

Full Length Research Paper

Toward the genomic roots of cancer

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Abstract

The article presents further development of new paradigm of cancer origin and epidemic spread based on the hypothesis of carcinogenic transformation of personal genomes over xenogamous crossbreeding. The newly performed updates to the paradigm were based on multidisciplinary integrative reassessment of data about the main traits of cancer from the viewpoint of recent all-pathological, immunological, genetic and evolutionary discoveries. The supplemented set of evidence allowed reveal a chain of the disease traits that can function as milestones for the discovery of relevant genome transformations. Cancer is considered as multicellular parasite of mammalian origin that lives in the afflicted bodies at the expense of substances composed of the victim. Most important trait of cancerous cells is predestined by their constitutional immunity to normal regulators of cell replication. The immunity arose out of genome mutations which determine constitutional interethnic differences. Over xenogamous formation of a descendant's zygote its genome becomes admixed with carcinogenic genes. The cancerous cells appear in and disperse around the descendant's body before postnatal ontogenesis and then exist in it as smallest subpopulations of different sizes. Subsequent growth of primordial subpopulations leads to the formation of tumors. Cyto-regulators produced by cancerous cells inhibited the functions of the host cells thus inducing the diseased state. Cancerous components of the host genome can be transmitted into descendants' zygote. The current pandemic spread of cancer is brought about growing expansion of interethnic admixture.

Keywords: Cancer biology, Cancer epidemiology, Cancer genetics, Genomics cancer immunology, Cancer pathogenesis, Cancer prevention, Cancerous cachexia, Genomic mutations, Hereditary immunity, Heterozygosity, Noncancerous genealogy, Regulator-Receptor Systems, Xenogamy.

INTRODUCTION

To the middle of 20th century cancer overtook many infectious diseases as an important human killer. A little bit later, cancer became one of the biggest threats to global human health that takes a terrible and growing human toll and its incidence continued to grow. Today cancer is responsible for one in eight deaths worldwide (American Cancer Society, 2007). The War on Cancer, the "cancer crusade" started by the U.S. National Cancer Act of 1971, created a new mandate for National Cancer Institute: "to support research and the application of the results of research to reduce the incidence, morbidity and mortality from cancer." The Act has forced to spend about \$90 billion on science, treatment, and prevention of cancer (Marshall, 2011) but met its 40th anniversary with

very moderate achievements. The number of diseased peoples continues to grow. The efficacy of means exploited currently for cancer prevention and treatment appeared to be very low. Cancer continues to present one of the biggest and epidemically growing problems in the modern world whose extensive counteracting efforts appeared to be shamefully impotent. One can say it was not a set of moderate achievements but a disastrous debacle.

The strategy of "cancer crusade" was based on the 80 years old hypothesis of cancer origin out of somatic mutation of alone cell. According to the hypothesis, consequent dividing of the maternal cell leads to the formation of maternal tumor. Some cancerous cells separate from a maternal tumor and metastasize to other parts of the body through the bloodstream or the lymphatic system. This process has never been proven or fully elucidated. In reality the idea of the metastazing of cancer was based only on the existence of several

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identical tumors in different parts of a diseased body was observed. The details of the supposed metastasis remain hypothetical and mysterious. The lack of evidence of the metastatic pathway prevents effective interventions for cancer healing and prevention. The search for subtle links between diet, lifestyle, or environmental factors and disease leads to an unending source of fear - but often yields little certainty. Studies on weak associations - or small effects - often produce contradictory results which confuse the public. Thus initially accepted paradigm of cancer origin and pathogenesis appeared to be impotent.

Based on the hypothesis hypothesis of cancer origin out of somatic mutation of alone cell, current oncology faces its limits. New insights into the origin, pathogenesis and epidemic spread of the disease are therefore sorely needed. A need has emerged to develop a more enlightened paradigm that might capture the most essentials about the cancer. There are many observations, experiments and theoretical discoveries to be made in this way initiated by a new integrative paradigm – the hypothesis of genome intrusion - about the origin and pandemic spread of the disease (Rumyantsev, 2009b;Rumyantsev, 2010b;Rumyantsev, 2011b).

The article is devoted to further development of principally new paradigm of cancer origin, pathogenesis and epidemic spread based on the hypothesis of carcinogenic transformation of personal genomes. Main aim of the present article was to promote a more systematic search for such new insights and to find firm new point of view on the origin of cancer and its pathogenesis, including the dispersion of cancerous cells around affected body and forces propelling these processes.

MATERIALS AND METHODS

The article presents new results from reconsidering and re-sensing of various either direct or indirect data regarding cancer epidemiology, clinical manifestations, and molecular pathogenesis from the viewpoint of up-to-date all-pathological, immunogenetic, genetic, and evolutionary discoveries followed up to cellular, subcellular and molecular level. To reach the goal, various appropriate data regarding the theme from the literature have been summarized with the data of long time investigations performed by the author together with the team he leads. The main accent was on the search of the disease traits that can function as milestones for the discovery of make-up and location of relevant genome transformations first of all on the observations of genetic predilection to cancer amongst different human populations, ethnoses, and individuals. Special attention was paid to the revealing of uniqueness of cancer pathogenesis, first of all of the immunity of cancer cells to regulation by host and the origin of non-foreignness of

cancer antigens to host. Functions of xenogamous fertilization and embryogenesis in the establishment of cancer were analyzed and re-sensed as objects of primary importance

RESULTS AND DISCUSSION

The term “cancer” brings about more than 100 distinct clinical forms of the disease. Each of the forms is named following to main organ that is affected by its initially detected unit. At the same time all cancers are thought to share a common pathogenesis (Stratton et al., 2009). In general, personal responsibility of genome for the development of any case of cancer was stated by various observations. Nevertheless multiple tries to determine the genes responsible for the phenomena of malignancy were unsuccessful. The hope to reach a success in the search for cancerous genes can grow when it will be oriented on some landmarks.

Landmarks to genomic roots of cancer

Universal all-pathological traits of cancer

Any disease displays a set of universal all-pathological features that are also characteristic of any other diseases. The set of universal features includes at least a dozen intrinsic signs: 1) different incidence of a disease among different races and ethnic groups, 2) increased prevalence of diseases in developed and civilized countries, 3) genetic predilection to the disease, 4) age differences in the disease incidence, 5) stochastic distribution of individual cases amongst a population, 6) individual variations in constitutional (genetic) predilection to the disease, 7) the mosaicism of affections, i.e. intra-individual diversity both in the predilection of different parts of a tissue and in the quantity and sizes of affections, 8) dappled distribution of affections amongst a body, 9) molecular bases of genomic and cellular pathogenesis and 10) the identity of involved cells in any locations of specific affections around the body (Rumyantsev, 2008). Each of these universal features of pathology is of genetic origin and belongs to any form of cancer too. The details of these traits and their diverse manifestations should be used for the launch of guiding landmarks in the way to decipher the puzzled web of cancer genomic roots.

Each of these universal features expresses the all-pathological phenomenon of heterozygous mosaicism created by genetic admixture arising as a result of hybridization between two genetically different organisms. One of which is constitutionally immune to the relevant ecological or physiological agent whereas its mating partner is constitutionally sensitive to it. The heterozygosity results in the coexistence of at least two

active allelomorphous genes in the offspring's genome. Both alleles function dominantly and create two allelic cell clones whose subpopulations are formed and distributed in the body before postnatal ontogenesis. The heterozygous offspring expresses both alleles equally but in different sizes and separated locations around the body. The features and functions of codominant clones may become obvious at different steps of ontogenesis (Rumyantsev et al., 2000). This is a kind of intra-individual biodiversity - chimerism or cellular mosaicism, the occurrence in an individual of two or more cell populations of different chromosomal constitutions, derived from different parental individuals (Bonnicksen, 2009; McLaren, 1976).

Genetic admixture (also called xenogamy, outbreeding, cross-fertilization, crossbreeding) refers to the reproductive union of genetically dissimilar or unrelated organisms within the same species that inevitably results in offspring heterozygosity of various kinds. The states of heterozygosity are responsible for the origin of spotted mosaic manifestations, individually different course and severity of most diseases, both infectious and non-infectious (Rumyantsev, 2006a; Rumyantsev and Gerasimov, 2007). The mosaicism is revealed in genetically determined variations in the location, size and other pathological manifestation of any disease. Every human disease is extraordinarily diverse in its manifestation and association with other diseases. Affected people may have many individual differences in the manifestations of their illnesses as well as in the grade of their expression.

