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Psychogenic carcinogenesis: Carcinogenesis is without exogenic carcinogens

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SUMMARY

The history of researches of a problem of cancer has cleared a number of key cellular–molecular–genetic mechanisms of carcinogenesis, however process of carcinogenesis, is still out of control and a world forecast is unfavorable despite the advanced pathogenetically focused medication and excellent results of cancer treatment in vivo. Numerous researches have shown that chronic psycho-emotional stress by means of stressful hormones and endogenous mutagens (reactive oxygen and nitrogen species) are capable to damage cells DNA and to compromise immune system. Actually, chronic psycho-emotional stress is capable to activate the key mechanisms of carcinogenesis. It specifies an opportunity of existence psychogenic carcinogenesis – "carcinogenesis is without carcinogens" which can function as independent and in a combination with physical, chemical and biological carcinogens, strengthening their carcinogenic effect. At cancer patients with psychogenically induced carcinogenesis use only the somatically focused therapy of a cancer (surgery, radiotherapy, chemotherapy, immunotherapy), apparently, is not enough for achievement of steady remission. At psychogenically induced carcinogenesis creation of effective anticarcinogenic medicines is also apparently problematic. The presented hypothesis allows to hope for search in the future of diagnostic criteria of revealing of persons with psychogenic also and development of new strategy of the second prophylactic, treatments and rehabilitations such cancer patients. The hypothesis psychogenic carcinogenesis expands existing representations about pathogenesis of malignant tumors and forms holistic approach to the decision of problems of a cancer at the person.

Introduction

Moreover according to WHO forecast annual oncological disease in the world by 2050 will increase from 11 up to 24 million new cases and death rate – from 6 (in 1999) up to 16 million [1]. Now three groups of carcinogenic factors (chemical, physical and biological carcinogens) are known and key mechanisms of carcinogenesis in which are certain on the one hand there are infringements of genes expression and DNA methylation, DNA damage, genome instability, mutagenic processes activation and malignant transformation of cells [2,3]. On the other hand infringements of immune system, which are connected with dysfunction of a cellular part of immunity, immune tolerance and impossibility of the effective immune answer to a developing tumor are proved [4]. Despite of enormous progress in understanding of biology of malignant tumors and mechanisms of carcinogenesis, the five years' survival rate of cancer patients has increased only by 14% (from 50% up to 64%) [5]. Even the initial positive answer to cancer therapy does not guarantee further durability of medical effect, absence of relapse of a cancer and a lethal outcome which is similar to a guessing "will it happen or not" [6]. Available representations about carcinogenesis are insufficient for an explanation of unpredictability of current of tumor process and modern lines of growth of malignant tumors at the person.

The hypothesis

We consider that the cancer problem includes very important system carcinogenic factor which is not officially considered. This is a psychogenic factor. The significant amount of the data is saved up allowing to see an opportunity of development of psychogenically caused carcinogenesis.

We hypothesized, that chronic psycho-emotional stress (CPS) is capable to activate key carcinogenic mechanisms and to induce malignant tumor growth without active participation exogenous carcinogens.

Development of new hypothesis

Our long-term (1998–2008) experimental and clinical work preceded the occurrence of a preceded psychogenic carcinogenesis hypothesis during which the development of more than 1000 cases of malignant tumors of 23 kinds has been analysed. Results have shown that 50–70% of patients before cancer detection were in a condition of chronic psycho-emotional stress within 1–4 years. Reasons for CPS were: a death of the close person, divorce, frequent family conflicts, change of a residence, appearance of the disabled

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in family etc. Basic characteristics of CPS were loss of the purpose, meaning in life with the advent of sensations of feebleness, the hopelessness, helplessness not often realized by the patients. In view of the received data we developed the pathogenetically proved technique of hypno-suggestive psychotherapy for correction of a psychogenic component of cancer disease. Inclusion of a hypnotherapy technique in complex treatment of patients with malignant melanoma has allowed to improve their mental condition and quality of a life authentically, to render pathogenetically significant influence on immune system and to increase five years' survival rate of patients. Scientific researches which have laid down in a basis of a psychogenic carcinogenesis hypothesis are stated in our monography [7].

