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Detection of Early Cancer: Genetics or Immunology? Serum Autoantibody Profiles as Markers of Malignancy

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Abstract: The search for effective methods for detecting cancers at very early stages is currently a top priority of cancer research. While numerous oncogenes have been identified in and associated with human cancers, the last 50 years of molecular and genetic studies have not led to a breakthrough in either the diagnosis or the treatment of cancers. Therefore, the role of oncogenes in carcinogenesis is still unclear, as is their usefulness in the diagnosis of human cancers. In the present review, we discuss the concept of oncogenes and summarize the current approaches for the early detection of human cancers based on antibodies arrays.

Keywords: Antibodies, cancer development, early diagnosis, immune changes, oncogenes.

THE ONCOGENE CONCEPT

In the first half of the 20th century, the knowledge on carcinogenesis was primarily of the perspective that "embryonic" cells got beyond the organism's control, and the phenomenon of malignization was classified with reference to the whole-organism systemic impacts made on the organs or tissues in which the cancer was found. With the rapid development of molecular biology and identification of oncogenes, the research interest in carcinogenesis has shifted to analytic approaches and led to the substitution of systemic views on cancer to simplistic reductionist concepts. The apotheosis became the concept of the oncogenes as a ground for explanation of cancer development [1,2]. The idea that cancer is a genetic disease [1] has dominated the mind of oncologists. Briefly, carcinogens, cause irreversible changes (mutations) in the genome, resulting in abnormal activation of proto-oncogenes and/or inactivation of their inhibitors. Persistent changes in the structures and activities of proto-oncogenes may directly cause the development and growth of malignant tumors. Due to dedifferentiation and immortalization, malignant tumor cells gain unlimited and uncontrolled malignant proliferation. Therefore, optimal anti-cancer therapies should efficiently eradicate tumor cells, and the assessment and diagnosis of cancer should be based primarily, or even exclusively, on genotyping. Unfortunately, significant progress on molecular genetic studies of cancer over the last 50 years has not led to a breakthrough in the treatment or diagnosis of cancer. This raises the question of whether or not oncogenes significantly contribute to carcinogenesis and serve for revitalizing modifying systemic approaches to explain the phenomenon [3-7].

One major inconsistency of the genetic concepts of cancer is the reversibility of tumor cell transformation, i.e., the principal ability of cancer cells to differentiate and to lose malignancy. If we proceed from irreversible carcinogenic genome changes, the fact that tumor cells may be normalized is nonsense, which is contrary to the concept's basics, as no reversible mutations have ever been observed. None the less it has been shown that teratocarcinoma cells injected into blastocysts of mice were able to fully differentiate and no tumors were found in animals [8]. Likewise, the differentiation

of tumor cells of the other types, such as breast adenocarcinoma or chondrosarcoma can also be induced [3]. On the other hand, the development of malignant tumors can be induced without preceding genetic mutations – merely by placing normal embryonic cells in an ectopic site [9].

Moreover, the current concept of the oncogene does not fit well with pre-cancer situations, i.e., progressive pathological changes, associated with activation of cell proliferation in the absence of malignancy. It is known that the pre-cancer state transforms into cancer only months or years after nascency, whereas mutations (including those in oncogenes) are inherently momentary abrupt events. This brings out an inconsistency in the current theory of oncogenetics, namely the process of cell malignization due to the gradual accumulation of pathological changes, which are completely reversible for a long period of time (cells return to a normal state from pre-cancerous situations when the carcinogenic influence is terminated). Such reversibility suggests the requirement of long-acting factors to trigger pathological transformation. This, however, bears little resemblance to mutational changes. It is only when the pre-cancerous stage is surpassed that the gradual process of malignant transformation acquires uncontrolled invasive growth, which is the "common denominator" of any carcinogenic action [4].

Chronic inflammatory processes often occur as the precursor to tumor development. According to Ruggiero and Bustuobad [5], tumors that arise in response to incoming proliferation signals only occur in organs and tissues that have exhausted their regenerative potential and are unable to restore their original number of functional cells. In contrast, it is impossible to induce cell malignization in tissues that have full-fledged regenerative potential [5]. According to Dvorak [10], the phenomenon of malignant growth resembles ineffective attempts to repair tissue, which cannot be completed (his classic article on the subject is called "Tumors: wounds that do not heal") [10]. Observations of this kind suggest that changes in oncogenes and /or their inhibitors are probably a necessary, but evidently not sufficient, condition for malignant transformation. Moreover, there is evidence that, in at least some cases, genomic changes do not proceed, but are secondary to the process of malignancy [11]. The possibility of cell tumor growth is determined, not by changes in genome, but rather by the state of reparative and regenerative systems of a specific tissue and organ.