Genetic predilection to cancer

The hypothesis of cancer origin out of somatic mutation of alone cell did not allow the inheritance of cancer. Meanwhile, the undoubted genetic predilection to cancer is characteristic of both usual and unique features that can be observed at any level of the disease existence beginning mainly from ethnic and population ones. Beside, recent genetic investigations revealed a number of apparent paradoxes and alternative views of the traits of cancer genetics (Soto and Sonnenschein, 2004). On the one hand, it is known a well confirmed fact that genetic factors play an important role in all steps of cancer development and a person's genetic makeup has a principal influence on the fate of a patient (Hemminki et al., 2004; Ponz De Leon, 1994). On the other hand, very little is known about the special characteristics of the genome that determine the unregulated behavior of cancer cells and their distribution around the body (2008). There is known only a minority of cancer sites that arise as a result of inherited and highly penetrant cancer susceptibility genes (Hodgson, 2008). In contrast, the genetic principle of analogous distinct distribution in both infectious and most noninfectious diseases has been deciphered (Rumyantsev, 2008).

Cancer rates in the Californian population of South Asians, that comprise people having origins mainly in India, Pakistan, Bangladesh and Sri Lanka, are different from those breast cancer observed in other ethnic groups inhabiting the same state. Compared to rates in native Asian Indians, rates of cancer in South Asians of California were higher for all sites of cancer locations. In contrast to Asian/Pacific Islanders of California, the South Asian population experienced more cancers of the esophagus, gall bladder, prostate, breast, ovary and uterus, as well as lymphomas, leukemias and multiple myelomas. Compared to the non-Hispanic White population of California, South Asians experienced more cancers of the stomach, liver and bile duct, gall bladder, cervix and multiple myelomas. Significantly increasing time trends were observed in colon and breast cancer incidence (Jain RV et al., 2005). African-American women have a lower overall incidence of breast cancer than do Caucasian women, but a higher overall mortality and the differences between their breast cancer cell lines play a role in their different rates of cancer disposition around a body (Yancy et al., 2007).

Intra-species diversity in cancer predilection

Although cancer occurs in every country in the world, there are wide ethnic variations in its mortality rates (Figure 1). The rates used are the number of cancer deaths per 100,000 populations. They are ranked from the highest to the lowest. The data revealed four-fold difference between the lowest (54.4 in Thailand) and highest (235.4 in Hungary) male cancer mortality rates. The group of five most cancerous countries unites Hungary, Luxembourg, Belgium, France and Uruguay. Amongst a group of five least cancerous countries Mexico, Ecuador and Panama shares their neighborhood with Thailand and Kuwait. One can suppose in contrast to Hungary the population of Thailand could be named immune to cancer.

Inter-ethnic diversity in predilection to cancer

The rates of cancer incidence show far more variations (1992b). The rates for all cancer sites in males revealed an over eight-fold differences that ranged from 493.8 per 100,000 in Tasmania, Australia, to a low of 59.1 in The Gambia, that shows also lowest rates for cancer of colon, rectum, pancreas, bronchus, lung, thyroid gland, myeloid leukemia, bladder, tongue, mouth and testis. One can expect the key to the origin of cancer will be found in the ecology of The Gambia innate ethnos, which provided him with more than 5-fold resistance to cancer in contrast to the USA blacks and whites. Prostate cancer, one of the most common cancers in men, is especially frequent in men of African origin. Incidence rates for all cancer

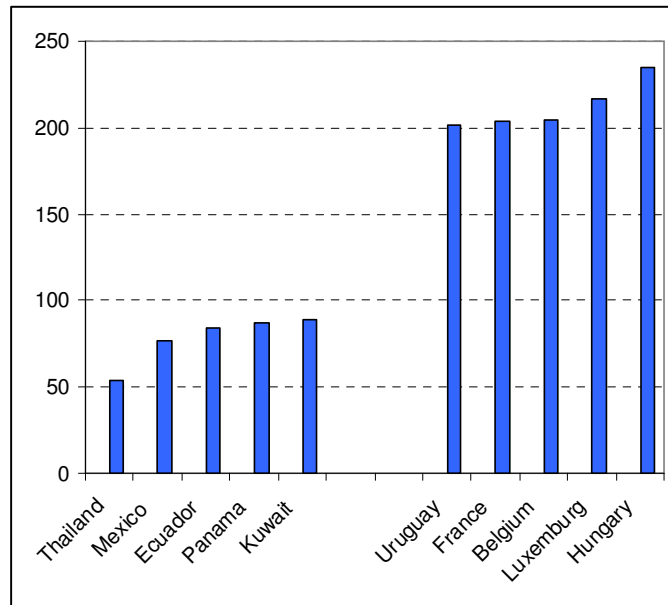


Figure 1. Variation in male cancer mortality rates among different populations. According to (1992a)

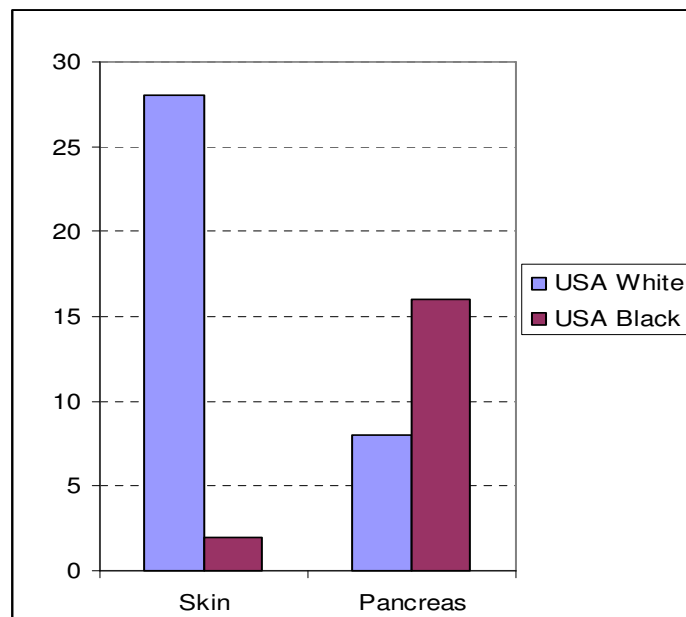


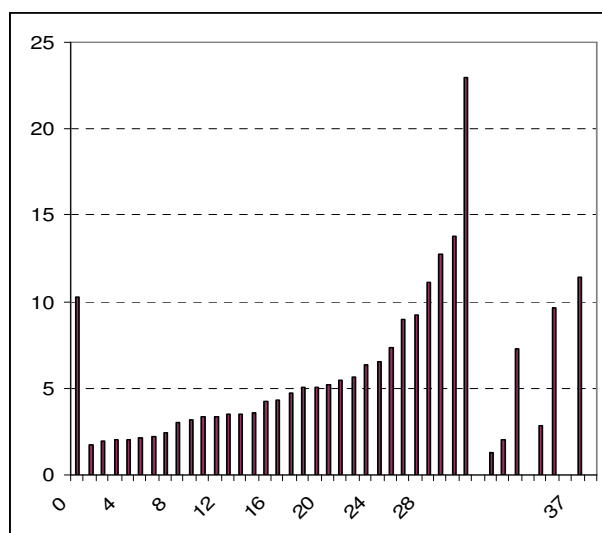
Figure 2. Opposite rates of male cancer incidence by primary site and race*
 (Rates are per 100,000 persons of the 2000 U.S. standard population)
 *According to (2007)

sites in African Americans are >1.5-fold greater than rates in European Americans (Haiman et al., 2011) that can be explained by 400 years old closeness between the ethnoses. Far more variations were observed at primary sites of skin and pancreas cancer (Figure 2).

The largest ratios of the highest rates to the lowest rates in worldwide cancer incidence (Table 1) among males were for melanoma of the skin, nasopharynx, and larynx, with ratios of 289, 285, and 204, respectively. For melanoma of the skin, the area reporting the highest rate

Table 1. The ratios of the highest rates to the lowest rates in cancer incidence According to (1992b).

