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Aging and Carcinogenesis - Insufficient Metabolic Cell Repair as the Common Link

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Carcinogenesis • Oncogenes • Cell transformation • Aging • Metabolic insufficiency • Cytology

Abstract
Background: The mechanisms of the development of cancer in old age and also the mechanisms of aging are not well understood. This paper tries to interpret consequences of malignant tissue transformation from the viewpoint of aging, or in other words, from an insufficient cell adaptation to the needs of repair and proliferation. ***Subject:*** A hypothesis is presented that a unified but quite opposite at different stages of ontogenesis mechanism is the basis of atypical growth and embryonic development. In the beginning of a malignant dedifferentiation is an insufficiency of an effective self-renovation and disturbed preservation of its adaptation capability. The suppression of regenerating cell proliferation is the primary event of the development of a dedifferentiated tissue growth. The transformation of normal cells into tumor cells is an adaptive reaction in reply to a shortage of self-regeneration capability and repair. Allowing for the process of rebirth, i.e. the complete restoration of tissues leading to the restrain of senescence proceeds by the type of embryonic growth of tissues, the possibility to use the potential of transformed cells for restraining senescence is proposed. The latter will permit to direct the process of transformation to an integrated growth channel, to prevent the clinical phenomenon of malignancy, and use the potential of transformed cells for realization of the self-renovation program and program of unlimited life duration of the whole organism. ***Conclusion:*** By a stimulation or compensation of the age-induced shortage of cell metabolism, two effects can be expected: prevention of cancer and retardation of aging.

Introduction

Phylogenesis or ontogenesis are driving forces in the evolution of different forms of life and mechanisms of vital activity. With reference to these processes the questions arise: Why was in the process of evolution the dedifferentiated growth of cancer not eliminated? What is the expediency of this paradoxical conservatism? Is it a cryptic mechanism of immortality? Is in fact in the mechanism of dedifferentiated growth the fundamental principle of a process of age prevention hidden?

The aim of this paper is to find some hypothetical answers to these questions.

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Life, Aging and Cancer

With reference to the figurative definition of cancer [1, 2] is its retrodifferentiation a daydream of Faust at the cellular level, or in other words, a daydream of immortality. The complex morphofunctional integration of cells into a multicellular organism with its submission to high regulatory mechanisms is characteristic for all eumetazoic beings [3, 4]. Is a disintegrating growth of cancer an attempt of the organisms to a self-renovation or the starting of a program of rebirth?

From the equation of Gompertz follows that a nonaging population may potentially reach any age [5]. Organisms with completely self-renewal tissues, as lobsters, have no internal reasons of aging [6] and live up to any age. Immortality is therefore not impossible and exists for some biological systems or can be at least imitated [7-9].

Evolution is much more directed to species reproduction and preservation of the particular species than to longevity and senescence. Longer life duration leads to an overpopulation of the particular species and is from an evolutionary point of view not intended [10]. No single population is capable of growing exponentially over a long time [11] and if so, it is compensated by the price of a decreased reproduction [12]. The motivation of this fundamental law is outlined in the monograph of Wynne-Edwards [13] on 'Animal Dispersion to Social Behaviour'.

The efficiency of tissue regeneration weakens with age. Self-reproducing systems show with increasing age a decline of environmental adaptation [6] and repair processes. If functional insufficiencies reach a critical level a disbalance develops with reference to an increased vulnerability to exogen factors. With the declining ability of regeneration is a dedifferentiation and the formation of an embryonal blastema combined [14, 15]. An embryonal induction with its capability of reproduction of form and function of tissues could ensure a complete regeneration [16].

Cell Transformation and Cancer Development

The age-dependent increase of tumor incidence results if the tissue of origin undergoes a reduction of reparation and an increase of tissue damage [7]. Shevelev [18] therefore concludes: 'Depression of the program of embryogenesis develops there and then, where and when the genetic program of a given organ and tissue is inconvertibly violated, in other words, 'cancer' is possible to consider as a compensation of cells and tissues normal genetic program defect by activation of a program, characteristic for the embryonal period'. It seems paradoxical that atypical growth is linked with an unlimited life. In fact, dedifferentiation of a tissue is known as a process of regressive evolution [19, 20]. Changes, beneficial for cells but deleterious to the organism, result from a missing stabilizing selection of cells by apoptosis.