Evidence in support of the psychogenic carcinogenesis hypothesis

It is known that two interconnected processes are necessary for development of a cancer under influence of chemical, physical or biological carcinogenic factors: damage of DNA cells and immune system compromising. However, these pathological processes can be generated without participation of exogenous carcinogens, i.e. can be induced psychogenically.

Population data about psychogenically induced carcinogenesis

Data of many population researches allow to see an opportunity of a psychogenic induction of malignant tumors. For example, depression and hopelessness can play the important role in etiology of breast cancer (BC) [8,9]. The people gone through massive stress or daily stress raise BC risk in 3.7 times [10]. Phenomena of a racial discrimination essentially raise BC rate among black women in the USA [11]. Population research of 10808 women who have gone through divorce or loss of a close person has shown sharp increase in risk of BC disease [12]. In one of provinces of Poland the high level of malignant neoplasms has been connected with psychological stress on a background of social and economic transformations in 80 and 90th years of the last century [13]. Death in war of 6284 sons led to increase at parents' disease of malignant tumors of lymphatic and hematopoietic systems, melanoma and if the cancer had been diagnosed before loss the risk of death has considerably increased [14]. Population research in Italy has shown that occurrence in children tumors of the central nervous system and Hodgkin's lymphoma has been essentially connected with the subsequent development in their mothers' cancer of the respiratory tract and among mothers of leukemic children cancers of the lymphohematopoietic system and BC were observed [15]. It has been collected a lot of similar data, however mechanisms of interrelations "mind-cancer" remain unclear.

Children psychogenic carcinogenesis

Greene and Miller informed about possible links of psycho-emotional stress with development of cancer in children 50 years ago in their work [16], later researchers also paid attention to these links [17]. Extremely negative influence of prenatal psychological stress and depression on mother–child symbiosis has been established up to an arrest of development of fetus and poor birth outcomes [18,19]. Death of one of parents of pregnant women is connected with high risk of development in the born children four tumor types: childhood acute lymphoblastic leukemia, Hodgkin's disease, embryonic carcinoma of the testis, and appendiceal carcinoid tumors [20]. Family psychological stress is associated with infringement of children immune system functioning and increase in frequency of their disease [21]. There is an impression that the fetus, neonatus and child even are more sensitive to CPS damaging influence in a continuum mother–child and parent–child than adults because of full dependence from mother/parent and absence of antistressful strategy of reaction to real or alleged dangers. It creates real conditions for a psychogenic induction of tumorogenesis in a developing children's organism.

Chronic psycho-emotional stress and DNA damage

It is known that CPS leads to dysfunction of telomere (the ends of chromosomes) and to reduction of their length [22,23], which is accompanied by genome instability, acceleration of biological ageing [24], reduction of life expectancy [25], formation of a lot of diseases including cardiovascular diseases and cancer [26]. Short telomeres are biomarkers of cell ageing; they specify stressful history of a cell and cumulative action of a high level of oxidant stress on a cell [27]. In its turn oxidant stress is capable to be activated in reply to CPS and damage DNA, lead to gene mutations by means of reactive oxygen and nitrogen species (RONS) that becomes critical event in activation of key tumorogenesis mechanisms [28–30].

Person in condition of CPS is very sensitive to damaging action of various mutagens, spontaneous and induced levels of damage of DNA are more often registered [31]. The chronic stress in model in vivo facilitates development of skin cancer almost in 3 times on a background of carcinogenic action of ultra-violet irradiation [32].

Chronic psycho-emotional stress and chronic inflammation

It is necessary to notice that CPS supports the centers of not stopped chronic inflammation which are always available in an organism due to activation in them of proinflammatory cytokines [33]. Generation of RONS in the centers of slow inflammation considerably exceeds their opportunities of neutralization and elimination therefore high levels of oxidative–nitrosative stress and DNA damage are always registered in these centers that associates with the raised risk of tumor genesis and the main substances transforming the center of inflammation in the center of a tumor, are prostaglandins and cytokines [34,35].

Chronic psycho-emotional stress and compromised immunity

Genetic damages are necessary but insufficient for the neoplastic transformation of the cells and tumor growth, cancer progressing or relapse as formation of tumor is impossible without infringements in immune system where stressful factors and mentality take active part [36], that is a subject of studying psycho-neuro-immunology and its sub-discipline – psychoimmunology of cancer [37].