Cancer	The values of rates per 100,000		Ratio
	Highest rate	Lowest rate	
Skin melanoma	28,9 (Australia)	0,1 (Kuwait, Thailand)	289
Nasopharinx	28,5 (Hong Kong)	0,1 (Quito, Ecuador)	285
Larynx	20,4 (Basque Country)	0,1 (Qidong, China)	204
Prostate	102,0 (Atlanta, Georgia)	0,8 (Qidong, China)	127,5
Lung	119,1 (Maoris, NZ)	1,0 (The Gambia)	119,1

**Figure 3.** Volumes (cm³) of solitary breast cancer unit appeared and resected at the age 74 years (0) and of 37 units explored 8 years after the resection, at the age 82 years (1-31 – bone tumors; 32-34 – lung tumors; 35 and 36 – lymph nodes tumors; 37 – soft tissue tumor).

was the Australian Capital Territory with 28.9 per 100,000; the lowest rate, 0.1, was reported among Kuwaitis in Kuwait and among persons in Khon Kaen, Thailand. For nasopharynx, the highest rate was 28.5 in Hong Kong while the lowest was 0.1 for Quito, Ecuador. For larynx, the highest rate was 20.4 in Basque Country, Spain, and the lowest rate, 0.1, was for men in Qidong, China.

Prostate cancer rates were highest for black men in Atlanta, Georgia (102.0) and lowest in Qidong, China (0.8 per 100,000). The worldwide range in lung cancer incidence among men ranges from a high of 119.1 in New Zealand Maoris to 1.0 per 100,000 in The Gambia. U.S. black men in New Orleans experienced a lung cancer rate of 115.9, just lower than that for Maoris in New Zealand.

These observations (Figures 1, 2 and Table 1) are seen very mysterious in the light of the orthodox postulates about the causes of cancer. This is one of the main riddles of cancer manifestations that should be

decoded. At the same time, they evidenced the existence of ethnoses (and persons) with very high grades of natural i.e. genetic immunity to cancer and thus reveal very important milestones in the way to the deciphering of both the origin of cancer and the genetic components of the disease pathogenesis. A more complete understanding of cancer origin, pathogenesis and epidemic spread will come from the discovery of relevant subjects in opposite ethnic and racial groups. One of the mile stones should be the relevant traits of ethnoses and populations which reveal opposite values of the rates of cancer prevalence. Most entangled but extremely important is the goal of deciphering of origin of individual variations in clinical manifestations of cancer as well as in its association with other diseases (2011;Gadalla et al., 2011;Renehan et al., 2008;Soder et al., 2012). The same should be accentuated regarding the trait of cancer units being local and variable in their sizes and spatial dispositions.

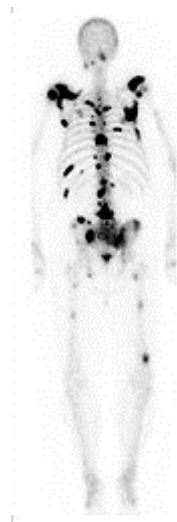


Figure 4. Mosaic dispersion of cancerous units in a case of prostate cancer

Individual diversity in disposition and sizes of cancer subunits

In an individual body, a cancer may exist in either as alone alien mass (tumor) or as several discrete subunits of it. Most cases of cancer are characteristic of severalty, a state of being several and discrete. In the case of discreteness, cancer may have more than two subunits which appear visually detectable in different times and at different areas of the body. It is taken to suppose that cancer can dispose in any organ or tissue of the body i.e. that any part of a body are accessible to cancer settlement. The first appeared tumor is called the 'primordial' tumor. It is usually named for the part of the body or the type of cell among which it appeared. The units which arose later are named the later appeared tumors. The last consist of the same type of cells and get the same name as the primordial tumor.

Patient age 74 years was diagnosed with stage III primary breast cancer. The volume of her primary tumor was found to be 10.3 cm³ measured through laborious reading of the whole body PET/CT scans. The tumor was resected. However, 8 years after resection of first appeared subunit, 31 bone, 3 lung, 2 lymph node, and 1 soft tissue secondary tumors were discovered.

Volumes of all tumors were measured through laborious reading of the whole body PET/CT scans. In particular, volumes of 31 bone tumors were 1.69, 1.98, 2.01, 2.04, 2.14, 2.20, 2.46, 3.05, 3.18, 3.31, 3.37, 3.48, 3.52, 3.57, 4.22, 4.34, 4.73, 5.04, 5.08, 5.25, 5.45, 5.64, 6.36, 6.55, 7.39, 9.01, 9.21, 11.15, 12.71, 13.81, 22.96 cm³ (Figure 4). Additionally, the patient had three lung tumors with the volumes 1.30, 2.01 and 7.26 cm³, 2 lymph node tumors with the volumes 2.85 and 9.66 cm³,

and one soft tissue tumor with the volume 11.41 cm³. In two other breast cancer patients 20 and 15 bone tumors have been revealed 5.5 years and 9 months after primary resection, respectively (Hanin and Korosteleva, 2010).

In total, 37 cancer units have been explored inside of the body of this patient. The units were disposed in bones (31), lungs (3), lymph nodes (2) and soft tissue (1). A visualized variant of analogous differences in the shapes, sizes and placement of cancerous units are seen at the stage of developed prostate cancer (Figure 4).

The data under consideration allow suppose that the term cancer does not means an alone tumor but a set of genetically identical tumors dispersed around afflicted body and differed only in shapes, sizes and dispositions. The data do not confirm the idea of stochastic settlements of cancer units. Quite possible the dispersion is perceived as stochastic only because its regularity is unknown for us as yet. Probably, there exists very important regularity. The aim to decipher its code should be among main landmarks in the way to the exploring the genomic roots of cancer.

Genetic reasons and origin of mosaic dispersion of cancer units around the afflicted bodies have not been systematically discovered. Meanwhile investigations in this direction could form effective hallmarks for the search of genetic roots of cancer. This is a kind of intra-individual biodiversity (Figures 4 and 5).

Unit - an individual thing regarded as single and complete but which can also form an individual component of a larger or more complex whole.

On the analogy of other kinds of pathology (Rumyantsev, 2006b; Rumyantsev and Gerasimov, 2007) one can suppose that the dispersion of cancer units is a kind of all-pathological phenomenon of heterozygous



Figure 5. Dispersion of pigmented spots on the horse skin is a well known result of genetic admixture

mosaicism created by genetic admixture and arising as a result of crossing between genetically different organisms. This is also the cause

Beside, cancer genetics holds some mystery traits which should be taken into account too. The phenomenon of focal dislocation of cancerous affections is one of these traits. Like any other disease cancer is characteristic by very wide individual variations in constitutional (genetic) predilection to the disease and in its manifestations and course. For instance, many prostate cancers are slow growing and could be left without treatment, whereas others are very aggressive (Hagglof and Bergh, 2012). Such variations are mainly realized in the differences among any clinical manifestations of the disease beginning from the stage of prodromes and prolonging up to exitus letalis. All the differences are of constitutional, i.e. genetic origin (Rumyantsev and Gerasimov, 2007).

There are more than a hundred distinct sites where primordial tumor can be disposed either alone or in the combinations with tardy appeared ones. The list of cancer names is very large. For instance, Muir et al (Muir et al., 1992) presented the names as follow: the cancer of lip, tongue, mouth, oropharynx, nasopharynx, esophagus, stomach, colon, rectum, liver, gallbladder, pancreas, larynx, bronchus, lung, melanoma of skin, prostate, testis, penis, bladder, kidney, brain, nervous system, thyroid gland, Non-Hodgkin's Lymphoma, Hodgkin's Disease, Multiple Myeloma, Lymphoid Leukemia, Myeloid Leukemia.

At least two paradoxes can be seen in the disposition of either primordial or later appeared malignant tumors. Firstly, in contrast to assumed ubiquitousness of primordial tumors there are both more favorite and far less favorite sites of their dispositions. The primordial tumors are mainly disposed at prostate, lung, bronchus, colon, urinary bladder, skin, kidney, rectum, pancreas, stomach. Besides, hypo pharynx, bones and joints, floor of mouth, nasopharynx, gallbladder, or pharynx, oral

cavity. Trachea, peritoneum and pleura are far less favorable for the disposition of primary tumors (Table 2). Secondly, there are only some most common sites where the late appeared tumors are preferably dispose - the lungs, bones, liver, and brain. Other places of a body are seen far less accessible for peared tumors. One question arise immediately – are these unfavorable places immune to the invasion of cancer? The way of existing of such variation as well as its reasons have not been discussed anywhere before.

