If the immune system is considered as an important participant of control-and-regulation function of the whole organism (together with the neuroendocrine system[15], it needs an "image" (model) of the object of regulation and must be equipped by multiple feedbacks. Luckily, the immune system possesses such instruments. Immunologic reflection-image of body state (or "Immunculus" as self-reactive and interconnected entity of the immune system[16]) is provided by a complicated net of natural a-Abs of different specificities that could be considered as a mosaic picture formed up by a great number of small "bits of smalt". Quantitative changes in each "bit of smalt" are related to variations of expression and secretion of the relative antigen. The immune system takes in account image information for permanently screening the current antigenic situation in different compartments of the body, and for comparison between now presented state and the desired (optimal) one. Substantial and prolonged deviations from the optimal state are the trigger for induction of compensatory and reparative processes, aiming to restore molecular and functional homeostasis. So, the Immunculus may be considered not only as a passive "mirror" of the health status but rather as an active "metabolic gyroscope" of homeostasis[1].

The idea of Immunculus as an image of the molecular and functional state of the body is to some extend similar to the neurologic homunculus. The later is considered as a specific "instrument" used by the brain for creation of an image of anatomical structure of the body mirrored by electrogenic activity (spikes) of neurons of the sensory-motor brain cortex. This similarity was first noticed by Irun Cohen, who proposed the term "immunologic homunculus"[13]. In contrast to neuronal nets, based upon morphologically and spatially determined inter-neuronal synaptic connections, the Immunculus is a wide spread system, represented by mobile molecular elements.

One of the most important features of a-Abs is their permanent presence in nearly every compartment of the body (in the blood stream, interstitial fluid, lymphatics). The content of IgG a-Abs with defined specificities is nearly the same in capillary, venous or arterial blood. Accordingly, quantitative evaluation of a-Abs directed against specific sets of heart, liver, lungs or other antigens in blood samples, may provide information about the health state of related organs or the organism in total[1]. The immune image-model seems to be organized on the holographic principle. The main feature of holographic image is virtual three-dimensionality where every small portion of the hologram does contain the image of the whole picture. This seems to be the most basic feature of the general net of the a-Abs-based "mirror" of the body (Immunculus)[1].

Quantitative changes in the network of autoantibodies as immunophysiologic phenomemon

A general rational of biologically active systems is

that quantitative changes in different physiologic parameters are directed to correct or compensate abnormal situation in the body. For example, increased physical efforts might be accompanied by an elevation of blood pressure, tachycardia, and rise of blood glucose level. Such reactions aim to provide the possibility for defense, justified evolutionally. Principally in the same way, physiological (secondary, sanogenic) autoimmune reactions may be seen, for example, in patients suffering from brain ischemic stroke: if prominent elevation of very different serum "neurotropic" a-Abs of IgG class is observed soon after stroke and elevated level of such a-Abs persist for o few weeks, it can be considered as a favorable prognostic sign. In the opposite, absence of a notable stroke-induced (secondary) autoimmune reaction – that is preservation of normal or low levels of "neurotropic" a-Abs during the first 1-3 days after stroke, can be considered as a bad prognostic sign, followed by bad outcome. Patients might later, if alive, be characterized by prominent motor and/or cognitive malfunctions[17]. Probably stroke-induced sharp and relatively prolonged (up to 1-2 months) elevation of a-Abs against multiple proteins of the brain cells (GFAP, S100, MBP and others) increase the efficacy of clearance of injured organ from endogenous products of local tissue destruction and amplify its functional restoration. Similarly, elevated production and serum content of "pulmotropic" a-Abs occurs during chronic pneumonia, and normalization of their levels may indicate effective treatment of the disease[18]. Another example is that after in vitro fertilization using large dosages of human choriogonadotropin during preparation to IVF, elevation of a-Abs against choriogonadotropin may be found in serum nearly in every women; up to 60% of women show elevated level of such a-Abs for six months or more[1].

These examples may illustrate additionally the Kovaliov's concept of the immunochemical homeostasis[5] on the grounds that the level of production of a-Abs is the result of antigen availability and that their main predestination is clearance from excess of antigens, formed during vital activity or exogenous influence in order to reestablish normal state and avoid pathology.

