Review

General network of natural autoantibodies as immunological homunculus (Immunculus)

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Abstract

The term ‘Immunculus’ has been proposed for designation of the global system (network) of constitutively expressed natural autoantibodies (na-Ab) interacting specifically with different extracellular, membrane, cytoplasmic, and nuclear self-antigens. In healthy persons the repertoires of such na-Ab are surprisingly constant and characterized by minimal individual quantitative variations. On the other hand, abnormal metabolic deviations, which precede or accompany different diseases show easily detectable prominent changes, rather quantitative than qualitative, in the network of na-Ab in the patient’s sera (Immunculus distortions). This phenomenon can be used for ‘mapping’ the state of physiological norm in terms of the millennia of na-Ab repertoires, and for the elaboration of methods for an early (pre-clinical) detection of potentially pathogenic metabolic changes. Can the individual features of the general network of constitutively expressed na-Ab reflect the functional state of the body and be used for ‘mapping’ of normal and pathological functional state? Can the changes in production of some biologically active na-Ab not only reflect the state of the body, but also be used for partial compensation of functional deficiency of certain molecular systems? These and related questions are discussed in this article. The research project ‘Immunculus’ is proposed for international cooperative investigations.

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‘Magic mirror, could you say Am I pretty just today?…’—A.S. Pushkin

1. Introduction

Let us imagine a linguist who is familiar with the alphabet but who does not understand English language. He decides to do the ‘mapping’ of a volume of Shakespearean plays. By using a personal computer and a combinatorial analysis he obtains data about quantity and frequency of any letter, word or phrase in any chapter of any play. It allows him to make a claim that the book is successfully decoded. Nevertheless, this linguist is hardly able to comprehend the essence of the text. The same reason generates the doubt of the Human Genome Project’s (HGP) suitability as an instrument for the construction of ‘bridges’ between genes and phenotype. HGP acquaints us with the
genetic alphabet but we do not yet comprehend the language. Perhaps, the most effective approach to study the languages of the living systems is an investigation of the main principles of transformation of strictly determined genetic ‘instructions’ into much less determined but very reliable physiologic functions of living beings. These principles are directly related to events which are responsible for the co-tuning of separate activities of many relatively autonomic cells in a harmonious symphony of life and depends on the production and secretion of a giant number of intercellular-inter-system communicator molecules.

Members of immunoglobulin superfamily (IS)—MHC products, receptors, adhesins, integrins, etc., also may be directly involved in functional ordering of the multicellular systems. The main feature of IS members is their collaboration in the intercellular interaction which establishes specialized molecular contacts (homo- or heterophilic). Genes of these molecules are the descendants of the common ancestral gene coding structure of the homodomain membrane protein, providing ‘intercellular couplings’ by homophilic cooperation [1]. As a result of tandem duplications there appear to be multiple loci controlling the production of different Ig-like molecules. Amplified genes are expressed in cells of different types, giving space to the mutation drift, bringing changes into the structure of their products, as well as their affinity, specificity, and regulating peculiarities [1]. The latest evolutionary acquisition of IS are the molecules of antibodies (Ab). Ab retain the main functional sign of the IS representatives—the capability to participate in homeostatically expedient specific intermolecular interactions. Besides, in contrast to the majority of members of IS, rigidly tied to the cell membrane structures, Ab have obtained freedom for the displacement and, accordingly, many principally new regulatory possibilities.

2. Natural autoantibodies and regulation of homeostasis

During the last few years efforts of many researchers in the field of immunoregulation of physiologic functions have been directed to study biological activity of different cytokines and chemokines. However, the unique characteristic of the immune system at the molecular level is determined not as much by the dozens of cytokines (which are produced by different cells in many organs and tissues [2]), as by its ability to produce a vast number of Ab and antigen-specific cellular receptors, including anti-SELF Ab (a-Ab) and anti-SELF membrane receptors of T- and B-lymphocytes.