Two principal variants for explanation of the reasons of cancer's discreteness can be discussed today. Firstly, for the last 80 years the prevailing paradigm in cancer origin and pathogenesis was exclusively based upon the 'somatic mutation hypothesis' (Bauer, 1928; Lockhart-Mummery, 1932), which states firstly that any case of cancer is derived from a single somatic cell that has accumulated multiple DNA mutations in genes which control cell proliferation. The mutations are resulted in unprecedentedly intensive reproduction of the transformed cell and in the formation of primary tumor inside the affected tissue. It means the disposition of any primary tumor is predestined by the location of maternal mutant cell.

The 'somatic mutation hypothesis' has also supposed that some maternal cells are able to move (metastasize) outside of primary tumor mainly through the bloodstream or the lymphatic system and form several secondary tumors in distant locations in the body mainly in the lungs, bones, liver, and brain. The dispersed disposition of cancer cells is paradigmatically considered as a result of their distant translocation (metastasis) from maternal tumor (Chaffer and Weinberg, 2011).

The explanation suggests that secondary tumor can be portrayed as a two-phase process: The first phase involves the physical translocation of a cancer cell to a distant organ, whereas the second encompasses the ability of the cancer cell to develop into a lesion at that distant site. In this way the cells should acquire invasive

Table 2. Opposite rates of male cancer incidence by primary site and race*
(Rates are per 100,000 persons of the 2000 U.S. standard population)

Cancer sites		All Races	White	Black
Sites of Highest Rates				
1.	Prostate	156,9	145,0	226,0
2.	Lung & Bronchus	85,0	79,9	95,1
3.	Colon	36,9	36,0	46,1
4.	Urinary Bladder	36,0	37,9	18,3
5.	Skin	25,6	28,0	2,0
6.	Non-Hodgkin L-ma	22,6	23,1	16,0
7.	Kidney	20,8	20,7	23,1
8.	Rectum	15,8	15,5	15,9
9.	Pancreas	13,2	13,0	15,7
10.		9,2	8,1	15,5
Sites of Lowest Rates				
1.	Hypopharynx	1,2	1,1	2,4
2.	Bones & Joints	1,1	1,1	0,8
2.	Floor of Mouth	0,9	0,9	1,1
4.	Nasopharynx	0,8	0,7	1,1
5.	Gallbladder	0,8	0,6	1,1
6.	Oropharynx	0,7	0,7	1,2
7.	Oral cavity	0,4	0,4	0,6
8.	Trachea	0,3	0,3	0,2
9.	Peritoneum	0,1	0,1	0,1
10.	Pleura	0,0	0,0	

*According to (2007)

traits, be chipped off the mass of primary tumor, invade toward either blood or lymphatic vessel and after all exit the circulation and invade into the distant foreign tissue. Besides, cancerous cells have diameters (20 to 30 μm) that are far too large to allow them to pass through 8- μm diameter bore of capillaries.

The data of cancer genome sequencing

The search for genetic roots of cancer was initiated in 1914 with the proposal by Theodor Boveri (Boveri, 2008) that cancer can be triggered by chromosomal mutations. Now the idea is deepened up to DNA, the molecular basis of human genome. The statements, like "All cancers arise as a result of changes that have occurred in the DNA sequence of the genomes of cancer cells" are now obvious and undoubted.

Direct evidence of driving function of genome in the origin of cancer was demonstrated by introduction of total genomic DNA from human cancers into phenotypically normal NIH3T3 cells that converted them into cancer cells (Krontiris and Cooper, 1981). Isolation of the specific DNA segment responsible for this transforming activity led to the identification of the first naturally occurring, human cancer-causing sequence change—the

single base G > T substitution that causes a glycine to valine substitution in codon 12 of the HRAS gene (Reddy et al., 1982). It is unknown up to now what the concrete function of cancer cell is driving by the codon.

Aberrant composition of DNA named BRCA1.185delAG (the missing of adenine and guanine from the DNA chain at the 185 site) is strongly associated with the predilection of women to either breast or ovarian cancer, or both. The aberration was identified in and located on chromosome 17 (Offit et al., 1996). Among Palestinian Jews the aberration appeared some 2,500 years ago and since this component resides in the DNA of many of their descendants. The concrete carcinogenic function of the codon is unknown.

Over the few past years, the field of cancer genomics has been profoundly developed by the application of DNA-sequencing technology. The discoveries aimed to illuminate commonly mutated genes and transcript-level events that contribute to the underlying tumor biology. Intriguing mutations were found in the genes for two isocitrate dehydrogenase isoenzymes, IDH1 and IDH2. The enzymes play a key role in normal and cancerous cellular metabolism, catalyzing the conversion of isocitrate to α -ketoglutarate. Mutated IDH1 was found in 12% of glioblastoma multiforme tumors analyzed (Parsons DW et al., 2008). It occurs early in glioma

progression (Watanabe T et al., 2009)]. The mutations occurred at arginine 132 (R132) of IDH1. Mutations of IDH2 at the analogous R172 residue were identified on examining glioblastomas, negative for IDH1 mutations (Hartmann C et al., 2009). The mutations affect only one allele at the given locus (of the two alleles of either IDH1 or IDH2, but not both in the same tumor). Although the biological impact of these mutations on enzyme function was identified their carcinogenic functions remain unknown.

Approximately 100,000 mutations from cancer genomes have been reported in the quarter of a century since the first somatic mutation was found. Of these only a small fraction are likely to be relevant to pathogenesis. Over the next few years several hundred million more will be revealed by large-scale, complete sequencing of cancer genomes growth advantage on the cells carrying them. That does not mean, however, that all the somatic abnormalities present in a cancer genome have been involved in development of the cancer. Indeed, it is likely that some have made no contribution at all. (Stratton et al., 2009).

That means the cancerous cells are substantially different from myriads of non-cancerous cells formed the body afflicted by cancer. Cancerous cells and tissues formed by them are genetically dissimilar from other parts of body they have intruded. Cancer should be considered xenogamous (allergenic) for its host. Unfortunately, until now, none of these 100,000 mutations has been associated with concrete step of cancer introduction, pathogenesis and development. It should be especially noted that all these mutations appeared to be heterozygous and present in nearly all cells in the tumor sample (Mardis et al., 2009).

Undoubtedly, the number of aberrant cancer genes, that confer growth advantage on the cells carrying them in an individual cancer is a central conceptual parameter of cancer development, but is not well established (Stratton MR et al., 2009). There is a huge knowledge of the plethora of aberrant genes existed in the genomes of cancer cells but the key DNA aberrations responsible for cancer pathogenesis of are not yet discovered. Beside, the hugeness of number of differences between the genomes of normal cells and their malignant relatives confirms the statement of the hypothesis of genome intrusion (Rumyantsev, 2011b) about genetic foreignness of cancers for organisms which are consumed by them.

The genotype of cancerous cells is not identical to those of normal ones. In contrast to a well-known fact that vast diversity of normal cell phenotypes in any living body is generated by the same genome the initiation and development of cancer is influenced by the inherited cancer-promoting genotype (Podsypanina Ket al., 2008; Podsypanina et al., 2004). In contrast to the somatic mutation theory the malignant phenotype is determined largely by early transforming events rather than being molded by somatic evolution during the clonal

expansion of neoplastic cells (Bernards and Weinberg, 2002).

Recent data of cancer genome sequencing show that almost all the changes in the gene structure of cancer are heterozygous and present in nearly all the cells in the discovered tumor samples (Mardis et al., 2009). This indicates the sameness and the unity of cancerous tissue as well as xenogamous origin of both malignant cells and their genomes /id;Liotta, 2003 1093 /id;Weigelt, 2004 1092 /id}. Many other genetic findings also confronted the somatic mutation theory with a number of apparent and alternative views (Soto and Sonnenschein, 2004).

Substantial advances achieved in the revealing of genes that are frequently and disease-specifically altered in tumor genomes. Cancerous genome contains approximately 750 point mutations, of which only indefinite fraction are likely to be considered as relevant to pathogenesis (Mardis et al., 2009). Concrete genetic factors responsible for concrete stages of cancer pathogenesis remain to be discovered.

The search for genomic roots of cancer should be navigated by the data of preliminary investigations of the multitude of cancer traits in their integrated unity. The genomes of cancerous cells contain genes that are aberrant from analogous genes presented in the genomes of non malignant cells of the same persons. Relevant discoveries should be aimed on the search of aberrant genes that operate on concrete stages of the development of human cancer.

Each of above mentioned universal traits of pathology belongs to any form of cancer too. However, the origin and development of malignancy reveals also some very unique features of this diseased state.

