Oncogerminative Hypothesis of Tumor Formation

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Abstract—The oncogerminative hypothesis of tumor formation states that during malignant transformation of somatic cells part of the germinative cell genome is activated. This part determines the phenotype property of the germinative cell: its potential immortality realized during its life cycle. In malignant cells this activated part of the genome also determines immortality in its life cycle.

The life cycle of the cell may be divided into five stages: 1) the reproduction stage under the influence of promotors; 2) the stage of multicellular oncospheroid formation (the parody of blastocyst) characterized by heterogenous composition of cellular population consisting of three major phenotypically different cells: oncogerminative ones (stem), oncotrophoblast (fulfilling trophic function) and oncosomatic ones (differentiated) imitating germinative, trophoblast and somatic cells of the embryo respectively; 3) the stage of malignant tumor formation which consist of the vascularization of the oncospheroid and its growth under the conditions of anatomic contacts with the organism; 4) the stage of disaggregation of the oncogerminative cells which manifested in the organism by process of metastatic spreading; 5) the stage of formation of metastatic tumors. The change of the ratio of oncogerminative, oncotrophoblast and oncosomatic cells in metastatic tumors is a basis of tumor progression.

Introduction

Recent research in experimental oncology draws on unique data of the ultrastructure and biochemical characteristics of malignant cells, their genetic rearrangements, characteristic markers, receptor complexes, biological characteristics of their behavior and many other facts. These data pave the way for modern theories explaining the mechanisms of malignant cell transformation. However, a malignant cell is not yet a malignant tumor. The laws of cell transformation do not explain the biological laws of the malignant tumor formation and tumor development in the organism.

Since the 19th century attempts to integrate the data on malignant cell property with the aim of explaining the biological phenomenon of the tumor growth in the organism at all the stages of oncology science development lead to the conclusion that there are certain similarities between the growth of tumor and development of an embryo (1–5). These 'embryonal' concepts however, do not explain the mechanisms of how the biological characteristics of the malignant

cell and tumor are being formed. In this work, we put forward the oncogerminative hypothesis of tumor formation which will permit us to analyse the true nature of the malignant cell and tumor based on the recent advances in developmental biology.

Oncogerminative hypothesis of tumor formation

One of the major characteristics of malignant cells which makes them different from the normal somatic cells is their immortality or ability of unlimited self-reproduction. This characteristic is endowed by the stem subpopulation of malignant cells. The stem cell population within a given tumor can remain a constant or even increase (6, 7).

We believe that the biological nature of a cells immortality during its malignant transformation is key to understanding the biological nature of both the malignant cell and its subsequent tumor.

According to the traditional theories on multistage process of the cell transformation and tumor development the first step of a transformation of the somatic cell (independent of the nature of the initiating carcinogenic factor), results in immortalization and formation of the tumor phenotype of the cell. Although the cell immortalization mechanism remains unknown oncogenes are a leading candidate in this mechanism (3, 8).

Immortality

In order to clarify our position on tumor transformation, we will first examine the phenomenon of cell immortality. All the Protozoa are potentially immortal, and in the Metazoa only the germ cells possess the immortality. Thus, to interpret the immortality of malignant somatic cells, it would be reasonable to assume that a tumor cell acquires one of the essential properties either of the Protozoa or of the germ cells of the Metazoa as a result of dedifferentiation. However, the assumption that the malignant cell becomes similar to single-celled organisms due to alteration in the differentiation level would contradict L. Dollow's law on the irreversibility of evolution and the biological laws stating that cell recapitulation is possible only within the limits of a given genotype. The process of recapitulation always starts with genetic alterations which change the course of cell development and are realized in the phenotype. Phenotypic immortality is characteristic of the malignant and germ cells only. Thus, the only one possibility for a somatic cell to acquire immortality is in its malignancy which implies obligatory derepression of the immortality mechanism of the germ cell. This con-

clusion seems very important to us since it enables us to explain the biology of the process of oncodevelopment.