The presence of natural autoantibodies (na-Ab) in healthy individuals was demonstrated by Besredka approximately 100 years ago [3], but only recently na-Ab have become a real object of research. In the 1960s–1970s, when immunology was rested upon a nearly unbreakable clonal-selection theory and episodic findings of na-Ab were discouraging since they contradicted this theory. The situation began to change following the appearance of the immune network theory [4], postulating that the immune system of a healthy individual can produce Ab to a variety of self-antigens. In the 1980s–1990s appeared a lot of evidence about the presence in the healthy persons of hundreds of na-Ab interacting with hormones, receptors, DNA, histones, enzymes, components of the MHC, intercellular matrix, and other endogenic compounds [5,6]. Probably na-Ab to any endogenic antigens, at some concentration, are present in healthy individuals and can be revealed by using suitable methods of detection. It was clearly confirmed by using expressing libraries of genes of the human B-lymphocytes (Professor W. Harris, Aberdeen University, Scotland, UK, personal communication).

For some time na-Ab were considered as low-affine polyreactive molecules of IgM class [7]. However, as is shown later, half or more of circulating na-Ab belong to IgG class [8]. Besides, a significant part of such na-Ab was monospecific and characterized by affinity up to 10^{-11} M [7,9]. It was established that na-Ab synthesis is programmed by constitutively expressing Ig genes almost without undergoing somatic mutagenesis [5]. Accordingly, in contrast to highly variable set of Ab against xenogenic antigens, na-Ab repertoires are very similar in all healthy persons of different age and gender [7]. Small individual differences may be explained by somatic mutagenesis.
differences (immune fingerprints) in na-Ab repertoires, typical for the normal condition, to a large extent are determined during the fetal development and under the influence of maternal na-Ab transferred transplacentally and performing the role of matrices, which tune the offspring’s na-Ab repertoires [10]. According to Coutinho [11], normal autoreactive B-lymphocytes form a strictly regulated network. One of the main characteristics of this net is the maintenance of the optimal levels of production and content lot of na-Ab, as well as elimination of occasional perturbations of such levels. As a result, a prominent stability between partial contents in na-Ab of different specificity is achieved, and a grandiose dynamic but settled whole-organism system of na-Ab is formed.

In the 1960s, the presence of the long-acting-thyroid-stimulating-substance (LATSS) in the patients with Graves’ disease was detected. The latter was bound with high-affinity to TTH receptors on the thyroid cells and induced an abnormal rise of synthesis and secretion of thyroid hormones [12]. LATSS was identified as a-Ab interacting with the hormone-binding sites of the TTH receptors. Much hope was placed on the possibility of using tests for the LATSS in the blood sera for diagnostic purposes. However, to the researchers’ disappointment, it appeared that such a-Ab (functionally similar to TTH), are present in blood of not only sick persons but the healthy ones as well, and the differences in their serum contents are only quantitative [12]. The same situation was repeated with the ‘taraxein fraction’ from sera of schizophrenic patients. ‘Taraxein’ was identified as a-Ab to some nuclear antigens in brain’s neurons [13]. Intravenous administration of such Ab in monkeys or human volunteers brought about phenomena of transitory acute psychosis accompanied by behavioral and encephalographic deviations [13]. It seemed that with a little bit more effort the schizophrenia puzzle would be resolved. But later, the same a-Ab have been detected in the blood sera of healthy persons as well, although, in lower concentrations [14]. Both examples clearly demonstrated that it was useless to try to create diagnostic methods based upon using some unique ‘pathogenic’ (qualitatively new) a-Ab. Should it mean that the detection of not qualitative but quantitative changes in the production of some a-Ab cannot be informative?

3. Imnunculus as the ‘mirror’ of the organism’s physiological state

The bright hypothesis of Cohen and Young states that the molecular specificity of the body is reflected in the plurality of anti-self receptors of autoreactive T-lymphocytes, a system of which forms the ‘immunological homunculus’ [15]. Today it seems reasonable to extend the frames of initial hypothesis and include in the ‘immunological homunculus’ or ‘Immunculus’ the general network of circulating na-Ab, directed to multitude of self-antigens [16] or against relatively few ‘key antigens’ of the body [17].