The uniqueness in cancer traits

There are at least three groups of unique traits of major importance belonging to all kinds of cancer. The first and most essential group of these traits is manifested by the genetic, structural and physiologic foreignness of the cancer in its host. The second group of unequalled traits is expressed in the absolute resistance of cancer cells and tissues to normal physiological regulation of cell growth and tissue formation. In contrast to all other disease, cancer comes into being when the division and growth of some cells in some parts of the body become uncontrollable. The third group of unrivalled traits of cancer is expressed in the phenomenon of the immunity of malignant cells and tissues to the destruction by both cell and humoral mechanisms launched by the lymphatic system of responsive immunogenesis. These unique traits perform their obligatory functions in the stages of initiation, development and subsequent progression that are common of all forms of cancer.

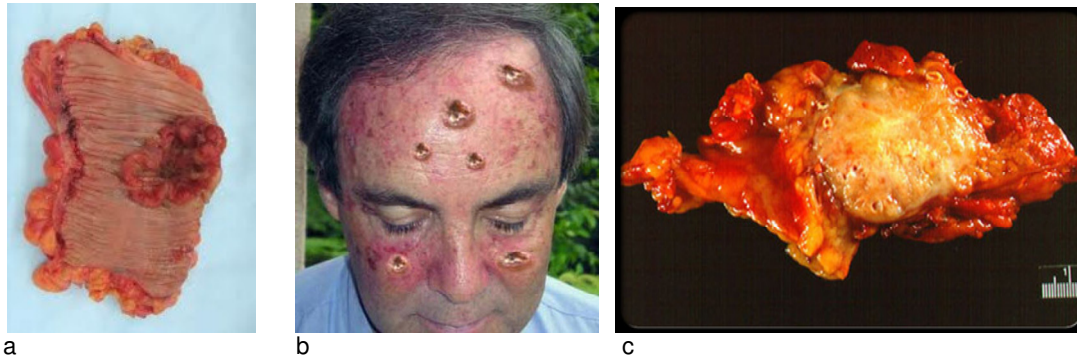


Figure 6. Visual foreignness of cancer
 a) Cancer on normal colon tissue (photograph courtesy of adruniverse.blogspot.com)
 b) Multiple cancer subunits on facial skin (photograph courtesy of adr universe. blogspot.com).
 c) Cancer intruding into the pancreas (photograph courtesy of E medicine health IMAGE COLLECTION).

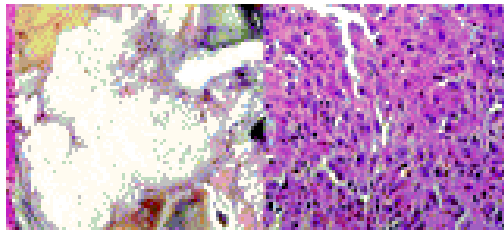


Figure 7. Gross and microscopic features of sarcomatoid renal cell carcinoma presented by (Albiges et al., 2012) as well as any other form of cancer disease attest the foreignness of malignancy.

The foreignness of cancer for its host

All cancer looks alien in the body afflicted by them. This is applicable both to the bodies of cancerous tumors (Figure 6) and their microscopic and molecular structures.

The cancer cells look abnormal and foreign under the conventional light microscope (Figure 7). Although they are considered versions of cells which compose the tissue of the supposed cancer origin; in reality, light microscopy cannot identify the tissue and site of malignancy origin (Briasoulis and Pavlidis, 1997).

There exist a plenty of various manifestations of the foreignness of cancer for its breadwinner. Some of them may remind the similar but not identical traits of those ones if any of infectious and parasite diseases. Their influence is revealed in any other features of cancer both unique and universal all-pathological traits of malignancy as well.

The uniqueness of cancer pathogenesis

Cancer presents a group of malignant diseases characterized by abnormal reproduction of some aberrant

cell clones and consequent growth of relevant aberrant tissues in different parts of afflicted bodies. At least four different kinds of such malignancies were discovered among human and animals. Firstly, some forms of malignancies arise from infection with specific contagious viruses or bacteria. Secondly, there exists transmissible venereal tumor among dogs and analogous contagious cancer among Tasmanian devils (Murchison EP, 2008), sea turtles and sea lion and so al (McAloose and Newton, 2009; Welsh, 2011). These arose after direct physical intrusion of viable cancerous cells from one host to another either over natural sexual contacts or by laboratory manipulations of animals and, occasionally in rare circumstances, over organ transplantation.

The tumors intruded sexually to dogs have a worldwide distribution and that probably arose thousands of years ago. Most cases of this form of cancer are eventually rejected by afflicted dog, who then is conferred lifelong immunity (McAloose and Newton 2009; Welsh 2011). Thirdly, there are tumors transferred from mother to fetus. And at last, there is human cancer of predominant kind that presents one of the biggest and epidemically growing problems in the modern world whose extensive counteracting efforts appeared to be shamefully impotent. The pathogenesis of this

predominant form of cancer is principally different from other kinds of malignancy. At the same time all human cancers of this kind are thought to share a common pathogenesis (Stratton et al., 2009).

Every kind of living being is constitutionally provided with a physiological system that maintains normal body structure within its genetically predetermined shape and size. Special part of this very effective system is dedicated to regulate the starting and revival of body structures and their functions on their molecular, sub cellular, cellular, tissue and organ levels. Normally, cells grow and divide to form new cells as the body needs them. When cells grow old and die, new cells take their place. The regulation is realized on the level of cells and performed by means of hormonal molecules.

In the case of cancer this orderly process goes wrong. The mighty system of body maintenance appears of being impotent in the relation to some of its initially smallest parts. That is happened because cancer is formed by of aberrant cell clone that is able to grow independently of normal physiological control. The cells are diverging and forming the masses of relevant tissue when the body does not need them. Beside, its old cells do not die when they should. The appeared extra cells form the masses of tissue, called malignant tumors.

Two intrinsic hallmarks belong to any kind of cancer. The first and most essential hallmark is the immunity of cancer cells and tissues to normal physiological regulation of cell growth and tissue formation. The second hallmark is expressed in the phenomenon of absolute immunity of malignant cells and tissues to the destruction by both cell and humoral mechanisms launching by lymphatic system of responsive immunogenesis that allows cancer evade the surveillance performed by the host immunogenic system. Both the hallmarks perform their obligate functions in the initiation, development and subsequent progression of any kind of cancer.

Immunity of cancer cells to regulation by host

Cancer is considered us a group of malignant diseases characterized by aberrant reproduction of some cell clones and consequent growth of relevant cancerous tissues in different parts of afflicted bodies. At least four path genetically different kinds of such malignancies were discovered among human and animals (Rumyantsev, 2011b).

The pathogenesis of this predominant form of cancer is principally different of those that function in other kinds of malignancies. Against growth inhibitory signals. This ability provides them with the capability for unlimited replication and to evade programmed cell death. This kind of specific immunity functions against ecological and physiological agents is known as hereditary, genetic or constitutional (Boyd, 1966).

Every kind of living being is constitutionally provided with a set of physiological systems that maintain normal body structure within its genetically predetermined shape and size. Special part of this very effective system is dedicated to regulate the starting and revival of body structures and their functions on their molecular, sub cellular, cellular, tissue and organ levels. Normally, cells grow and divide to form new cells as the body needs them. When cells grow old and die, new cells take their place. The regulation is realized on the level of cells and performed by means of hormonal molecules.

In the case of cancer this orderly process goes wrong. The mighty system of body maintenance appears of being impotent in the relation of some of its initially smallest parts. Thus any cancerous tissue is characterized by unrestrained proliferation of its cells. That is happened because cancer is formed by of aberrant cell clone that is able to grow independently of normal physiological control. As a result its cells are forming relevant tissue when the body does not need them whereas some of its old cells do not die when they should. The appeared extra cells from the masses of tissue, called malignant tumors.

Cancer comes into sight when the division of cells and tissue growth become uncontrolled in some parts of the body. The disturbance is associated with the resistance of cancerous cells to relevant molecular physiological regulators of cell dividing and tissue growth against growth inhibitory signals. This ability provides them with the capability for unlimited replication and to evade programmed cell death. This kind of specific immunity functions against ecological and physiological agents is known as hereditary, genetic or constitutional (Boyd, 1966).

Hereditary immunity arises in evolution as a result of natural selection performed by life threatening molecular ecological factors of infectious, animals and plant origin. In a case of relevant ecological danger, individuals possessing a mutantly modified molecular constitution rendering them incapable of being affected with the agent appear constitutionally immune to a particular disease. They give rise to immune progeny while susceptible individuals of the same species become ill and die without reproducing (Boyd, 1966; Haldane, 1949). On repeated exposure of many generations to a given pathogen, the progeny of inherently immune variants eventually predominate in a population; an individual protective variation becomes the property of a group, then of a population and, finally, of most of a species (Rumyantsev, 1992; Rumyantsev, 1998).