In genetics the question of the possibility of the reversion of somatic cells to 'an unending stream of germ cells' was rather related to academic discussions on the possibility of the inheritance of ontogenically acquired characters (9). In oncology it acquires a principal significance since the positive solution of this question enables us to give a new interpretation to such phenomena as immortalization, the heterogeneity of tumor cell population (10, 11), the epigenome mechanisms of the formation of tumoral phenotype (12), ectopic 'embryonalization' of tumor cells (3, 13). These questions will be discussed here in some detail.

Malignant transformation of a somatic cell which results in the acquisition of some phenotypic features of the germ cell is probably determined by the same laws that determine the divergent differentiation of cells during ontogenesis. During the realization of the genetic program of ontogenesis important 'decisions' are made by a relatively small number of regulatory genes that serve as switches between alternative states of the cell or between differentiation pathways (14). The regulatory genes, acting as switches, determine which of two alternative paths will be taken by a given cell or a group of cells. Once the decision is made, the possibility of further choice for the cells woulld be limited, hence their fate in development becomes more definite.

Initial stages of the ontogenesis are characterized by the development from a totipotent zygote of three cell types which form three types of tissues: somatic, extraembryonic and germinative. This divergent differentiation is based on the starting three basic programs of cell development: the program for somatic cells of the embryo, the program for the cells of extraembryonic tissues and the program for the cells of germinative tissue. The development of an embryo is completed with the settling of germ cells in its testis (ovaries) and the isolation of the embryo from the extraembryonic tissues. After the pubescence of a new organism the germ cells may accomplish their vital cycle again. Thus, the most important phenotypic feature of the germ cell is that its potential immortality is realized not through the line cell—cell—cell...etc., but by the mechanism of passage through the life cycle. In highly organized multicellular organisms the life cycle of the germ cells is the only mechanism providing their potential immortality. This law of developmental biology is extremely important in the understanding of the biological nature of the development of tumor from a transformed cell.

We believe that the most important event in the malignant transformation of a somatic cell is the partial switching over of its genetic program to the program of the germ cell. This means that like the germ cell, the potential immortality of a malignant cell is realized by passage through its life cycle. Therefore, we will hence refer to the formed malignant cell which mimics the germ cell in its essential phenotypic features (immortality, polypotent), the oncogerminative cell. However, the oncogerminative cell which developed from a differentiated somatic cell as a result of malignant transformation is not able in principle to possess all the functions of the totipotent embryonal cell. During ontogenesis the egg cytoplasm is distributed among differentiated cells. This distribution is accompanied by a gradual narrowing of morphogenetic potencies of these cells (14).

The first stage of the oncogenesis is completed with the formation of a malignant cell which develops into a tumor. The question on the biological laws that determine the development of malignant neoplasm is evidently a fundamental one.

Tumor formation

There are two possible paths of tumor formation that we can consider. The first tumor formation path may involve the multiplication of oncogerminative cells which can be represented in a linear scheme: cell—cell—cell...etc. This is similar to the formation of tissues during ontogenesis or their regeneration from somatic cells in a mature organism.

However, the assumption of this pathway of the formation of a tumor does not explain its biological properties: the heterogeneity of cellular population, the ability of cells for implantation, invasive growth, metastasizing, the similarity or complete identity of the antigenic and isoenzymic patterns to those of placental and embryonal tissues and finally the potential immortality of the tumor cells. The second possible explanation for oncogenesis is that tumor formation is a stage of life cycle of oncogerminative cell.

As was mentioned above, the only mechanism to provide the immortality of a somatic cell which undergoes malignant transformation is the derepression of a part of the genome of the potentially immortal germ cell. This part of the genome appears to determine the most conservative properties of the germ cell. These properties proved so evolutionarily conservative that, while the morphology of the late development stages and of the adults was undergoing profound transformations, the organization of the eggs and their cleavage remained persistently similar (14).