On background of CPS decreased hypothalamo–pituitary–adrenal (HPA) and sympathetic–adrenal–medullary (SAM) axes responsiveness is observed that is accompanied with disregulation of neuromediator systems, infringement of hormonal expression and functions of immune system [38,39].

At the cellular level stressed and depressed patients had overall leukocytosis, high concentration of circulating neutrophils, reduced mitogen-stimulated lymphocyte proliferation and neutrophil phagocytosis.

At the molecular level high levels of serum basal cortisol, acute phase proteins, chemokines, adhesion molecules, plasma concentration of interleukins IL-1, IL-6, and TNF-alpha and a shift in the balance of Th1 and Th2 immune response towards humoral immunity. Both stress and depression were associated with the decreased cytotoxic T-lymphocytes and natural killer cell activities affecting the processes of the immune surveillance of tumors, the accumulation of somatic mutations and genomic instability. DNA damage, growth and angiogenic factors, proteases, matrix metalloproteinases and reactive oxygen species were also related to the

chronic stress response and depression [38]. CPS induces apoptosis of lymphocytes and development of immune depression by means of glucocorticoid ways, participations of opiod systems [40], genes p53 and P13K/nuclear factor kappaB [41]. In its turn oxidative stress also induced by CPS and depression supports immune suppression at malignant tumors [42], and proinflamation cytokines, activated by mental depression, support a condition of mental depression [43], closing some vicious circles of psychogenically induced carcinogenesis.

Stressful brain and cancer

Brain – the key body providing adaptive/disadaptive reactions of an organism on stress through involving vegetative, endocrine, immune mechanisms [44]. On the background of CPS, infringements HPA axis activity and glucocorticoids influences structural remodeling dendrite neurons of hippocampus, amygdala, prefrontal cortex occurs [45], actually the atrophy of neurons in limbic structures of the brain responsible for processes of adaptation is observed, regulation of vegetative functions, generation of emotions and motivations, the organization of complete forms of behavior, etc [46]. It is worth noticing that reduction of cerebral metabolism in limbic structures of the brain in patients with various malignant tumors is observed [47]. It is possible to assume that difficult to diagnose (subclinical) infringements of functions of limbic systems are formed in cancer patients before detection of new malignant growths on a background of CPS cumulative influence. Besides, affective disorders (helplessness, depression) which are characteristic of cancer patients, are accompanied by dissociated changes in four major brain systems: (1) an unbalanced prefrontal-cingulate cortical system, (2) a dissociated HPA axis, (3) a dissociated septal-hippocampal system, and (4) a hypoactive brain reward system, as exemplified by a hypermetabolic habenula-interpeduncular nucleus pathway and a hypometabolic ventral segmental area-striatum pathway [48].

Thus, behind a facade of serious somatic (neuroendocrine, immune) and psycho-emotional (anxiety, depression) disorders at cancer patients infringements of integrative functions of brain systems are presumably hidden which can be defined as brain disintegration syndrome (BDS). BDS is characterized by infringement of functions of suprasegmentar vegetative structures, descending tonic influences on sympathetic-adrenal and pituitary-adrenic devices that is shown by decomposition of activity of physiological systems at all levels of an organism. Cancer is not only the pathology of genes it is the unique result of cumulative CPS influence with cumulative carcinogenic effect of catecholamines and glucocorticoids [49], serious infringement of antineoplastic activity of immune system and tissue morphofunctional homeostasis, actually, this is illness of a whole organism. However, the huge potential of brain is capable to supervise and modulate the processes connected with genesis and progression of a cancer [50].

Mental depression and cancer

CPS is closely connected with formation of affective disorders, in particular due to changes in expression of a gene 5-HTTLPR responsible for transport of serotonin [51], therefore anxiety and depressive disorders often go together and are characteristic of cancer patients [52]. Mental depression, serotonin system and proinflammatory cytokines are connected in uniform pathophysiological links participating in carcinogenic mechanisms [53]. For a long time there has been consent among a significant number of scientists and clinical physicians on depression as etiological factor in development of cancer [54]. Comorbid depressive and/or anxiety disorders aggravate development of any chronic disease [55], influence extremely negatively on immune basis of some infectious, autoimmune, cardiovascular diseases and malignant tumors [56,57]. Depression promotes progress of cancer and is a signal of a short life of oncopatients however the fact of fatal association "depression-cancer" is practically ignored in strategy of preventive prophylaxis and treatment of a cancer [58].