This kind of immunity is determined by constitutional incongruence between relevant ecological regulator and its molecular target in the body. Analogous mechanisms perform constitutional resistance against molecular physiological regulators which are also responsible for many noncancerous diseases. The principles of cell immunity to physiological agents are analogous to those

ones in hereditary immunity to infections (Rumyantsev, 2008).

Hereditary immunity of cells to relevant hormonal regulators is crucial cause of many diseases. It is created by mutant modifications of either the hormone or its receptor, that forms an incongruence between the coactors, i.e. constitutional immunity against hormone influence (Friedman, 2004; Montague et al., 1997; Stunkard et al., 1990). The blocking effect of mutant modifications of either hormones or their receptors leads to the development of obesity (Rumyantsev, 2006b; Rumyantsev, 2011a). Genetic immunity of cells to insulin is a major determinant of the decline of glucose tolerance. Non-insulin-dependent diabetes mellitus is characterized by pathological hyperglycemia in the presence of higher-than normal levels of plasma-insulin. A pathogenic decrease in cell sensitivity to vitamin D3 determines the familiar forms of rachitic. The immunity of cells to androgens causes the phenomenon of testicular feminization. Constitutional resistance of cells to corticosteroids determines the pathogenesis of Cushing's disease (Rumyantsev, 2006b). The grade of the cells immunity to thyroid hormone determines the range of relevant disturbances. This resistance is an inherited inability to respond appropriately to the T3 hormone linked to mutations in the thyroid hormone receptor (TR)-beta (Wan W et al., 2005). One can note that whereas the cell resistance to hormonal or infectious influences has no visible distinctions from the susceptible ones, the cancer cells look abnormal even under the conventional light microscope. They are considered versions of cells which compose the tissue of the supposed cancer origin, however, light microscopy cannot identify the tissue and site of a malignancy origin (Briasoulis and Pavlidis, 1997).

The analogous origin of cancer cells immunity against molecular physiological regulators of cells dividing and tissue growth has recently been hypothesized. The set of above data allowed explain the most unique feature of cancer, its aggressive behavior provided with uncontrollable dividing and growth of cancerous cells. It was supposed the physiological uncontrollability of cancerous cells is predetermined by their natural (genetic) immunity to the influence of relevant molecular cyto-ecological regulators of cell circle and tissue growth (Rumyantsev, 2010b). This supposition, together with mutual exposure, analysis and evolutionary comprehension of a set of relevant immunological data, allowed put forward the new idea about molecular pathogenesis of cancer.

Non-foreignness of cancer antigens with host

Cancerous cells and tissues formed by them are genetically and structurally dissimilar from other parts of

intruded body and hence should be immunologically incompatible. But it is not the case. The lymphatic system of responsive immunogenesis, it's both humoral and cellular agents are unable to destroy genetically and constitutionally aberrant cancerous cells as well as to neutralize molecular cytoecological agents produced and secreted by cancer. The "immune" system cannot prevent the initiation and development of cancer because it does not perceive the components of cancerous cells as foreign.

The coexistence in the bodies of some persons of genetically and constitutionally aberrant cells and cellular components is not a rare case among humans. Humans are extraordinary heterozygous. Their bodies are fulfilled, for instance, with a multitude of cell clones that differ one from another in many of their traits including, for instance, even the differences between clones in their own programs of maturation and ageing (Rumyantsev, 2003). Such variations present a kind of intra-individual biodiversity which played very important role in many forms of infectious and non-infectious pathology (Rumyantsev, 2002; Rumyantsev and Gerasimov, 2007).

The phenomenon can also be illustrated, for instance, by the case of blood groups. Blood of the group AB arise as a result of interbreeding between carriers of the blood of group A and carriers of group B. The resulted admixed genome provides the offspring's blood with two clones of erythrocytes differed in antigenic make-up of their outer membranes – some erythrocytes possess antigen A whereas others carry antigen B. Because the clones are formed over prenatal embryogenesis lymphatic immunogenic system perceive these different antigens as "self" and does not produce antibodies against them. Blood group AB does not contain anti-A and anti-B isoantibodies.

The same situation is observed in the case of Sickle cell anemia. In contrast to inherently immune (AA) form of erythrocyte, its mutant homozygote sickle cell variant (SS) contains mutant (S) hemoglobin molecules. In the blood of heterozygotes (AS) there are both A and S types of hemoglobin molecules and the consequent mosaicism of erythrocytes (Figure 8).

The two kind of erythrocytes arise as a result of xenogamous interbreeding between carriers of genotype (AA) and carriers of genotype (SS) that is resulted the formation in the offspring of admixed genome (AS). Because the development of such form of intra-individual biodiversity performs in early embryogenesis the system of responsive immunity does not produce antibodies against these aberrant structures of human cells. Beside the data allow to conclude that cancerous cells appear in afflicted human body also in prenatal stage of its ontogenesis.

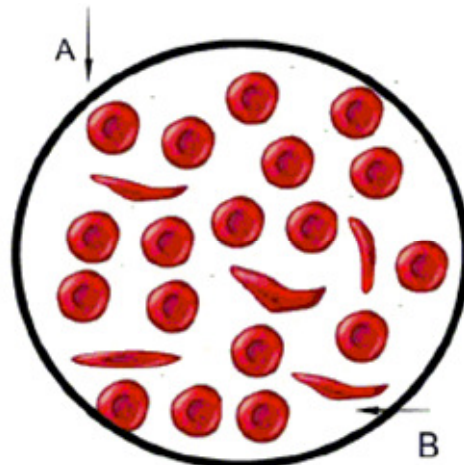


Figure 8. Mosaic population of erythrocytes in Sickle cell anemia: A– normal erythrocyte; B – sickle erythrocyte (Rumyantsev SN, 2008)

Prerequisites for cancer pathogenesis

Any disease displays a set of universal all-pathological features that are also characteristic of other diseases. The set of universal features includes at least a dozen intrinsic signs: 1) different incidence of a disease among different races and ethnic groups, 2) increased prevalence of diseases in developed and civilized countries, 3) genetic predilection to the disease, 4) age differences in the disease incidence, 5) stochastic distribution of individual cases amongst a population, 6) individual variations in constitutional (genetic) predilection to the disease, 7) the mosaicism of affections, i.e. intra-individual diversity both in the predilection of different parts of a tissue and in the quantity and sizes of affections, 8) dappled distribution of affections amongst a body, 9) molecular bases of genomic and cellular pathogenesis and 10) the identity of involved cells in any locations of specific affections around the body (Rumyantsev, 2008).

Each of these universal features expresses the all-pathological phenomenon of heterozygous mosaicism created by genetic admixture arising as a result of hybridization between two genetically different organisms: one of which is constitutionally immune to the relevant ecological or physiological agent whereas its mating partner is constitutionally sensitive to it. The heterozygosity results in the coexistence of at least two active allelomorphous genes in the offspring's genome. Both alleles function dominantly and create two allelic cell clones whose subpopulations are formed and distributed in the body before postnatal ontogenesis. The heterozygous offspring expresses both alleles equally but in different sizes and separated locations around the body. The features and functions of codominant clones may become obvious at different steps of ontogenesis

(Rumyantsev et al., 2000). This is a kind of chimerism or cellular mosaicism, the occurrence in an individual of two or more cell populations of different chromosomal constitutions, derived from different parental individuals (Bonnicksen, 2009; McLaren, 1976).

Genetic admixture (also called xenogamy, out breeding, cross- fertilization, crossbreeding) refers to the reproductive union of genetically dissimilar or unrelated organisms within the same species that inevitably results in offspring heterozygosity of various kinds. The states of heterozygosity are responsible for the origin of spotted mosaic manifestations, individually different course and severity of most diseases, both infectious and non-infectious (Rumyantsev, 2006a; Rumyantsev and Gerasimov, 2007). The mosaicism is revealed in genetically determined variations in the location, size and other pathological manifestation of any disease. Every human disease is extraordinarily diverse in its manifestation. Affected people may have many individual differences in the manifestations of their illnesses as well as in the grade of expression.