It is reasonable to assume that the evolutionary ancient property of potential immortality, activated in oncogerminative cells, is also realized during the passage of these cells through their life cycle, whose stage the formation of malignant tumor is (Fig. 1).
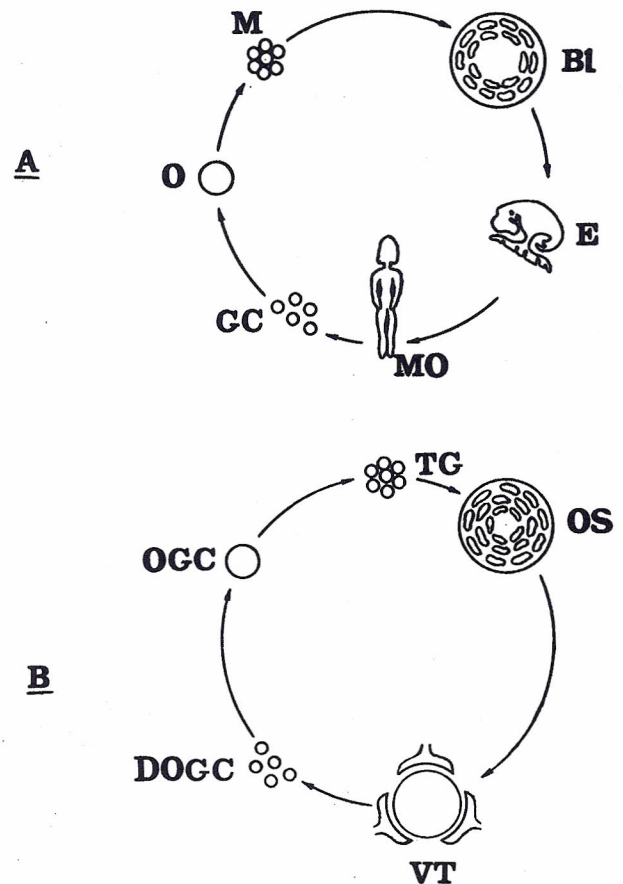

Fig. 1 Scheme of live cycles of the germ (A) and oncogerminative (B) cells. O—ovocyte; M—morula; Bl—blastocyst; E—embryo; MO—mature organism; GC—germ cells; OGC—oncogerminative cell; TG—tumor germ; OS—oncospheroid; VT—vascularized tumor; DOGC—disaggregated oncogerminative cells.

Given this assumption we can then define five stages of tumor formation. During the first stage the multiplication of oncogerminative cells takes place. The second stage consists of the aggregation of oncogerminative cells and formation of a tumor germ. The third stage is the development and maturation of oncospheroid which contains three cell types; oncogerminative (stem), oncotrophoblastic and oncosomatic. The fourth stage involves the vascularization of the oncospheroid and its development under the conditions of anatomical contact with the organism.

During the fifth stage of oncogenesis, the oncogerminative cells of malignant tumor disaggregate, which is manifested in dissemination and formation and of metastases. A metastatic oncogerminative cell passes again through the phases of multiplication, formation and development of a metastatic tumor germ and an oncospheroid which contains oncogerminative, oncotrophoblastic and oncosomatic cells. Disaggregation of the oncogerminative cells of the metastatic tumor may occur again thereby initiating a new cycle of the development of metastases. As a result the fraction of the most differentiated oncosomatic cells in the tissues of the metastatic tumors may progressively decrease. In our opinion this phenomenon is the essence of tumoral progression (Fig. 2). For further clarification of our hypothesis we will describe each of the five stages.

The immortality of a sexual cell which is realized during its passage through the life cycle, is coupled to another essential phenotypic property—the ability for cleavage after fertilization or as a result of parthenogenesis. Likewise, the oncogerminative cell may start the parthenogenesis at the beginning of its life cycle. Both cells thus realize an evolutionarily more ancient mode of reproduction than the sexual one. According to Meinard (15), parthenogenesis which has a 2-fold advantage over sexual reproduction appeared about 3 billion years ago whereas, sexual reproduction in eucaryotes—about 1 billion years ago.

The parthenogenetic mode of the formation of malignant tumors from embryonal tissues has been established (16–18). According to several authors (19, 20), some particular stages in the development of tumors of other histogenesis also share common features with the parthenogenetic activation of the ovocyte. It should be mentioned that the question of parthenogenesis of malignant cells is closely connected with the unsolved question of the developmental biology of ameiotic parthenogenesis in mammals (21).