Malignant cell change can be induced by a variety of mutagens. Nevertheless, cancer growth can also be brought on without mutagens, for example, by prolonged tissue irritation with some

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inert foreign matter, which may not be attributable to the mutagen category (e.g., a rod made of glass or ebonite, hemmed under the skin or introduced into the gallbladder) [12, 13]. Malignant growth can be induced with prolonged and repeated local mechanical or thermal damage [4]. Therefore, cancer can be caused by factors that do not have genotoxic or mutagenic qualities, which is a contradiction of the molecular-genetic concept. The nature of the irritating factor does not apparently matter. The reduction of the reparative potential of an organ or tissue under conditions of long-term injury is the determining factor.

In accordance with the current concept of oncogenes, only the cell (or, more precisely, its genome) is considered to be an anatomical unit of the malignant process. On this basis, it is difficult to resolve the "paradox of the whale and the mouse", which was first noticed by Dawe [14], and is also called Peto's paradox [15]. Spontaneous neoplastic processes occur during life with about the same frequency in mice and whales, though the number of cells in the whale's body is 3,000,000 times greater than in that of the mouse. If the frequency of tumor formation was proportional to the number of cells in the body, a whale would suffer from millions of tumors during the course of its lifetime. In reality, the incidence of tumors among whales, mice, and other mammals is roughly the same. This paradox is resolvable if we assume that the anatomical unit for cancer is an organ, rather than a cell. There is homology between the organs of mice and whales (both have one liver, one stomach, a pair of lungs, and two kidneys, etc.). This way of looking at the generation of cancer can explain why the frequency of liver cancer is approximately the same in both species, despite the fact that the number of cells in the whale's liver is many times greater than in the liver of the mouse (3×10^{15} to 1×10^9). Naturally, tumor occurrence is primarily determined by changes in an organ's condition, not by the genome of one particular cell.

Numerous attempts to detect qualitative biochemical and antigenic differences between normal and malignant cells have been unsuccessful. When tumor cells are compared to normal cells (especially normal stem cells), no fundamental differences can be found [4]. According to the theory of the oncogene, normal cells have proto-oncogenes, which are pathologically activated during the transformation process. However, this idea is applicable only to differentiated cells, and not to stem cells. Within this perspective, the malignant properties that would appear in a cell in consequence with 3-4 mutations are already present in the stem cells: they are clonogenic, minimally differentiated, immortalized, have autonomic division (autocrine stimulation of mitosis), and activated oncogenes [4]. But usually not give the malignant tumor formation! If stem and cancer cells are nearly identical in their basic properties, there is no need for genetic damage to trigger the malignant transformation. This transformation can be carried out, not by mutation, but only as a result of a system control fault, which is responsible for the proliferation of stem cells and their derivatives. In the beginning of the twentieth century, Karl Bauer (one of the founders of the tumor formation and mutation theory) said: "In the strict sense, there is no hereditary transmission of cancer. ... We are talking about tissues' inheritance of the propensity to form tumors under certain conditions" [16].

CANCER IN THE ABSENCE OF DISEASE

Transplanted malignant cells can induce tumor growth in recipient animals, but not always and not immediately. The result may depend on the extent and nature of tissue injury during the replanting of foreign cells [5]. Similarly, malignant transformation of plant leaves (formation of galls) under the influence of *vir-regulon* – analogue oncogenes – does not occur if there is no mechanical damage to the leaf, for example, by pin. In other words, the oncogene is introduced (as confirmed by PCR data), but, if the

leaf is not damaged, malignant transformation is not observed [17]. Tumor development only occurs after tissue injury – before that event, the growth-regulating tissue signals effectively prevent malignant growth, despite the presence of active oncogenes. Most likely, the "collusion of the tumor microenvironment with a growing tumor", that is the state of connective tissue stroma, also has a vital (although not yet clear) impact on the progression or inhibition of neoplastic processes [18, 19].

These observations correlate well with Folkman's data [20], obtained by histological examination of autopsy samples from organs and tissues of deceased humans. In seemingly healthy persons, isolated populations of malignant cells are detected very often. Thus, "dormant" breast cancer tumors are found in more than 1/3 of women aged 40-50 years, although, breast cancer (as a disease) is diagnosed thirty times less frequently for these women (1% of women in this age group). In slices of the thyroid gland from humans aged 50-70 years, localized malignant cell populations can be detected in almost 100% of cases, in spite of the fact that occurrence of cancer as a disease exhibits a thousand-fold lower frequency in this organ (less than 0.1%). High occurrence of dormant "buds" of malignant tumors (with no clinical signs) was described as characteristic for the prostatic gland and other organs. In all probability, most humans harbor these hibernating tumors, but, fortunately, cancer only develops in a small proportion of individuals. This paradox is hardly explainable from the position of oncogene-dependent malignancy, which perplexes many clinicians. It is, however, quite compatible with the notion of tumor growth depending on tissue control as the primary determinant. If cancer cells originated only as a result of oncogene mutations, they would have to produce specific cancer proteins that did not previously exist in the body. However, in this case, the apparent failure of the anti-cancer activity of the immune system is not rationally explainable. Contrarily there are tumors whose formation stems from abnormal proliferation of autologous stem, and not fully differentiated, cells that went beyond control of tissues. It is clear that their self-antigens (from stem cells and their descendants), which are constantly present in organs and tissues, are not perceived by the immune system as foreign or dangerous and, therefore, do not induce destructive immune response.

