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Natural Autoantibodies are Biomarkers of Immunosurveillance System

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Medical Science meets nowadays with a particular community pressure of translating more rapidly and efficiently basic knowledge into clinical practice. This new formula of translational research prompted the concept of *theranostics* based on joined molecular diagnostic markers and therapeutic targets.

Translational medicine is the building road of Systems Medicine as an inter-disciplinary field of study that pull together all structural and functional levels of the human body as fractions of an integrated whole.

Inclusion of genomics, biochemical, physiological, and biosphere category as rationale of a closed self-regulating system aims at resuming the Hippocratic principle of personalized medicine. This comprehensive approach of an individual health status implies the existence of large-scale trial biomarkers that can efficiently record self structures and interrelated functions. Biomarkers of this kind should act not only as a pictorial representation of anatomical body divisions like cortical homunculus is doing, but also as a sensor of individual normal or abnormal constitution and function.

This holistic scrutiny is satisfied by innate immune system which begins to operate early in ontogeny and further in adult life sustaining development, homeostasis, regeneration and management of healthy and pathological inflammatory program.

Innate immune system task match basically with immune surveillance concept postulated successively by Ehrlich, Thomas and Burnet in the early-to-mid 20th century [1].

At present it was recognized an entire family of innate lymphoid cells that includes natural killer (NK) cells, lymphoid tissue–inducer cells and developmentally related cells proficient to produce a regulatory range of cytokines but expressing a transmitted germ-line coded pool of specific receptors [2].

The path of surveillance program in regulating recognition and remodeling of self tissue components across intrauterine and after birth life, including the generation of adaptive immune system, have put forward the idiom of *immunological homunculus or immunculus* to cover up a very complex interaction networks that goes beyond our private cellular and molecular compounds into the surrounding biosphere [3,4].

A prominent component in this program is represented by natural autoantibodies that recognize both self and non-self antigens with low affinity and elusive specificity expressing their function rather as non-clonally articulated pattern recognition receptors that a specific complementary paratope. By itself this characteristic gives the attribute of autopolyreactivity to the natural antibodies.

Since autoantibodies of the IgM isotype are present both in invertebrates species and in vertebrates could be interpreted as a sign of an early appearance in human ontogeny, eventually connected with progenitor B-cell development in fetal splanchnic area, specifically the omentum, being maintained further in adult life throughout their autonomous replicative cycles in peripheral tissues [5].

Natural IgM autoantibodies are encoded by non-mutated germline genes and do not present affinity maturation. However in higher vertebrates natural antibodies can switch from IgM to IgG or IgA isoptype, when a certain amount of mutation can occur in variable region coding genes, although maintaining an unrestricted poly or oligoreactivity [6].

This feature allowed the natural autoantibodies, by virtue of their reactivity and cross-reactivity with structurally different antigens, often conserved molecular patterns, to generate a large surveillance network. The network actively and continuously inspect complex functions going from sustaining and controlling development and maintenance of self identity, active tissue clearance and regeneration, up to scrutinizing the frontier with external nonself antigens and eventually counteracting them. Equally, the natural immune response can shift to the more specific adaptive reactivity narrowing polispecificity through affinity maturation and repertoire expansion until a monospecific high affinity autoantibody is shaped [7,8].

This dynamic character of natural and adaptive autoantibody network, lastly potentially including also an idiotype regulatory interaction, highly recommend it as a source of biomarkers or molecular tools of intervention dedicated for recovering cell or tissue pathology [9].

Obviously, cancer could be a first and foremost beneficiary of such an approach.

Cancer cells express often structurally different carbohydrates epitopes of their surface glycoproteins and glycolipids in contrast with their normal counterparts allowing quantitative distinction (cit 5) in immunohistochemistry staining with IgM antibodies isolated from patients or healthy people. Moreover some antibodies can be tumor specific or can be capable of inducing lipoapoptosis following accumulation of lipids in cancer cells [10].

Another mechanism through which IgM antibodies are able to annihilate transformed cells is complement mediated cytotoxicity. In gastric cancer IgM antibodies bind to a specific carbohydrate epitope of modified isoform of decay acceleration factor (DAF), and induce apoptosis. Anti-carbohydrate antibodies represent the humoral component of tumor immune surveillance and that could explain their presence in the peripheral blood of healthy persons. Perhaps this could lay the groundwork of natural IgM immunotherapy [11].

While most polyreactive antibodies belong to the IgM isotype, IgA, and IgG natural antibodies can evolve and recognize proteins, nucleic

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acids, lipids and carbohydrates eventually bridging the way towards adaptive immune response. Adaptive affinity maturation is currently present in disease-associated autoantibodies harboring monoreactivity and high affinity [12].

Cancer cells release small and undetectable amount of antigen whereas complementary antibodies persist for long time in large concentration acquiring the value of biomarker.

However the sensitivity become clinically relevant only after tumor-associated antigens are pooled together as compared to single tumor antigen after extracting targets identified by antibodies present in healthy individuals [13].

Different methods were exploited to render autoantibodies measurable when sera from cancer patients were tested: serological proteome analysis, protein microarray, reverse-capture antibody microarray and phage library.

Therefore the facility to establish molecular imprint of autoantibodies may provide practical clinical diagnostic and prognostic information [14].

Also antibody signature prove to be a hopeful approach for early detection and diagnosis of breast cancer suggesting that applying the assay to a prospective patient population could reveal applicability. In addition autoantibodies screening in cancer patients might divide subgroups with high relapse risk and poorer prognostic in contrast to other subgroups with a better perspective [15].

Autoantibodies have proved to be of recurrent and specific incidence in patients with malignancies and linked with clinical parameters.

The conclusion is that natural and adaptive autoantibodies, reactive with cell surface, or intracellular structures, mark the body state and signal molecular abnormalities offering a source of clinical useful biomarkers and/or therapeutic tools.

Tumor development breaks homeostatic balance rendering immunogenic some cellular components. A panel of autoantibodies targeting dissimilar antigens, rather than a particular one, can reach high sensitivity and specificity, and may be functional as early detection biomarkers prior the standard clinical positive diagnostic. Also the autoantibody profiles will differentiate among types of tumors, and propose an instrument for monitoring the response to treatment, including immunotherapy.

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