The parthenogenetic development of an oncogerminative cell results in the formation of a tumoral germ which is the essence of the second stage of oncogenesis. However, we believe that the mimic parthenogenesis of the oncogerminative cell is not the only mechanism of the formation of tumoral germ. The latter may also be formed as a result of the aggregation of the malignant cells. The ability for aggregation, which is a phenotypic feature of the cells of the early embryo (the morula stage), appears to be ectopically derepressed in malignant somatic (oncogerminative) cells and coupled to their immortality. Confirmation of the aggregation properties of embryonal cells comes from the results of Mintz et al (22) who ob-
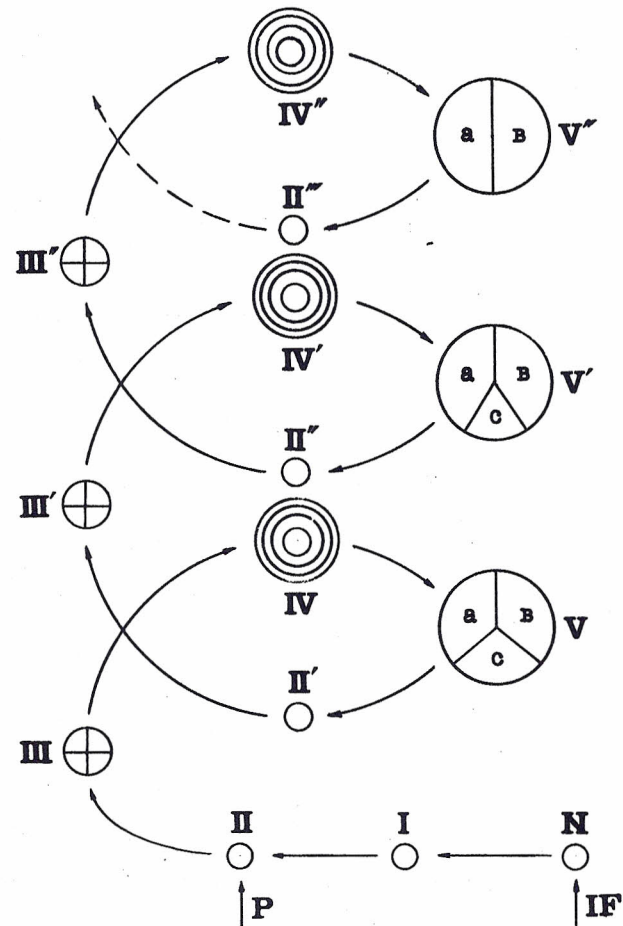

Fig. 2 Scheme of malignant tumor formation and tumor progression. N—normal somatic cell; IF—initiating carcinogenic factor; II—transformed cell whose program was switch over to the oncogerminative one; P—promoter; III—multiplication of the oncogerminative cell; IV—multicellular spheroid; V—primary tumor; a—population of the oncogerminative cells; b—population of the oncotrophoblastic cells; c—population of the oncosomatic cells; II', II'', II'''—disaggregated (metastatic) oncogerminative cells; III', III''—multiplication of the disaggregated (metastatic) oncogerminative cells; IV', IV''—secondary multicellular oncospheroids; V', V''—secondary (metastatic) tumors.

tained a reaggregated chimeric morula from the cells of two disaggregated mouse embryos at the morula stage. These experiments will be described in some detail below.

The next stage of the oncogenesis is the formation and development of an oncospheroid. Multicellular spheroid may be formed in vitro from normal embryonic, fetal and postnatal cells and from malignant tumor cells. Unlike the multicellular spheroids

formed from malignant cells (the oncospheroids), the spheroids from normal cells do not attain a large size, practically do not grow in tissue culture and do not initiate tumor formation when inoculated subcutaneously (23, 24).