APPROACHES TO EARLY DIAGNOSIS OF TUMOR GROWTH

There is no need to suffer delusions about the possibilities of universal and omnipotent gene diagnostics: if there are no competitors to molecular genetic methods for the prognosis or diagnosis of monogenic diseases, the same methods are not a practical option for multifactorial diseases. In particular, only small proportion of malignant tumors are imminently dependent on abnormality in a single gene. These are so-called "family cancers", derived from hereditary tumor syndromes. Such syndromes are mostly caused by dominant inactivating mutations in tumor suppressor genes. For example, the individuals who bear the defective BRCA1 or BRCA2 genes ("hereditary breast-ovarian cancer", or HBOC syndrome) have more than a 50% chance of developing breast and/or ovarian cancer in their lifetime. Those who carry the defective p53 gene (Li-Fraumeni syndrome) have a 90% chance for developing cancer. These patients most frequently suffer from sarcomas, leukemia, lung cancer, breast cancer, adrenal cortex cancer, and brain tumors. Apparently, there are dozens of similar genetic syndromes associated with a significantly elevated risk of cancer. However, the total frequency of "hereditary cancers" composes only 2-5% of all malignant tumors. The origins of the other 95% of cancer cases are a result of multifactorial disease, and cannot be predicted with the help of molecular genetic markers. This does not mean, however, that the majority of cancers are completely free of genetic peculiarities – certain dependence, undoubtedly, exists. However, this dependence is caused by dozens to hundreds of housekeeping

genes, and plays the same role as genetically mediated resistance (or susceptibility), for instance, to influenza – different combinations of individual “bad” genes (certain molecular-genetic backgrounds) may cause the minor metabolic changes that cripple the general defense of an organism against unfavorable environmental factors. In this vein, selected genetic peculiarities associated with increased risk of cancer can be revealed with the help of broad genetic screening (GWAS), as well as with heightened risk of succumbing to influenza or myocardial infarction. Nevertheless, the predicative value of such investigations is insufficient and hardly useful for the implementation of effective measures for the prediction and prevention of malignant disease in individual cases.

NATURAL AUTOANTIBODIES IN NORMAL AND PATHOLOGICAL TISSUES

The last thirty years of clinical immunology can be characterized by the appearance of a number of seemingly paradoxical ideas that have contradicted established views of disease. Alfred Tauber recently stated, “host defense is only part of the immune system's functions, which actually comprise two basic tasks: protection, i.e., to preserve host integrity, and maintenance of organismic identity. And thus if the spectrum of immunity is enlarged, differentiating low reactive 'autoimmune' reactions from activated immune responses against the 'other' is only a matter of degree. Simply, all immunity is 'autoimmunity,' and the pathologic state of immunity directed at normal constituents of the organism is a particular case of dis-regulation, which appropriately is designated, autoimmune. Other uses of 'autoimmunity' and its congeners function as the semantic remnants of Burnet's original self/nonself theory and should be replaced” [21].

Natural autoantibodies (a-Abs) can be attributed to the same cohort. Identification of a-Abs in human serum was, previously, nearly exclusively considered to be a pathological phenomenon associated with the development of autoimmune diseases, but it has now reliably been established that the development of any chronic disease, not just autoimmune, is necessarily accompanied (not induced!) by the secondary growth of certain a-Abs types. This is confirmed by studies of sera from patients with atherosclerotic vascular lesions, cerebral accidents, complications of pregnancy, various forms of cancer, and others [22,23]. Moreover, it has been shown that natural a-Ab against IgG and IgM, directed against various antigens of own body, are always present in the serum of any healthy person throughout the individual's life [24]. One of the main homeostatic functions of a-Abs is their participation in the general clearance of organism from waste products. According to Hans Lutz, “Immunoglobulins have been developed in evolution to provide specificity for clearing body waste in the first animals with three germ layers” [25].