In most cases a-Abs provide clearance indirectly – as opsonins. IgG specific for apoptosis-generated DNA fragments can enter B-cells bearing according receptors and activate them to proliferation[19]. Probably the same could be observed with DCs and macrophages. It is interesting that substantial number of autoantigens – targets for a-Abs preferentially migrate to the blebs on the surface of apoptotic cells[20]. Thinking about inflammation as a central mechanism of repair of injury and restoration of impaired function[21], and the pro-inflammatory cytokine related activation of a-Abs production as well as activation of macrophages and DCs[21], the general picture of sanogenic activity of the immune system (driving and directioning a-Abs) could be outlined.

From the medical point of view, it is crucial to demarcate primary and secondary autoimmune processes. Primary autoimmune reactions (for example induced by lymphotropic viruses) may be observed less often, they usually are pathogenic in essence and may become a cause of systemic or organ specific autoimmune diseases.

In opposite, much more often, secondary and transitory (physiologic) activation of natural autoimmunity, following primary (pathologic) molecular changes in organs, are targeting to clearance of involved organs and to recovery of the disturbed physiology of functions. Another bright example of sanogenic function of natural autoimmunity has been presented by Schwartz et al. (facilitation of restoration of damaged nervous fibers after administration of autoreactive T-lymphocytes against components of the nervous fibers)[22].

Quantitative changes in autoantibodies as indicators of disease

The immune system is essentially self-reactive and able to holistic perception of the image (antigenic) of the body in normal state and disease. So, it is reasonable to use these immune characteristics for the needs of medical practice, as diagnostic and prognostic instruments. In most cases the grounds of any chronic disease are the primary biochemical (antigenic) deviations in certain specialized populations of cells, which derives from abnormalities in production, secretion, and presentation of the different antigens and happen long before clinical manifestations of the disease. Molecular deviation of such kind is the reason for quantitative changes in the serum content of a-Abs with according specificity. Therefore long-term changes in the content of a-Abs of certain specificity could reveal the abnormal molecular disturbances in any population of specialized cells of any organ. This phenomenon allows for early detection of the "disease-before-disease" and occasionally could allow to reverse pathology development by applying preventive measures.

For example, an ELI-test method (**E**nzyme-**L**inked-**I**mmuno-**Test**) were elaborated in former USSR after Chernobyl disaster, in order to help investigators to screen individuals at radioactively polluted areas and reveal different forms of associated pathologies at early stages. The method analyzes the serum content of 24 patterns of a-Abs that could reflect the state of main organs and systems of human body. It proved to be helpful for the diagnosis of pre-clinical Diabetes and the introduction of preventive measures[1,5,21].

Another example could be the application of this method for early detection of malignancies. As it was mentioned above, the immune system can see grooving malignant tumor as it is reflected by quantitative changes in the production and serum content of a-Abs against multiplicity of tumor-associated antigens[2,6]. Quantitative changes of this kind seem to be secondary to the tumor-dependent expression of antigens and the rise of apoptotic/necrotic events, related to clearing functions of the immune system. This situation is similar to immune recognition of any other non-malignant pathology in any

organ, leading to secondary, specific changes in the production of multiple of a-Abs against antigens of injured cells.

Concluding remarks

It is generally accepted that the destination of the immune system is not discrimination between Self and Non-self. Non-self does not induce immune response by definition although it can be the object of specific response and destruction. Moreover, during the last decades, it became evident that weak self-reactivity is not only possible but obligatory condition for T- and B-lymphocyte maturation and survival throughout all lifespan[24]. Many non-Self entities constantly or temporary presented in the organism (normal microflora, fetus) usually do not induce immune responses[11], because the immune system does not simply ignore homeostatic non-hazardous Non-Self but actively recognize and integrate them[12]. Natural self reactivity and the internal autoantibody mirror participate greatly to the maintenance of homeostasis and under conditions of increased or altered antigenic pressure this homeostatic status is disrupted giving opportunities for the emergence of diseases.

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