The morphogenetic features of spheroids are determined by the morphogenetic potencies of the constituting cells. Normal cells obtained by disaggregation of the thyroid gland, liver, and pituitary body tissues formed spheroids that synthesized thyroid and hypophyseal hormones, respectively, and closely resembled the tissues of origin in their morphological structure (24).

Cells of the disaggregated teratocarcinoma tissues under in-vitro conditions form multicellular spheroid: the embryoid bodies (18). Their distinctive feature is the presence of a large number of morphological structures of varying differentiation degrees formed from the three germinal layers and characteristic of the early stages of egg development. Subcutaneous inoculation of embryoid bodies usually brought about the development of teratocarcinomas or teratomas.

Mintz et al (22) dissociated mouse embryos at the morula stage under in vitro conditions and then pooled the cells of two embryos that differed in their genes of hair coloration. In a culture the cells aggregated with the formation of a chimeric morula and a blastocyst. The latter was in fact a multicellular hybrid spheroid developed from the aggregated cells of the two early embryos. When hybrid blastocysts had been implanted into the uterus of an adoptive mother, healthy chimeric mice were produced. Implantation of a normal early embryo at ectopic sites resulted in disordered development of this embryo which was converted into a solid tumor.

Schematization of the multicellular spheroid formation by different cells may lead to the following conclusion. The fertilization or parthenogenetic development of ovocyte brings about the formation of a multicellular spheroid—the blastocyst. When implanted into the uterus of a recipient, the blastocyst gives rise to the development of a normal fetus; transplantation at ectopic sites leads to the development of malignant embryonal tumors. The multiplication of an oncogerminative cell results in the development of a multicellular oncospheroid which initiates tumor growth when transplanted into the recipient's tissues. Normal cells cultured in vitro may form multicellular aggregates which do not practically grow in tissue culture and do not give rise to tumor growth when transplanted into the recipient's tissues. Hence the characteristics of the oncospheroid are much closer to that of the blastocyst since both are the sources of the development of neoplasms. Besides, it is significant that the oncospheroids are regularly found in the tissues of in vivo growing tumor whereas the multicellular spheroids of normal cells have not been found in normal tissues (24, 25).

The ability for multicellular spheroid formation is explained by the laws of synergetics and apparently belongs to the basic most ancient and therefore evolutionarily most conservative properties of the Metazoa. According to Villee and Dethier (26), the fertilized egg is comparable to the unicellular flagellate ancestor of all living organisms, and the blastula stage is comparable to the colonial protozoan or to the spherical multicellular organism which all the Metazoa may originate from.

This thesis is consistent with Haeckel's 'biogenetic law'. To prove the correctness of this law, a scheme is usually cited which compares successive stages of embryonic development of the fish, chicken, pig and man. This scheme proved so illustrative and was reproduced so many times in different courses on biology and embryology that it has gradually produced a false impression of fully representing the essence of the formula 'ontogenesis repeats the phylogenesis'. However, in the scheme mentioned, the embryos are compared at the late development stages, whereas ontogenesis starts from the cleavage of a fertilized ovocyte and passage through the morula, blastula and blastocyst stages. In the latter stage this gives rise after implantation, to embryonic, extraembryonic and germinative tissues.

Embryos of practically all the Metazoa species pass through these development stages. According to Jacob (27), the evolution acts by way of 'turning' the old. Structures do not appear de novo, the evolution prefers to create innovations by altering the already existing structures. Such evolutionarily ancient structures probably include morphological formations characteristic of the earliest stages of the development of a fertilized ovocyte.

The above biological laws enable us to assume that the earliest evolutionarily conservative stages of the multiplication of the totipotent embryonic cell and oncogerminative cell are similar. This similarity is retained until the formation of multicellular structures, the blastocyst and oncospheroid, and their vascularization. During the postvascular stage of the development of the blastocyst and oncospheroid, the fundamental differences between them rapidly increase. In the first case, a development of ordered morphogenetic processes and tissue differentiation are observed; in the second case, a growth and volume expansion of the vascularized oncospheroid take place and no new morphogenetic processes occur.