The overwhelming majority of healthy individuals have a similar serum concentration/affinity of a-Abs interacting with the same organ-specific self-antigen, because of a roughly equal production of waste in the same organ. This is not true, however, in disease: there are significant and very specific variations in the levels of a-Abs, which reflect the situation of the illness [22]. This is explained by “Kovaliov's rule”, which states that the production level of certain a-Abs is regulated by the quantity (accessibility) of relevant antigens, operating on a feedback loop [26]. It is clear that the level of dying and regeneration of cells in the liver, lungs, kidney, colon, etc., as well as the expression and coming-out in extracellular spaces of certain organ-specific antigens, is approximately equal in all healthy adult individuals, which determines approximately equal production levels of the different “hepatotropic”, “pulmotropic”, etc., a-Ab. At the same time, the development of any chronic disease, including cancer, is directly caused by altered levels of apoptosis and necrosis in different cells types and/or abnormal expression of certain antigens that are specific for different cell

populations. This, according to the feedback principle, is reflected in the production changes of relevant a-Abs. In other words, the immune system can “see” the pathological focus from the earliest stages of the disease, and respond to it by changing a-Ab production to target antigens of the affected tissue (organ) structures. Such secondary autoimmune reactions are physiologically justified and have a compensatory (sanogenic) nature, aimed at the maintenance of homeostasis by way of the clearance of redundant and products and dying cells from the affected organ [27].

Measuring marker a-Abs may potentially be useful for detecting diseases in preclinical stages, as well as for monitoring their dynamics. “Our common diseases lie in (changes of metabolic) networks, rather than in single molecules” [28]. This kind of systemic phenomena makes itself known by dynamic changes in large networks of marker autoantibodies more than changes in one autoantibody of any single antigenic specificity. The architecture of the serum antibody network remains stable for a long period of time if the situation in the organism is physiologically normal [29]. Contrarily, any pathological change in tissues and organs is accompanied by peculiar changes in a-Ab networks, and is reflected by shifts in profiles (patterns) of normal serum immune reactivity [27, 30]. This is also the case for malignancy; Merbl and colleagues [31] noted that antibody patterns, but not any single antibodies, were informative biomarkers of body-tumor dynamic interactions.

CANCER REFLECTION IN THE “IMMUNE MIRROR”

Thirty five years ago, Husby and colleagues [32] showed that tumor infiltration by T-cells made up 72% of the total population of lymphocytes in the infiltrate, and the infiltration level of B-lymphocytes was 25%. Immune complexes were also found to have infiltrated the tumor matrix. Unfortunately, in those days, any attempts to purify and identify the tumor-infiltrating a-Abs were unsuccessful, which was the case for many years. However, in the last decade, attention has returned to the a-Ab. Tumor formation processes observed in laboratory animals [31] and humans [33] have been shown to accompany increased production of certain a-Abs. The profiles of serum immune reactivity due to relative proportions of different a-Abs [30] regularly and significantly change in cervical cancer development [34]. In addition to the quantitative changes in the antigenic composition of tumors, there are also changes in the compositions of a-Abs that are only quantitatively significant in contrast to the normal state. In typical cancer development, there is an increase in fetal protein synthesis (AFP, CEA, embryonic forms of isoenzymes, etc.). Such antigens are not new to the organism and do not induce an effector immune response to the cells synthesizing the proteins (the reaction does not usually reach the level required for tumor destruction). However, this shift leads to amplified production of multiple a-Abs and creates unprecedented opportunities for the development of new immunochemical technologies for the early diagnosis of tumor growth, predicting cancer months or years before the first signs of the disease.

In studies carried out since 2005, we have obtained direct experimental confirmation of the possibility of creating an effective diagnostic enzyme immunoassay test based on an assessment of the profiles of a-Ab immune reactivity, directed against a number of tumor-associated antigens. During the last 8 years, our group has been involved in the elaboration of diagnostic technology based upon a multi-component immunochemical kit, the “ELI-Onco-Test”. Selection of the appropriate set of antigens will permit the development of diagnostic kits, making it possible to detect changes in the profiles of serum immune reactivity (grounded on selective changes of some natural a-Abs) typical for malignant neoplastic processes of the different types. Our search of the informative tumor-associated antigens is an on-going process, aiming for analysis of the a-Abs that would allow for the diagnosis of

emerging active malignant tumors of different localizations and histological structures in a reliable manner. It should be noted that the empirical selection between some dozens of cancer-associated antigens provides the possibility to construct a specialized ELISA-Kit, which permits us to achieve an accurate result with sensitivity and specificity nearly 75 and 80%, respectively on blind serum samples from cancer patients and individuals without malignancies (Poletaev, unpublished data, 2012-2014). The obtained results may be considered to be confirmation of the primary idea, but are not sufficient for introduction in clinical practice. Additional selection of the most informative antigens should suffice to elevate the sensitivity and specificity of the diagnostic kit to clinically acceptable limits.

We believe that, within 3-5 years, the detection of these cancer a-Ab biomarker changes can become a very effective diagnostic tool suitable for large-scale clinical use, aimed at detecting cancer at an early stage of development.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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