Adverse growth forecasts in cardiovascular diseases rate, malignant tumors and depression in the world should be paid attention to. By 2020 depression becomes the second leading reason of disease in the world after ischemic heart disease [59] .It is possible that depression is pathogenetically connected with development of the specified diseases and under certain conditions can act as the starting factor for psychogenic carcinogenesis.

Chronic stress and cancer in vivo model

In vivo model chronic stress is accompanied by a hypermetabolic syndrome with the severe loss of lean body mass, hyperglycemia, dyslipidemia, increased aminoacid turnover and acidosis. This was associated with hypercortisolism, hyperleptinemia, insulin resistance and hyperthyroidism that lead to a significant reduction of power reserves, compensatory opportunities and abilities of an organism to cope with infection or cancer [60]. Proof of chronic emotional stress connection with cancer development and progress was a result of experiments which have shown presence of IL-6-independent activation signal transducer and activator of transcription-3 through mediators of stress (norepinephrine and epinephrine), beta 1-/beta 2-adrenergic receptor and protein kinase A that has led to increased matrix metalloproteinase production, invasion and tumor growth [61]. Besides chronic stress by means of beta-adrenergic activation induced the atrophy of thymus and the host resistance to tumors [62], and also induces resistance of tumoral cells to chemotherapy drugs through biological effects of adrenaline, alfa-2-adrenergic receptors and increase expression of a gene mdr1 which codes transport activity of plasma membrane ATPase, capable "to expel" molecules getting into a cell of cytostatic [63]. It is also impossible to exclude that chronic stress by means of p38/stress-activated protein kinase and endoplasmic reticulum stress promotes formation in an organism of dormant tumor cells based for many years and decades, refracted to the chemotherapy, participating in cancer metastasis formation and relapse [64].

It is necessary to tell that at animals high efficiency of treatment of a cancer is observed which unfortunately is not present at the person and results in vivo cannot be extrapolated on the person [65]. Distinctions are hidden in absence at animals of the second signal system (mentality as a whole) which is the imperceptible factor interfering with an effective cancer treatment.

Schema of psychogenic carcinogenesis

The basic parts of psychogenic carcinogenesis are presented in Fig. 1. The hypothesis allows to see participation of a psychogenic component (a) in the development of known key mechanisms of carcinogenesis (b) and formation of the cancer disease closing a vicious circle of carcinogenesis (c).

Evidence in opposition to the psychogenic carcinogenesis hypothesis

- The basic problem in reception of strict scientific proofs of psychogenically induced carcinogenesis is the complexity of definition of "carcinogenic CPS doze" for each concrete person.
- The establishment of an exact time for the beginning of oncoprocess from the moment of the beginning of CPS action is not less difficult.