In case of cancer results the violation of the law of impossibility of unlimited growth in the ruin of the organism because of the tumor progression. Catastrophy begins when the genetic program of embryogenesis continues to work instead of differentiating into specific functions. This leads to tumor progression and finally to death from cancer.

The main driving force of cell dedifferentiation is a deficit of tissue repair and metabolic hypofunction which implies a missing ability to respond to damaging influences. The inversely proportional dependency between regeneration ability and tumor frequency [3, 4] and the speed of homologous tumor growth by a partial resection of a normal organ [20] is in favor of the preceding statements.

The development of a dedifferentiation of a cell into a cancerous cell is only a process of further cell development [21], characterized by uncontrolled growth and blocked redifferentiation. It is worthwhile to be aware that these tumor characteristics lie within the 'repertoire' of a normal genome and appear in the ontogenesis of cell differentiation [22]. The expression of oncogenes at cell dedifferentiation is comparable with the picture of embryogenesis of the homologous organ [23, 24]. It follows that the mechanism of transformation into embryonal development can be started without any carcinogenic influence. Carcinogenesis only accelerates'the process of compensation of a critical level of metabolic tissue deficit [25-27]. It may be, therefore, expected that a revitalization of a particular tissue may be triggered into a developmental condition without dedifferentiation by the normal genome of an aging tissue.

Life develops, constantly adapting to changing environmental conditions, to an age-depending'decline of its functional redundancy. Effective self-reproduction of tissues and preservation of adaptation capability are the key conditions for an unlimited life. Decline of adaptability in general and functional interaction abilities in particular, are main reasons of senescence and death.

Increasing entropy with age results in an incomplete adaptation to toxic necrosis-as demonstrated by CCU poisoning of liver tissue. Chemical carcinogens, organogenic

in its actions, often influence tissue cells which have not forfeited its morphogenetical potencies [28].

Oncogenes, Cell Division and Cancer- Are the Current Concepts Still Valid?

A hitherto unshakable dogma is the conversion of normal cells in cancerous ones as a result of oncogenic activation. It is considered as a matter of fact that these oncotic genes cause such important processes as gametogenesis [29], different stages of embryonal development, growing, differentiation and regeneration. For the explanation of mechanisms of dedifferentiation, examples are used as mutation, virus promotor insertion, chromosomal reorganization with breaking of the genetic program and loss of suppressor genes [30]. But, are these mechanisms really defining the nature of pathological growing? The ras proto-oncogene is several times more growth activating than cell transforming [31]. The myc oncogene which is often responsible for the Burkitt lymphoma, cervix and mamma carcinoma can be found also in nonmalignant cells [32]. The ras protein interfaces the glucose tolerance factor and restores the activity of adenylate cyclase when introduced into tumor cells and causes a loss of tumorigenicity [33]. C-myc oncogene [34] and SV-40 vacuolating virus also possess such a potential [35]. Schafer et al. [36] have shown that loss of tumorigenicity does not correlate with quantitative changes in ras, myc and fos oncogene expression. Jaenish [37] reported that virus DNA, introduced into DNA of a fetus, which is actively transcribing in the fetal organism, has no influence on normal delivery and the postpartal development. Neither aneuploidy [38] nor conservation of polyploid modal class [39] are obstacles for the loss of tumorigenicity. Immortal cells, even with significant changes of chromosomes, do not lose their differentiation abilities [40], show normal maturation, loss of tumorigenicity and preserve their proliferation potential [41]. According to Roschke et al. [42], chromosome translocation with involvement of c-myc oncogene, which is considered to be the critical event in the origin of plasmacytoma, is associated with a normal B-lymphocyte differentiation. All these reports do not agree with the traditional concept about gene mutation in carcinogenesis [43]. Tumor cells do not lose their potential to redifferentiate and even the genetic program is not disturbed [44]. In all tissues there are spontaneous regressions of tumors and their metastases are described [45-47]. There exist reports about mutations of the p53 gene without a manifestation of a malignant tumor [48]. Deficiency of the amount of p53 protein does not lead to an accelerated tumor development in mice liver under the influence of dimethylnitrosamine or other oncogenes [49]. But overexpression of p53 is an early event in cancer of the oral cavity [50] and is often associated with the development of multiple tumors [51].