In recent literature the oncospheroid is considered an in vitro micro-model for the avascular stage of the in vivo growing tumor (24). Confirmation of this conclusion comes from the data on the identity of the basic features of the oncospheroid and tumor node: the heterogeneity of cell population, the ability for three-dimensional growth, the presence of proliferation gradient, similar growth kinetics patterns, extracellular matrix formation, glucose content, oxygenation conditions of the tissues, the presence of central necrosis, the identity of antigenic composition, the ability for the secretion of angiogenesis factors and other growth factors (24, 25). Some even consider that spheroid formation is an obligatory avascular stage in tumor development (28, 29).

From the standpoint of the oncogerminative hypothesis of tumor growth, the idea that there are no fundamental differences between the oncospheroid and tumor but for the growth of the latter under the conditions of vascularization introduces a tangible content into the formula of Potter (30) 'the oncogenesis a blocked ontogenesis': during oncogenesis the ontogenesis is blocked at the stage of mimic blastocyst, the oncospheroid.

The fourth phase of tumor development involves an intensive local tumor growth. It starts from the moment of the vascularization of the oncospheroid when it comes into anatomical contact with the organism tissues.

Heterogeneity

One of the basic properties of the oncospheroid and tumor is the heterogeneity of their cell composition. According to Sutherland (25), the fraction of stem cells in solid tumors and oncospheroids comprises less than 1%. Multiple data have been reported on the presence in malignant tumors of cells at different differentiation stages (31, 32, 33), including the benign cells (34). Despite the attempts undertaken to explain this property, the heterogeneity of the tumor cells remains a mystery till the present time. An analysis of the mechanisms providing the nutrition of the early embryo and tumor is necessary for a better understanding of the phenomena of heterogeneity.

The development of mammalian embryos prior to implantation results in the formation of a blastocyst— a hollow structure consisting of two types of cells: the cells of the trophoblast that cover the embryo from the outside and the inner cell mass located in the cavity limited by the trophoblast. The trophoblast gives rise to the placenta, and the inner cell mass is the origin of the extraembryonic tissues and the embryo itself. In the mammalian embryos, in contrast to the embryos

of animals of low organization, e.g. Amphibian, the predetermined sites in the cytoplasm of the dividing ovocyte proved to have no role in the blastomere differentiation, the direction of the latter being determined solely by the localization of the blastomere in the early blastocyst. A cell localized outside the blastocyst becomes a part of the trophoblast, and a cell localized inside gives rise to the inner cell mass (35, 36). When labelled blastomeres are transferred to the inner or outer sites of unlabelled embryos, they differentiate to the trophoblast or inner cell mass in accordance with their localization (28). A pathologically developing blastocyst may be devoid of the inner cell mass (the trophoblastic vesicle), but it would possess an external layer of cells which are always trophoblastic.

During the passage through its life cycle an oncogerminative cell forms a number of morphological structures resembling those of the early embryonic development (Fig. 1). These structures include a multicellular spheroid which usually consists of three distinguishable cell layers surrounding the cavity with the necrotized cells. The oncospheroid is quite comparable in size with the tumoral germ at the avascular stage of its development. The oncospheroid vascularization is considered to start on attaining a diameter of 1–3 mm (25, 28).

According to the oncogerminative hypothesis an oncospheroid is formed consistently with the laws of the development of the blastocyst. Therefore cells that are localized in the outer layer of the oncospheroid should possess the function of the trophoblastic cells. We call these cells oncotrophoblastic cells. In several types of tumors, such as those originating from embryonic and germinative tissues, the presence of trophoblastic cells has been established (17, 18). In other tumor types the presence of such cells is less evident. Indirect evidence of such cells in tumor development is suggested by the presence of cells fulfilling the role of trophoblastic ones. This evidence is based on the persistent detection in tumors of proteins, isoenzymes, growth factors characteristic of the fetal placenta (37, 38).

Trophoblastic cells at the stage of blastocyst implantation and cells localized in the superficial layer of the oncospheroid, reveal invasive properties and a pronounced ability to lyse organism tissues and to phagocyte the destroyed cells. When a blastocyst is cultured in vitro, its gigantic trophoblastic cells are able to invade and to lyse not only the simultaneously cultured other tissues, but also the cells of the embryo itself (39). This fact strikingly resembles the ability of oncospheroids for the invasion into other tissues during coculturing (40).

