Immune system as a part of regulatory and integrating apparatus of the body: A biomedical philosopheme*

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This conceptual article addresses different underrecognized aspects of the immune system physiological activities. These ones include: the role of the immune system and physiologic autoimmunity in maintaining normal body's own cell populations; its involvement in placentation and mother-to-fetus interactions; its embedding into immune-neuroendocrine communicative and integrating apparatus designated first of all for support of unique multicellularity of the organism and for regulation of its somatic cells' growth and life. Besides cytokines, a powerful instrument of somatic regulation is agonistic (functional) autoantibodies, able to act on their receptors in hormone-like manner. The regulatory potential of antiidiotypic immunity is underappreciated. There is evidence, that anti-idiotypic antibodies can create internal immunological images and copy the ligand properties of different bioregulators and even drugs. What makes the regulatory interactions even more complex is the fact that antibodies are capable of penetrating living cell membrane, permeating the nucleus and produce a wide spectrum of regulatory effects on transcription, translation and post-transcription modifications.

Keywords: agonistic autoantibodies, functional autoantibodies, idiotype-antiidiotypic network, immunoglobulin-mediated regulation, antinuclear antibodies, physiologic autoimmunity, anti-receptor antibodies, gene expression, immune homunculus (immunculus).

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The immune system is by large considered to be an assortment of highly effective defensive mechanisms against microbial pathogens. Even its profound involvement in maintaining healthy, intact, young and normal macroorganism's own cell population by means of timely recognition of sick, injured, senescent or tumor cells and forcing them to commit suicide or killing them although apparent to experts in Immunology looks much less acknowledged and seldom realized even by medical professionals. Its major role in various spheres of reproduction including important processes and phenomena like placentation, mother-to-fetus interactions, etc. is usually limited to negative aspects like rhesus conflict and alloimmune neonatal hemolytic disease. Naturally seemingly less obvious aspects of the immune system activity like its embedding into immune-neuroendocrine communicative and integrating apparatus designated first of all for regulation of somatic cells growth and life — are very seldom discussed [1–2]. Meanwhile, immune system is now interpreted as sensory one (for the sense of antigenicity) [3] and analytical one (for recognition and memorizing of stereo-chemical individuality) [4]. Immune homunculus (immunculus) is as real as cerebral cortical one [5–6]. Even DNA maybe is double-strand because it encodes mutually recognizing proteins, a sort of quasi-antibodies and quasi-antigens out of which a body consists. Regulatory functions are usually associated only with nervous and endocrine systems. However, the immunoglobulins, products of genes' super-family which is a part of cell adhesion molecules' genes are associated with evolutionary achievement of multicellularity and with tasks of cell regulation [1]. But, besides cytokines which are produced by immunocytes and regulate growth and functions of non-lymphoid target cells, a powerful instrument of somatic regulation represent agonistic (functional) autoantibodies, able to act on their receptors in hormone-like manner [2–3; 7]. Thus, in addition to regulation of immune response only, the antibodies may accomplish integrative regulatory effects outside the immune system using the very same principles (receptor complementarity, positive and negative feedback, etc.), that are characteristic of the nervous and endocrine bioregulators [1]. Nowadays the old dogmas of purely pathologic character of the autoimmunity and non-penetration of immunoglobulins into living cells are rejected; the physiologic character of both immune self-recognition and moderate autoimmunity has been proven, as well as the facts of intracellular and intranuclear penetration of antibodies or emperipolesis of lymphocytes [3; 5; 8–9]. The general principles of the antibodies' regulatory effects in physiologic and pathologic processes as well as mechanisms that help them penetrate intact cell membrane and travel further into the nuclei and the principles of their intracellular activity by means of repression/derepression of key cellular structures, including genes, have been studied in detail [3; 9] but are still not giving birth to the new paradigm of Integrative Physiology and require profound analysis. Paradoxically, pathologic deregulatory effects of autoantibodies are much better known then physiological regulatory ones [7], just because in disease non-obvious normal phenomena are exaggerated. Thus, blocking anti-insulin receptor immunoglobulins have been proven to cause type II diabetes mellitus, while stimulatory antibodies towards TSH receptors have been reported to cause Graves' disease. The fact that antibodies can be involved with much more subtle physiological effects, that through binding various cells' receptors they can perform up- and down regulation by means of blocking or stimulating certain functions is not so easily recognized. Idiotype-antiidiotypic theory of self regulation within immune system has got Nobel Committee recognition as early as in 1984 [9], but regulatory potential of antiidiotypic immunity beyond the borders of immune system itself is still underappreci-

ated. Meanwhile, anti-idiotypes can, in principle, create internal immunological images and copy the ligand properties of any bioregulators and even drugs [2–3]. There are numerous examples of that — both in experiment and in disease [10]. We designate such a phenomenon as the "effect of Immunacea" and link it with the well known wide therapeutic efficacy of polyclonal intravenous donor's immunoglobulins [5]. One must specially point out the role of idiotype-antiidiotypic interactions in body regulation by means of autoimmune mechanisms. It was I. P. Pavlov who emphasized that the entire comprehension of normal physiological laws can be achieved in disease only. Using pathology as a parody of physiological interaction one may take Graves' disease as an example: it is well known that stimulation of thyroid functions and growth occurs due to autoantibodies binding to receptors. However, these antibodies are technically not anti-TSH-receptor ones but rather TSH's anti-idiotypes (antibodies against antibodies to TSH) [10]. In fact, there may exist a physiological idiotype-antiidiotype network including both antibodies and lymphocytes playing an important part in normal cells' activity regulation. These effects of anti-receptor antibodies are not random. The immune system as an important part of immunoneuroendocrine trinity utilizes positive and negative feed-back principle delicately and precisely balancing stimulatory and inhibitory effects [1–2]. The extent to which maintaining physiologic optimum depends on immunologic (mostly immunoglobulin-mediated) regulatory effects remains to be established yet, however we can indirectly estimate it through profound disregulatory consequences developing in case of serious immune deficiency. What makes these regulatory interactions even more complex is the fact that whole antibodies or their Fab-fragments bearing all traits of specificity are capable of penetrating living cell membrane and entering the cytoplasm and even permeating the nucleus [3; 8]. There they can produce a wide spectrum of regulatory effects from stimulation to inhibition through binding to various key structures and even interfering with (or taking part in) transcription, translation and post-transcription modifications [1–3]. Regulatory potential of immune system in health and disease is based not only on phenomena which firmly entered into routine thesaurus of every biomedical scholar, like immunologic clearance of debris, hormone-like cytokine effects and morphogenetic autophagocytosis, but also on the direct antibody-mediated receptors' alteration. Most probably, not only surface receptors, but also cys-regulatory elements of chromatin, and not only on immunocompetent, but on all somatic cells — are included into idiotype-antiidiotypic regulatory network [3].

The Autoimmunology should continue its rapid development, but not solely in uniform of a pathologic discipline dealing just with certain kind of diseases. Its real content and meaning is much more plentiful: it is future branch of Integrative Physiology.

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