

Editorial

The Natural Autoimmunity: Self-Recognition, Self-Interaction, and Self-Maintenance

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EDITORIAL

Within the last 20-30 years, the field of clinical immunology has been subject to some paradoxes that contradict the positions adopted by most physicians. The puzzle of natural autoimmunity is an example. In spite of habitual ideas about the immanently aggressive nature of any forms of autoimmunity (“*horror autotoxicus*”) autoimmune phenomena are permanently present in any individual and not always reflect the potentially self-destructive activity of the immune system [1]. Therefore, the question remains: should inborn autoreactivity be considered a potentially hazardous evolutionary fortuity? Could an increase in the production of autoantibodies (auto-Abs) of certain specificities, induced in response to tissue damage, be functionally senseless? This eventuality appears more than doubtful. From an evolutionary point of view, there is no place for senseless fortuitousness.

Explanation of necessity of natural autoimmunity is evident: the immune system directly involved in physiological activity of the body, therefore its functions directed rather “inward”, not “outward”, and are based on the intrinsic recognizing components of the “SELF”.

The “prophet” of the new attitude to immune functions became Elia Metchnikoff. He claimed that it would be wrong to consider the immune system mainly as a “gendarme” of the body, because struggle against microbes is only a fragment of a much broad biological destiny – namely dynamic participation in self-maintenance, self-reparation, self-optimization, and providing of a harmonious state under the constant pressure of the environment [2]. Metchnikoff’s concept was far too ahead of his time and only now may we only wonder at his staggering intuition. Today, owing to the pioneers E. Metchnikoff, P. Matzinger [3], O.Parnes [4], and others, we must recognize that the global function of the immune system is the maintenance and regulation of an optimal molecular homeostasis of the entire body (including but not come to struggles against hazardous microbes).

To provide self-preservation, the immune system requires special mechanism for the identification the components of the own organism – self-reactive entity, based on a complicated and interconnected network of natural auto-Abs or “Immunculus” [5].

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In accordance with the main idea of the concept of Immunculus, the whole-organism system of natural auto-Abs with different antigenic specificities could be likened to a *sui generis* mosaic picture, reflecting the organism molecular (antigenic) state. The immune system has used this image for permanent screening- & watching the current antigenic situation in various compartments of the body. Prolonged deviations from the optimal molecular (antigenic) state does induced by pathology molecular changes in any population of the cells, and lead to changes in the general structure of the image (Immunculus). The last is an impetus to induction of multiple endogenous mechanisms aimed at restoring molecular and functional homeostasis.

Both molecular (auto-Abs) and cellular elements (autoreactive lymphocytes) are permanently present throughout the organism life and form the interconnected system of self-recognition. The desired, non-destructive level of physiologic autoimmunity is ensured by mechanisms of combined negative/positive selection during maturation. Lymphocytes that express any autoreactive receptors of too high affinity, as well as lymphocytes that do not express anti-self receptors (or insufficiently affine) are eliminated. Consequently, any initial clone of T- and B-lymphocytes passing selection, are characterized by weak to moderate reactivity to components of the SELF by definition.

It is clear that autoreactive lymphocytes supply the continuous production of a certain amount of auto-Abs with various antigenic specificities as an intrinsic feature of the immune system [1]. Multitudes of natural auto-Abs of IgG and IgM classes have been permanently synthesized, secreted, and presented in the blood serum of all healthy persons during life span. The last 30 years, together with colleagues, we have studied over 500 antigens belonging to various organs and tissues and never revealed among them a single antigen that would not serve as a target for specific IgG auto-Abs present in the bloodstream of healthy individuals. Thus, it is more likely that all self-antigens (not a subgroup of “key antigens”) are subjects of recognition for natural auto-Abs. Concentrations of the different auto-Abs may vary dramatically in healthy adults. For example, the average serum content of auto-Abs against Fc-fragments of immunoglobulin is nearly twenty times greater than that of auto-Abs against myelin basic protein [1]. On other hand the serum concentration of auto-Abs with the same specificity in healthy

adult individuals of both sexes (having no tissue or organ damage to express corresponding antigens) is roughly equal [6].

The natural autoimmunity in particular is a ground for immune autoclearance. The clearance function of the immune system, mediated by natural auto-Abs, was first proposed more than half a century ago by Pierre Grabar [7]. A multitude of immune functions, including those related to antimicrobial defense, derive from the basic function of autoclearance [1]. Large portions of natural auto-Abs specifically bind to oxidation-associated neo-antigens that become exposed on dying cells [8,9] as well as senescent-associated determinants and becomes a molecular “eat me” signals (opsonines) for macrophages consumed “wastage”. Every day billions specialized cells dyed by physiological apoptosis and replaced by new ones in a various compartments of an organism. Clearance of apoptotically dying cells (efferocytosis) is required for normal tissue homeostasis and prevention of inflammation, and providing by joint activity of antigen-specific self-reactive auto-Abs together with non-antigen specific macrophages. Obviously, the homeostatic importance of local activation of autoclearance increases dramatically in the case of tissue damage of any etiology.