The Immunculus concept to some degree is similar to the idea of Homunculus proposed by neurologists. Neurological Homunculus is presented by well-ordered populations of neurons (mostly of the sensory-motor cerebral cortex), which reflect and control topically different parts of a human body. The damage of corresponding neurons after stroke, wound or tumor accompanied by motor or sensory dysfunction—speechlessness, disability to arbitrary motions, etc., and character of clinical disturbances is strictly related to the topic of brain’s destruction [18]. If Homunculus implies the reflection of individual three-dimensional structure of a body, Immunculus rather reflects not the anatomical structures, but individual molecular features and metabolic transformations, which are the base for the living activity. In other words, the principal difference between Homunculus and Immunculus is that if the first is ‘the mold of anatomy’ (body’s structure), the second one is ‘the mold of physiology’ (body’s state). Hence, the idea of ‘Immunculus’ seems to be much more virtual and more difficult to perceive, but it is not less realistic and important in the biological and medical sense.

A remarkable uniformity of na-Ab repertoires is established in early ontogenesis and normally lasts for decades. At the same time, many diseases are accompanied by significant deviations in serum contents of na-Ab. That is the immune system has memorized and mirrored organ’s, tissue’s, or entire
body’s disease-related biochemical changes, following the quantitative changes in na-Ab repertoires. Therefore, the analysis of serum content of many thousands of na-Ab and characteristic of abnormal na-Ab changes may become a precision instrument for the evaluation of the state of the body in the present, as well as for the prognosis of supposed changes in the near future.

According to our observations the serum content of na-Ab of IgG class, which interacts with some proteins involved in embryonic development (these na-Ab are detected by ELI-P-Test [18]) is very similar in healthy women. At the same time, the content of such Ab in women suffering from miscarriages, infertility, or giving birth to newborns with developmental defects, differs significantly. In other words, the serum content of ‘embryotropic’ na-Ab is one of the physiological constants reflecting the state and condition of the reproductive functions. The importance of evaluation of the ‘embryotropic’ na-Ab content in planning pregnancy is evident.

Another example: our data [19], and other results [20], indicate that certain, nearly the same, levels of Ab to different proteins of the nervous tissue (‘neurotropic’ na-Ab) and corresponding anti-idiotypic na-Ab are present in the serum of any healthy person. The content of such Ab may vary within rather limited bounds—thus demonstrating the presence of some mechanisms called upon to ensure maintenance of production, secretion, and catabolism of such Ab. In contrast, to the most patients with manic-depressive disorder, epilepsy, schizophrenia and other forms of the nervous system pathology are quantitative discoordination in the levels of synthesis, secretion and/or catabolism of many ‘neurotropic’ Ab are typical.

It should be underscored that deviations in production of na-Ab (‘embryotropic’, ‘neurotropic’, etc.), as a rule, represent a reaction on non-physiological changes in synthesis or degradation of the respective endogenous compounds [21] and appear at the initial (pre-clinical) stages of metabolic disturbances which may lead to pathology. The changes in the na-Ab repertoires can be detected much earlier (sometimes months or years) before clinical manifestations appear. We have observed a few dozens of newborns who were evaluated as ‘clinically healthy’ but characterized by long-lasting deviations in repertoires of ‘neurotropic’ na-Ab. Unfortunately, after 6–36 months 60–70% of such babies revealed neurological problems, serious at times [22].

We suppose, quantitative mapping of the serum repertoires of thousands of na-Ab may lead to appearance of principally new diagnostic technologies for ‘early notification’, i.e. pre-clinical diagnosis of the reversible molecular changes long before the development of the real disease.

4. Regulatory Immunculus

In accordance with some estimates, 20–30% of lymphocyte clones in healthy persons produce 20–30 thousands of na-Ab molecules per minute (few grams of different na-Ab daily) during the entire life-span [23]. Should this phenomenon be considered as potentially hazardous wastefulness of the body?