Each of these universal traits of pathology belongs to any form of cancer too. The shape, disposition, size and rate of cancer progression are also very different in different individuals. However, the origin and development of malignancy reveals some unique features. Firstly, in contrast to any other disease, cancer comes into sight when the division and growth of some cells in some parts of the body become uncontrolled. Secondly, the cancer cells look abnormal under the conventional light microscope. They are considered versions of cells which compose the tissue of the supposed cancer origin, however, light microscopy cannot identify the tissue and site of a malignancy origin (Briasoulis and Pavlidis, 1997). Thirdly, cancer genetics holds some mystery traits which should be taken into

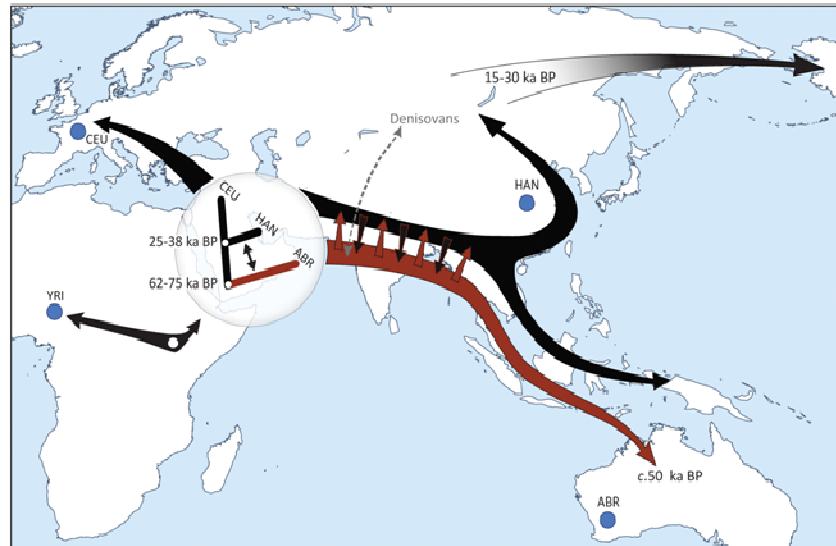


Figure 9. Reconstruction of early spread of modern humans outside Africa (Rasmussen M et al., 2012).

account too. The whole set of oncologic knowledge allow agree with opinion (Stratton and Rahman, 2008) that all over 100 cancers share a common pathogenesis.

The stages of cancer pathogenesis

Xenogamous fertilization

According to xenogamous paradigm of cancer origin, pathogenesis and epidemic spread, cancerous cells appear in a body as a result of genome transformation performed over the heterozygous crossbreeding between parental gametes owned partially different (divergent) genotypes (Rumyantsev SN, 2011b). Over such xenogamous formation of descendant's zygote its genome becomes admixed with a block of aberrant, potentially cancerous genes.

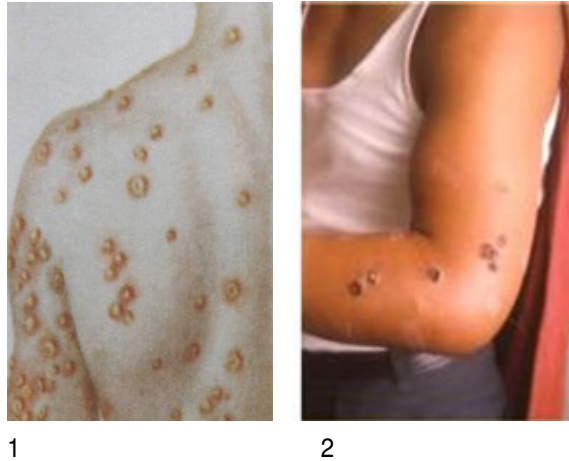
The heterozygosity results in the coexistence in the offspring's genome of at least two active allelomorphic genes. Both alleles function dominantly and create two allelic cell clones whose subpopulations are formed and distributed in the body before postnatal ontogenesis. One the clones is became prevalent in the phenotype of the offspring's organism whereas other clone is deviant, departing from usual standard. The heterozygous offspring expresses both alleles but not equally in different sizes and separated locations around the body. The features and functions of such clones may become obvious at different steps of ontogenesis (Rumyantsev et al., 2000; Rumyantsev and Gerasimov, 2007).

The continuous evolutionary process of divergence between genomes of different subdivision of Homo sapiens has intensified after exodus out of African

savannah, the Eden of human descent. According to the generally accepted Out of Africa Theory and its latest development (Novembre and Stephens, 2008), anatomically modern humans emerged in Africa's savannah. The earliest known fossil of anatomically modern humans dates from around 195,000 years before present (White et al., 2003). Nearly 75,000 – 62,000 ya some small (20-60 persons) groups of early Homo sapiens began to sweep out of the African Savannah territory where their descent and initial establishment has been accomplished. This initiated the dispersion of humankind around the world (Figure 9).

Some groups of migrants moved out of former savannah's "Eden" back into the remnant of tropical forest that was the homeland of their faraway ape predecessors. Other groups began migrations along either South Asian or North Eurasian directions. All non-African populations currently living in the world probably derived from a single dispersal of early humans out of Africa (Rasmussen et al., 2012). The South Asian migration continued toward Australia and eventually reached this continent ~50,000 ya.. The North Eurasian dispersal divided (38,000 – 25,000 ya) in European and Asian directions. The last one continued its way toward American continent (30,000 - 15,000 ya) and reached it nearly 14,000 ya (Rasmussen M, 2012 1233 /id).

The wandering of human groups around the world substantially expanded both the quantity and quality of evolution's driving forces. Thousands of wandering generations were subjected to various selective pressures especially of infectious origin (Rumyantsev SN, 2010 1133 /id). This process resulted in the establishment of racial and huge (over 10,000 names) ethnic polymorphisms which are now characteristic of all



1
2
Figure 10. Duppled dispersion of susceptible cell clones revealed by smallpox (1) and anthrax (2) infections

levels human make-up beginning from racial and ethnic differences in the molecular structures of genomes, cells, tissues and organs.

Beside, before and after the dispersion, most principal genes flowed between the different human populations by mixing together. Most their features could be successfully improved during the following dispersion stage of anthropogenesis. Nearly all differences between current human populations are due to evolutionary events that occurred outside of Africa, and most first appear in East Asia (Coop G et al., 2009).

In contrast, Bushmen, the indigenous hunter-gatherer peoples from the Kalahari Desert of southern Africa, present the oldest known lineage of modern human that diverged from main part of humankind near 70.000 years ago (Figure 6). They did not leave Africa and thus their evolution has been drawn by biological and physical environmental conditions that were very different from though surrounded their far mobile Eurasians, Americans and Australian cuisines.

The structure of the Bushmen genome is genetically divergent from other humans. Whole-genome and exome diversity revealed among them include 1.3 million DNA differences genome-wide, including 13,146 amino acid variants (Schuster et al., 2010). Observed genomic differences between the Bushmen hunter-gatherers and others human lineages reflect genetic adaptations to entirely dissimilar biological and physical environments existed over their evolutionary history of various human lineages (Rumyantsev, 2010a).

Like all the cells that constitute the human body, a cancer cell is a direct descendant, through a lineage of mitotic cell divisions, of the fertilized egg from which the cancer patient developed and therefore carries a copy of its diploid genome (Stratto et al., 2009). However, the DNA sequence of a cancer cell genome has a set of differences from normal cells that constitute the human body.

Embryogenesis of cancer

The early post zygotic stages of human embryogenesis are not sufficient for current discovery. There is only a need to accentuate that divergence between normal and aberrant cell clones could begin far before antenatal embryogenesis. Like the clones susceptible to infectious agents (Rumyantsev and Gerasimov, 2007;Rumyantsev, 1997) the cancerous clones are formed and dispersed around the body in concordance with general rules of embryonic differentiation of tissues and their dislocations inside of appropriate organs.

More sufficient is to take in account that any aberrant cell clones are usually presented among the clones of normal cells in fare lesser quantity. In a discovered case of sickle cell anemia (Figure 8) aberrant erythrocytes consisted 22% of total number of red blood cells. Individual variations in the sizes and focal locations of relevant susceptible cell clones can be seen also at the observations of many infectious diseases. (Figure 10).

The dispersion of observed clones can be individually extremely variable in the number of locations and in their sizes. The number of patches may be less than a dozen in a minor case of illness (Figure 7A), or they may number in the thousands in a severe course of disease of the same kind. Beyond the edge of aberrant location the regular tissue is normal. All the discussed traits of the dispersion of cell clones susceptible to relevant infectious agents (places of locations, their number and sizes) are formed before postnatal ontogenesis (Rumyantsev, 2008;Rumyantsev and Gerasimov, 2007). This may mean that distribution of aberrant clones is programmed by genome.