From this hypothesis, we then can predict that the malignancy of a tumor will be determined by the ratio of the oncogerminative (stem) tumor cells and the oncotrophoblastic cells. Differentiated cells ubiquitously observed in the tumors are probably represented by the oncosomatic cells. The presence of the latter cells mainly determines the histological type of the tumor. To prove these ideas, several data on the properties of cells of different teratocarcinomas will be discussed.

It is considered that the stem cells of teratocarcinomas are the embryocarcinoma cells (EC–cells). The latter cells strikingly resemble on their biochemical properties and ultrastructure the polypotent embryonic cells (EK–cells) of the epiblast which are the precursors of the sexual cell line (41, 42). The EK–cells, when implanted at ectopic sites, give rise to teratocarcinomas (42). During normal embryogenesis the EK–cells exist for a short period, comprising an insignificant fraction of cell population of the epiblast at the stage of its development (5.5–6.5 days) that precedes the isolation from it of definitive germinal layers. According to A P Diban (43), the short existence of EK–cells in the epiblast is a manifestation of mechanisms that prevent the transformation of an embryo into a teratocarcinoma. The EK–cells give rise to the EC–cells of two types; the nullipotent cells, a part of which under in vivo conditions retains the properties of the polypotent EC–cells, and another part may differentiate to the cells of normal definitive tissues (18, 44).

In our opinion, the represented data on the presence in teratocarcinomas of different cell populations ranging from the stem polypotent EC–cells to highly differentiated cells of definitive tissues support the ideas of the suggested hypothesis on the existence of the polypotent oncogerminative (stem) and oncosomatic cells in tumors.

However, it is not known, to which normal precursors (the EK–cells of the epiblast, the primary sexual cells, etc) the phenotypic 'repertoire' of characteristics ectopically derepressed in a malignant somatic cell belong. Such a precursor should evidently possess immortality as the main property realized by way of the mechanism of passage through the life cycle. This requirement is satisfied by the sexual cells starting their development under natural conditions after activation and by the early embryo cells, their reaggregation and subsequent development being established in principle under experimental conditions. We believe that the elucidation of this question will be of fundamental significance not only for the experimental oncology, but also for the developmental biology.

Metastasis and tumor progression

The essence of the fifth oncogenesis stage is the formation of metastases. In our opinion, the metastatic potential of a tumor is mainly determined by the presence of the oncogerminative cells. These cells apparently constitute a part of a cell population of the tumor that was named 'transient metastatic compartment' by Weiss (45). This assumption becomes clear when considering that the germinative tissue is an obligatory product of the development of an activated ovocyte. A property of germ cells that has developed during phylogenesis and is revealed during ontogenesis is the ability for aggregation and formation of germinative tissue with subsequent disaggregation of this tissue into germ cells during the period of embryonic development directly preceding the migration of these cells from the yolk sac to the embryo's gonads. This phenotypic feature of germ cells is evolutionarily ancient and is persistently observed in animals staying at different stages of evolutionary development. From the standpoint of our hypothesis the ability for disaggregation is a phenotypic feature of the oncogerminative cells and is manifested in host organism by the process of metastatic spreading.

After settling in the organism tissues a metastatic oncogerminative cell may accomplish its life cycle again which will bring about the formation of a metastatic tumor. The latter in turn may give rise to metastatic oncogerminative cells and to the development of new metastatic foci. With diminishing fraction of the oncosomatic cells in the metastatic tumors their malignancy increases. In our opinion the 'washing away' of oncosomatic cells during the development of metastatic tumors underlies tumor progression. The extreme version of tumor progression are the dedifferentiated tumors which appear to consist mainly of the oncogerminative and oncotrophoblastic cells (Fig. 2).