It is a matter of fact that oncogene activation and cell transformation are nothing else than mechanisms of growth and adaptive processes. Here we approach one of the strongest myths of oncologic cell proliferation as a major risk factor for carcinogenesis. The analysis of Farber [52] who balanced different findings and arguments against each other, came to a negative conclusion: The primary effect of all carcinogenic factors is a suppression of cell proliferation and vice versa. In accordance to model investigations of morphogenesis [53], is it possible to confirm this transformation with dedifferentiation and extension of cells' potential to be the first step of morphological and functional reintegration of damaged or hypofunctioning tissue. Not stimulation but suppression of growth is the initial mechanism of tumor promotion which becomes obvious in chronic damaged tissues [17]. With reference to investigations of Rubin et al. [54] is damaging, inherited by the whole cell population, the moving power for the development of a tumor. Defects in the gene reparation system are connected with sporadic cancers [55]. Partial hepatectomy studies have that in these livers, carcinogens are much more effective [56]. Intensive regenerating cell proliferation preserves liver from cancer by carcinogens, but low proliferation intensity is under identical conditions a cancer risk factor.

To summarize these findings, the following statements are possible: (1) Cells of a cancer are normal cells with a blockade to enter the normal growth channel. Only this is the course of the disintegrative character'of its growth and not the expression of so-called oncogenes. Oncogene expression does not induce a loss of the normal morphogenetic potential of cells. (2) Cancer realizes a developmental program in a reverse direction. (3) Transformation into tumor cells is an adaptive reaction in reply to the shortage of the self-regenerating process.

Our hypothesis does not ignore that* qualitative or quantitative changes in oncogene expression exist in malignant tumors. For qualitative and quantitative restoration of a tissue, which runs in an involutive condition or undergoes chronic damage, an intensive cell division or the compensation of a terminal replication is needed. This requires: (1) Cell proliferation to reactivate the growth genes (so-called oncogenes) and different genome reorganizations do not promote a disintegrating character

of the growth. (2) Different genome modulations activate enzyme systems which supply the dividing cells with the necessary metabolites. (3) The intensive cell proliferation and tissue restoration needs a telomerase reactivation. Tissue transformation and dedifferentiation is often caused by a critical length of the telomeres [57]. This process can be regulated by tissue growth factors. It was shown by Wu et al. [58] that c-myc oncogene activates telomerase by stimulation of the expression of the catalytic subunit telomerase reverse transcriptase. (4) Adequate energy provision by an increase of aerobic metabolism which is particularly important in postmitotic cells [59], is the prerequisite for an intensive growing process and also a prevention of aging.

Telomerase reactivation is a marker of tissue repair [60, 61] and prevents mutations of cells which induce precocious aging [62]. Restriction of telomeres is an important reason for many degenerative changes in old age [63]. Telomerase reactivation prevents cell apoptosis.

Expression of the telomerase reverse transcriptase extends the life span of fibroblasts, of pigment epithelial cells of the retina, and endothelial cells of arterial vessels preventing in this way age-induced alterations [64]. Telomerase reactivation may reverse in these cells the aging process [65]. But the stressing of the quantitative approach of telomerase is not completely correct, because telomerase activity in malignant and normal cell samples can show a superimposition [66].

Consequently, independent from the significant metabolic reactivation by telomerase activity, a regeneration of degenerating cells in old age cannot be expected. A regeneration always needs an intensive cell proliferation.

Cancer treatment by telomerase suppression is highly doubtful. Even though it has a certain therapeutic effect, there exists as an alternative mechanism a telomere lengthening [67].

For a transformation of cells in a given tissue, a metabolic and proliferative deficit of tissue is much more important than an immunodeficiency. That does not mean that the immune system is without any function in cell transformation. Tumor growth induces normally an immune answer by autoimmune enhancement, but this seems to be a secondary phenomenon.

Conclusion

It is quite obvious that aging is characterized by latent functional insufficiency, a decrease of repair functions, a progressive apoptotic loss of cells and the final death of the organism. The preservation of homeostasis is the single alternative to prevent a deleterious collapse of a biological system due to aging. In this connection it is important to be aware that cancer is an expression of an ontogenetic anomaly which is strongly linked to an insufficiency of cell replication. Malignant dedifferentiation is therefore characterized by a metabolic insufficiency of the particular tissue which is one of the fundamental mechanisms of aging. This is the reason that tumor frequency increases with age. As soon as we are able to enhance cell performance again, we shall increase life expectancy. But, we shall be able at the same time to develop more effective principles to treat in a causal way malignant tumors.

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