In the 1950s, Grabar proposed a ‘sewage’ role for na-Ab [24]. Similar views were held by Kovalev, who indicated that an overproduction of any biologically active molecule would entail compensatory rise of serum levels of ‘inactivating Ab’ [21]. However, to consider these molecules only as ‘scavengers’ seems to be an unjustified restriction. Constantly synthesized na-Ab against regulatory peptides have protected these labile molecules from premature degradation [8]. Some na-Ab provide transportation of molecules-ligands to specialized binding sites where the dissociation of antigen–Ab complexes take place and the peptides interact with respective receptors. The protective role of na-Ab is revealed here not only in protection of ligands from proteolysis but also in preventing their ineffective ‘spreading’ upon sites with low affine (unspecific) binding. For example, activity of somatotropin, which is present in the blood circulation as a complex with a specific Ab, turns out to be 200–400% higher than that of the free hormone [25]. Besides ligands, specialized receptor structures of cells can also be the targets of specific na-Ab. Ab against receptors of insulin, TTH, estrogens [26], acetylcholine, serotonin, dopamine, and norepinephrine have been previously described [27].
Some Ab may influence the functions of ion channels [28] to change transmembrane ion’s transport and, by any means, modulate the cell’s excitability. Excessive production of such Ab may be the cause of some forms of neuromuscular pathology [29].

The fact that Ab can modulate functions of intranuclear proteins in vivo [30], estrogen receptors included [26], suggests that even the most ‘closed’ compartments of living cells are accessible to Ab. The findings suggest the presence of effective energy-dependent mechanisms for translocation of Ab of IgG class (but not IgM, IgA, IgE, or IgD) both through the histiothematic barriers and through the cell membranes [31]. As a result, a specific Ab gains an access to the intracellular target antigens in cells in any organ [16,30], and specifically interacts with the corresponding antigens [30,32]. After binding an Ab influences conformation of antigen, block or activate certain functional sites of the latter.

Some compounds, which fail to penetrate histiothematic barriers on their own, acquire trans-barrier permeability in complex with Ab [34]. These data illustrate an additional aspect of Ab biological activity. Previous ideas that histiothematic barriers are a kind of impenetrable ‘Chinese Wall’ for Ab became outdated. Nevertheless, there is some selectivity of the barriers for Ab of certain specificity as well as to Ab belonging to different classes and subclasses of Ig. It may help to ensure arrival of the required Ab to the organs, and cells expressing the respective antigens (just as lymphocyte homing has provided a peculiar cell transport to the desired place and time). It has been confirmed experimentally that Ab to vasopressin, introduced into the paraventricular nucleus of the hypothalamus, are selectively accumulated by live neurons synthesizing this peptide, but not other nearby oxytocin-producing cells, serve as an illustration of the aforesaid [33]. Undoubtedly, ‘molecular homing’ can contribute to the realization of na-Ab regulatory functions.

It is necessary to bear in mind that Ab directed to the same cell may induce multiple effects. For example, Ab to some antigens of oligodendrocyte membrane are causally related to the development of demyelinating diseases [35], however some other anti-oligodendrocyte na-Ab can induce myelination [36]. Ab to the same protein molecule also may induce diversified effects. The reason is that ‘anti-tubulin’, ‘anti-insulin’ or any other Ab, strictly speaking, are not bounded to antigen as such. Ab are able to interact only with small portions (epitopes) of the target protein. Different Ab can bind with different epitopes of the same molecule and the consequences of such interactions may principally differ. For example, Ab–receptor binding may lead to the receptor activation and induction of the secondary intercellular events (Ab as the receptor agonists). Other Ab, binding to different sites of the same receptor, may inhibit or block their functions, i.e. stand as specific antagonists [23], or may induce quite unexpected events (some Ab to TTH receptor may stimulate mitotic activity of thyroid gland cells [37]). Ab may not only stimulate but also inhibit proliferation and cause atrophic changes by mechanisms of apoptosis in both normal and malignant cells, or, in the contrary, to block apoptosis [38,39]. Evidently, principle of epitope specificity repeatedly multiplies precision and selectivity of regulatory potencies of na-Ab.