Conclusion

The oncogerminative hypothesis of tumor growth postulates five stages of tumor development. The first stage is the malignization of the normal cell and its transformation into the oncogerminative one characterized by the derepression of the evolutionary conservative phenotype property of the normal germinative cell, the ability to realize its immortality within its life cycle. The second stage consists of the reproduction, including via parthenogenesis of the oncogerminative cell under the influence of promotors. The third stage results in the formation of a multicellu-

lar spheroid (the parody of blastocyst) characterized by heterogenic composition of the cellular population and consisting of oncogerminative (stem) oncotrophoblast and oncosomatic cells. The fourth stage is characterized by the vascularization of the oncospheroid and its growth under the conditions of the anatomic contact with the organism. The biological characteristics of the malignant tumor are stipulated by the ratio of the oncogerminative, oncotrophoblasts and oncosomatic cells in it. Based on this hypothesis, we can say that oncosomatic cells are predominant in high-differentiated slowly growing tumors. The growth of the tumors with the predominance of the oncotrophoblasts cells is characterized by the expressed invasive properties. Tumor type where oncogerminative (stem) cells predominate is characterized by high metastatic potential. The development of the majority of malignant tumors is accompanied with dis-aggregation of the oncogerminative cells, their migration into the organism tissues and development of metastatic foci of tumor growth.

The metastatic characteristics of the oncogerminative cells are phenotypically conditioned since the normal analogue of the latter—germinative cells—possess the property developed within phylogenesis and manifested in ontogenesis, periodic aggregation and formation of the germinative tissue which at a certain stage of embryogenesis disaggregates into separate germinative cells beginning their migration way to the embryo gonads.

The metastatic oncogerminative cell may realize its new life cycle having settled down at another site of the organism and give rise to the development of the metastatic tumor. As a rule, the latter is characterized by a different ratio of oncogerminative, oncotrophoblast and oncosomatic cells. There is the possibility of the progressive decrease of the oncosomatic part up to their complete disappearance. In this extreme case an undifferentiated tumor develops. The process of metastases formation is the main within the fifth stage of the tumor growth while the changes in oncogermantive, oncotrophoblast and oncosomatic cells in metastatic tumor form the basis of tumor progression. Based on these principles, the following definition can be suggested: a malignant cell is a cell in which a part of the genome of either a germ or an embryonic cell is operative and which possesses the basic phenotypic property of the latter—the ability to realize its potential immortality by the mechanism of its life cycle. In our opinion, the use of the term 'oncogerminative cell' to name the malignant cell is justified, since this term emphasizes the basic essential property of the malignant cell—the ability to re-

alize its immortality by the passage through the life cycle.

From the standpoint of the suggested hypothesis a malignant tumor is a neoplasm with heterogeneous cell composition developed from an immortal oncogerminative cell during its passage through the life cycle. In other words, a tumor is a mimic embryo with its development blocked at the stage of mimic blastocyst. The biological features of a tumor depend to a large extent on the ratio of oncogerminative, oncotrophoblastic and oncosomatic cells in it.

We believe that the suggested oncogerminative hypothesis explains the biological nature of the phenomenon of malignant tumor development and enables us to draw a number of important conclusions. The discovery of the common nature of the blastocyst and oncospheroid given an interpretation of the tolerance of the organism for a developing neoplasm since this tolerance is phylogenetically determined (46). From the standpoint of the oncogerminative hypothesis multiple data can be explained on the community of the markers of tumors and embryonic tissues, on the variable effect of pregnancy on tumor growth, on the possibility of the inhibition of tumor growth by immunization of the organism with placental and embryonic tissues and by administration of antiserums against pregnancy markers (47, 48). In our opinion, the most important conclusion is that the elucidation of physiologically controlled mechanisms of the blastocyst implantation, invasive growth of the trophoblast cells, of migration properties of the germ cells, of the modifying effect of the developing embryo on neurohumoral, metabolic and immune organism status, of the development of reversionary organism reactions at the final stage of pregnancy aimed at the expulsion of the fetus and elimination of trophoblastic cells from the organism will provide the basis for the elucidation of mechanisms of malignant growth and for the develoment of essentially new methods of antitumor influences.

Acknowledgement

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