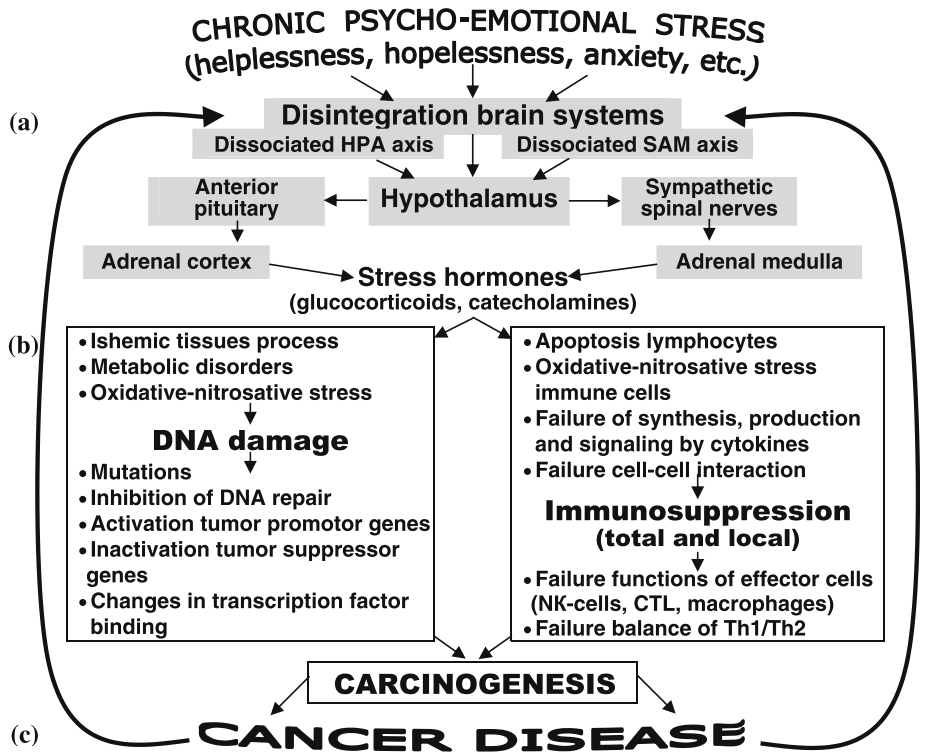

Fig. 1. Schema of psychogenic carcinogenesis. (a) Chronic stressful dysfunction of a brain with descending tonic influences on pituitary–adrenal and sympathetic-adrenal systems. (b) Stressful damages of the cell genetic device and oppression of supervising functions of the immune system, leading to emergence and growth of a malignant tumor. (c) Formation of the cancer disease closing a vicious circle of carcinogenesis.

– Results of psychological and psychotherapeutic help to cancer patients express ambiguity of researchers' opinions: from the complete uselessness [66] to obvious efficiency of application of psychotherapy to increase the survival rate of cancer patients [67].
– In many population researches any links between psychosocial or personal factors and development of a cancer are not found [68].
– Mental depression does not always lead to cancer development.

Testing the psychogenic carcinogenesis hypothesis

Model in vivo

It is necessary to investigate a level of HPA and SAM axes activity, metabolic infringements, oxidant stress, DNA damage and parameters of immune system in all experimental models. Carrying out of the following experiments is expedient:

- Definition of frequency of spontaneous malignant tumors at the animals subjected to various kinds of chronic stress.
- Estimation of chronic stress influence on the development of already available tumors.
- Simulation of a psychogenic component (chronic stress) at chemical, physical and biological carcinogenesis.
- Definition of a potentiation frequency degree by chronic stress and the tumors malignancy caused by chemical, physical or biological carcinogens.
- Estimation of efficiency of cancer treatment at animals on a background of chronic stress will allow to simulate participation of a psychogenic component in cancer treatment at the person.

Clinical check of a hypothesis

- Define how features and degrees of psycho-emotional frustration influence the key parts of carcinogenesis.
- Study how effective pathogenetically significant correction of psycho-emotional frustration influences the development of tumor process within the limits of complex antineoplastic therapy.

Hypothesis implications

(1) The presented hypothesis allows to expand existing representations about mechanisms and kinds of carcinogenesis.
(2) There is an opportunity of development of new complex approaches and interdisciplinary strategy in preventive maintenance, treatment and antiy-relapce rehabilitations of cancer patients.
(3) In treatment of the cancer patients it is always necessary to influence a psychogenic component of cancer disease irrespective of fabric localization, the stage and prevalence oncoprocess.
(4) Development of ways of specific preventive prophylaxis and treatment of patients with psychogenic carcinogenesis has the practical importance as creation of universal anti carcinogenic medicines for such category of patients is practically impossible.
(5) The hypothesis allows to prove distinction of carcinogenesis at animals and at person, to develop adequate experimental and clinical models for search of effective methods of cancer treatment.

Conclusion

There are essential distinctions between experimental (on animals) and clinical (for the person) results of cancer treatment.

The psychogenic carcinogenesis hypothesis allows to explain these distinctions and to expand understanding of carcinogenesis mechanisms at the person. Holistic approach to a problem of a cancer at the person allows to hope for development in the future the new pathogenetically proved strategy directed to increase the efficiency of treatment and preventive prophylaxis of oncological diseases.

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