In accordance with the basic statements of the immunochemical homeostasis concept by Igor Kovaliov [10], rates of natural auto-Ab production are regulated by quantity/availability of respective antigens via a feedback principle. The rates of production, secretion and/or release of any cytoplasmic, membranous, or nuclear self-antigen into the intercellular space are nearly equivalent in all healthy individuals (or differ insufficiently); therefore, serum levels of auto-Abs of respective specificity should also demonstrate only slight individual variability. This picture changes dramatically in cases of pathology. Many disorders, especially those of a chronic nature, are directly associated with either abnormally elevated apoptosis or cell necrosis in the involved organ, or deviations in the abnormal production and/or excretion of certain antigens. In turn, a stable increase in the extracellular concentration of any endogenous antigen is inevitably accompanied by deviations in the concentrations of cognate auto-Abs according to Kovaliov’s rule.

Pathological processes of any kind in any organ are usually accompanied by elevation of apoptosis/necrosis of the resident cells and, accordingly, by increased extracellular concentration of intracellular components (“danger signals”). There are compelling reasons to reconsider the biological meaning of universal pathology-associated autoimmune reactions from a physiological point of view. This phenomenon can be interesting not only *in abstracto* but also in the context of everyday medical practice. These events induce the secondary activation of natural sanogenic (adaptive) autoimmunity and rise in production of autoantibodies with appropriate specificity (opsonines), which provides augmentation of clearance by facilitating the efficacy of macrophage-dependent consumption of debris in the affected organ. Secondary rise in production and secretion of particular auto-Abs (against antigens of damaged or pathology changed cells) [11] should not be considered a side effect but rather a reflection of one of the major roles of the immune system – the function of autoclearance.

A stable increase in the extracellular concentration of any endogenous antigen is inevitably accompanied by deviations in the concentrations of cognate auto-Abs according to Kovaliov’s rule. For example, during the preparation phase before in vitro fertilization (IVF), most women receive pharmaceutical (excessively large) doses of human choriogonadotropin (HGT). As a result, more 60% of these women exhibit an increased production of autoAbs against HGT within six months and beyond [1].

It is typical for some isoforms of insulin receptors to be elevated in skeletal muscle fibers at the pre-disease and early stages of diabetes mellitus (probably as compensation for deteriorating receptor functionality). Accordingly, many patients with pre-clinical diabetes mellitus demonstrate abnormally increased serum levels of auto-Abs against insulin receptors [12]. In most cases, this increase did not relate directly to the pathogenesis of diabetes but, instead, reflects abnormally increased expression of receptors in accordance with Kovaliov’s rule: elevated quantity of antigen leading to rise of production of corresponding auto-Ab.

Malignancy-associated increases in auto-Abs against the phosphoprotein p53, a regulator of apoptosis, may be attributable to the same principle. It is known that p53 alterations (missense mutations) appear to be present in 40 to 45% patients with different forms of malignant diseases. Frequently, these alterations are accompanied by compensatory elevations in p53 expression and, secondarily, by a rise in corresponding auto-Abs [13].

In accordance with the general logic of living systems, quantitative changes in physiologic parameters are usually aimed at correcting or compensating for an abnormal situation in the body. For example, tremendous physical effort is accompanied by elevation of blood pressure, tachycardia, rise of blood glucose level, and other abnormalities that are all untypical of the resting state. Such reactions provide additional resources for “fight or flight” and are physiological and evolutionarily justified. Principally the same physiological (sanogenic) autoimmune reactions may be observed, for example, in patients suffering from ischemic stroke. It was shown that prominent temporary elevation of “neurotropic” IgG auto-Abs in the serum, if observed soon after stroke and for a few weeks thereafter, is a favorable prognostic sign. Conversely, the lack of a notable stroke-induced secondary autoimmune reaction — that is, preservation of normal or low levels of “neurotropic” auto-Abs during the few days following a stroke — is a bad prognostic sign that is typical of non-survivors and of survivors suffering prominent motor and/or cognitive deterioration [1]. As one may suppose, stroke-induced sharp and relatively prolonged (up to 1-2 months) elevation of auto-Abs against proteins of the injured brain cells (GFAP, S100, MBP, and others) is a deeply rational autoimmune sanogenic phenomenon aimed at increasing clearance of damaged neural structures and functional restoration.

Similarly, increased production and serum concentrations of “pulmotropic” auto-Abs are typical of chronic pneumonia, and normalization of serum levels may indicate the resolution of the disease (for example, in response to effective treatment) [14]. These examples underscore and further justify the concept

of immunochemical homeostasis based on two points: 1) the amount of auto-Abs produced is a function of antigen availability; 2) one of the main purpose of natural auto-Abs is the clearance of excessive antigens that are formed during normal or deviated vital activity.

Changes in production and serum content of tissue-specific autoantibodies can be considered the most universal and earliest detectable molecular marker of any chronic disease. Any tissue damage reflects by evolutionarily-fixed phenomenon of a secondary increase in the production of auto-Abs against tissue-specific antigens. This "magic mirror" of auto-Abs reflecting pathology changes, seems very attractive to use for the needs of medical practice – namely for precision diagnostics and prognostic tools for most early detection of pathological situations long before any clinical manifestation.

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