The biological activity of Ab molecules per se, depending on the giant number of possible variants of hyper-variable sites of their Fab-fragments, also may be extremely important. Ab, as such, may possess enzymatic activity (‘abzymes’). Ab which display activity of superoxide dismutases, stimulating hydrolysis of phosphoinositides, catalyzing formation of carbon–carbon bonds, cyclization, stereospecific aminolysis, proteolytic and nuclease activity, etc., have been previously described [18]. The giant number of possible variants of the hyper-variable sites potentially may give to Ab a possibility to display any type of enzymatic activity. There are no theoretical prohibitions about the existence of molecules of Ab whose active centers can be a conformational copy of not only enzymes, but any biologically active molecules. Ab which posses the activity of hormones, neuromediators, and neuromodulators have actually been described recently. Besides ‘TTH-substituting’ [12], there were described Ab ‘mimicking’ substance P, insulin, serotonin, norepinephrine, estrogens, gangliosides [23,27], which enable the activation of the
respective receptors, increasing the production of the secondary messengers and inducing the coupled intracellular events. Therefore, the possibility that na-Ab do not only modulate the activity of their targets, but may replace the shortage of certain hormones, enzymes, or trophic factors (the dubbing principle) should not be rejected.

5. Project ‘Immunculus’

The immunity, as a biological phenomenon is directly related to identification, actualization and maintenance of dynamic complexity of the ‘SELF’ during the individual lifespan. The ‘SELF’ protection (including protection from pathogenic microbes) is only one of the facets. This conclusion is similar to the ideas of Mechnikoff [40], who proposed a century ago that the ‘phagocyte system’ (immune system in modern terms) should not be considered as ‘body gendarmes’. Its participation in the interspecies struggle for the ‘host–parasite’ is only an episode of the global biological function of the phagocyte (immune) system, with the latter designed to take part in the strive of the organism for self-optimization, self-maintenance, and self-reparation under the constant environmental pressure. Adaptive changes in production of certain na-Ab may be one of homeostatic acts of the immune system, which reveal a partial compensation of some molecular systems’ functional deficiency. It may extend the ‘inertia of health’ under pathogenic influences.

If the genetic program provides an individual ‘Textbook of instructions’ for strictly ordered protein syntheses in cells of multicellular organism, Immunculus, or whole-organism net of na-Ab, supposedly participates in basic mechanisms of epigenetic functional integration (co-tuning) of the multitude of different cell types of the body. Evidently, intracellular homeostasis (ensured by genome) and intercellular- intersystem homeostasis (ensured by Immunculus) both provide the basis for the normal state of the healthy organism.

Experimental ‘mapping’ of healthy individuals’ Immunculus and creation of respective computer databases can describe the functional norm of any organ and tissue in terms of quantities of different na-Ab. We suppose, the research area briefly delineated above may become a basis for a prolific research project ‘The Immunculus’. As it seems to us this endeavor may be an alternative (or rather an additive) to the Human Genome Project.

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Take-home messages

- Constitutively expressed natural autoantibodies (na-Ab) which interact with different self-antigens are normal components of a healthy organism. The general network of na-Ab has been named Immunculus.
- In any healthy person the repertoires of na-Ab are nearly the same and characterized by only minimal individual quantitative variations. Pathologic changes at the molecular level, which precede or accompany different diseases have been mirrored in notable quantitative rather than qualitative changes in the general network of na-Ab in the patient’s sera (Immunculus distortions).
- If the genetic program provides the individual ‘Textbook of instructions’ for ordered protein syntheses in cells of a multicellular organism, Immunculus, in turn, participates in basic mechanisms of epigenetic functional integration (co-tuning) of different cell types of the body. Both comprise the basis for the normal state a healthy organism.
- Creation of ‘maps’ of na-Ab which interact with different self-antigens should help to describe the functional norm of any organ and tissue in terms of quantities of different sets of na-Ab. This approach could be used to develop an effective ‘pre-clinical diagnostic technology’, which would be based on the early detection of changes in na-Ab repertoires indicative of the beginning of pathologic metabolic changes before the clinical manifestation is reached.
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