Cancerous cells appear in and stochastically disperse around the descendant's body also before postnatal ontogenesis and initially exist in it as subpopulations (subunits) of smallest but different sizes. Genomic roots of these traits also should become the subjects of a

special investigation. In contrast to the steadfast places of locations the sizes of cancerous subunits enlarge over postnatal life.

The primordial and late appeared subpopulations of cancerous cells and the tumors formed by them fare later continue to reside stably in their initial places at different areas of the body. They do not metastasize. In reality we can only observe non-simultaneous appearance of several identical tumors in different parts of a diseased body. This explanation of the reasons and propelling forces of cancer's discreteness has been proposed and developed just recently (Rumyantsev, 2009b; Rumyantsev, 2010b; Rumyantsev 2011b; Rumyantsev, 2009a)

Postnatal development of cancerous units

Uncontrollable cancerous growth

At a relevant time of a breadwinner's life (mainly after 40 years of its age), probably according to specific program of the clone ontogenesis and aging, the potentially cancerous micro-populations get their specific impulse to awake. Different cancerous units appear visually detectable in different times and at different areas of the body. They come into sight as hereditary immune against prevailing regulators of cell reproduction and begin to multiple uncontrollably thus initiating the cancerous growth. The initially largest one of the cancerous populations achieves detectable tumorous size far earlier in comparison to the initially smallest one. The first appeared tumor is usually called the 'primary' tumor. The tumors which arose later are named the 'secondary' tumors. Maximally early extirpation of the first appeared cancer unit does not prevent subsequent appearance of "secondary" tumors (Giuliano et al., 2011; Pockaj et al., 2010). This may mean that to the time of the resection the last once already existed in the form of undetectable micro-populations.

All subunits continue to stay stably on their primordial positions appointed over the stage of embryogenesis. The postnatal stage of intensive cell dividing may lead to the increasing of their sizes whereas it does not change the places of their dispositions. Large quantities of cancerous cells circulate in blood and lymph channels but without overt new tumors (Jiao and Krasna, 2002; Pantel and Otte, 2001). This may mean that in such cases the body does not contain the sites acceptable for realization the ability of circulated cancer cells to develop into secondary (metastatic) tumors at distant sites.

Except the sites of primordial tumors of different sizes the other sites of whole body appear absolute immune to the inception of metastatic tumors. On the other hand secondary tumors may remain unseen ones for a very long period of time. For instance, it can take many years for breast cancer to appear in visually detectable sizes.

The appearance of secondary breast cancer was reported to occur after 20-25 years of disease-free period (Karrison et al., 1999).

The quantity of growing cancerous subunits in a body but especially the enlargement of their total mass are mutually responsible for as much as 90% of cancer-associated mortality. Then the hosting functions of diseased body are ultimate and the host is killed before its genetically predetermined long-life. The growing of tumors inevitably led to the death of both the breadwinner and its cancerous sponger. Prostate cancer in elderly men may not place them in danger of eventual death resulting from cancer. The same can be said for small, estrogen receptor-positive breast cancers in elderly women. However, for patients aged <70 years, with a life expectancy >15 years, the outcome of active surveillance is less certain (Chabner and Smith, 2012).

Self-maintenance of cancer

The physiological unity of cancer parts has recently been evidenced by observations on the fate of cancers partially deleted over oncologic surgical procedures. It has been shown the deletion of some tumors by partial hepatectomy initiated proliferation of other parts the cancer has been left after the surgery which resulted in a rapid growth of secondary tumors ("metastases") in the remaining liver after hepatectomy. Significant increase in tumor growth was found after 70% hepatectomy (Sorin et al., 2009). The inception of the first appeared secondary tumor occurred 29.5 years prior to the primary diagnosis, and resection of primary tumor was followed by a 32-fold increase in the rate of secondary tumors growth (Hanin and Korosteleva, 2010). This may mean the growth of all of a cancer unit is under united control performed by their own physiological mechanism which maintains the whole volume of cancerous tissue within its genetically predetermined size.

Accelerated progression of cancerous units after foregoing resection was also noted in experimental (de Jong et al., 1995; Garcia-Alonso et al., 2003; Ikeda et al., 1995) and clinical (Elias et al., 1999; von Schweinitz D et al., 1998) studies. Partial hepatectomy impacted on the growth of tumor size in the remaining places of diseased liver. Besides the growth rate of liver's tumors was more rapid than that of the liver parenchyma. It means their growth rates are regulated by different systems. The set of dispersed parts of a cancer functions like an entire self-reliant living being settled in the affected body. That may mean cancer cells can produce their own growth regulators.

Cancer patients have a 20% higher risk of a new primary cancer compared with the general population (American Cancer Society, 2009). As the numbers of cancer survivors and of older people increases, the occurrence of multiple primary cancers is also likely to

increase (Levi et al., 2008; Milan et al., 2000; Nugent et al., 2005; Soerjomatara et al., 2008; Soerjomataram and Coebergh, 2009). Approximately one-third of cancer survivors aged >60 years were diagnosed more than once with another cancer. Possibly, these variations are associated with the phenomenon of clonal diversity in the genetic programs of the progression of senescence (Rumyantsev, 2003). Such observations prompt the idea of the possible existence of a few potentially cancerous clones in the body (Rumyantsev, 2010b) and few foreign intrusions in the genome.

Cancerous cachexia

Cancerous cachexia is a diseased state of progressive weight loss provoked by intensive atrophy mainly of skeletal muscle and adipose tissue. This state is associated with poor quality of life, poor physical function, and poor prognosis in cancer patients (Dewys et al., 1980). Certain tumor types are more commonly associated with cachexia. Depending on the tumor type, weight loss occurs in 30–80% of cancer patients and is severe (with loss of >10% of the initial body weight) in 15% (DeWys, 1986). Thus, in pancreatic cancer, 85% of patients become cachectic even at diagnosis, but 15% do not (Tisdale MJ, 2003). The prevalence of cachexia is thought to be up to 80% of upper gastrointestinal cancer patients and 60% of lung cancer patients (Evans et al., 2008).

Pancreatic or gastric cancer induce the highest frequency of weight loss, while non-Hodgkin's lymphoma, breast cancer, acute nonlymphocytic leukemia, and sarcomas provoke the lowest frequency of weight loss (DeWys, 1986). Nevertheless, with the same tumor type there are variations in the extent to which patients exhibit cachexia. Individual variations are characteristic of many aspects of cancerous disease. Some people are predilected to cancer whereas other once are either partially or totally resistant to it. Here we have very poor discovered genetic phenomenon the deciphering of which can serve the landmark in the way to discovering the genetic roots of cancer.

The development of this state is induced by the appearance and symbiosis in the afflicted organism of a population of xenogeneic cells. The population settles inside of afflicted organism and exists in it like a sponger. It develops intensively at the expense of both the structures (the proteins, lipids, saccharides) and functions (the supply with oxygen, nutrition and reproduction) owned by breadwinner's organism.

The cancerous atrophy of skeletal muscle is created by intense degradation of muscle protein associated with the depression of protein biosynthesis. The degradation of muscle protein is performed by proteolysis-inducing factors produced by developing cancer (Todorov et al., 1996). The action of the factor is specifically targeted on

the destruction of muscle proteins while the nonmuscle protein remains relatively intact (Fearon, 1992). Activation of proteolysis is an early event during cancer growth and it may be present for a long time prior to its clinical manifestation (McMillan et al., 1994). The results of proteolysis, free aminoacids, can be utilized by cancerous cells among other nutrients provided by breadwinner. The massive loss of adipose tissue is incited by extensive fat degradation performed by lipid-mobilising factors secreted by cancerous cells (Hirai et al., 1998).

The factors of cancer self-procuring

Cancerous cachexia is ultimate state of cancer disease characterized by catastrophically progressive weight loss provoked by intensive atrophy mainly of skeletal muscle and adipose tissue. The cancerous atrophy of skeletal muscle is characterized by intense degradation of muscle protein associated with the depression of protein biosynthesis. The massive loss of adipose tissue is incited by extensive fat degradation. Cancer functions here as a marauder which sucked up the body of its victims just up to dry. Beside, one can suppose some cyto-ecological regulators produced by cancerous cells inhibited the growth of normal cells thus aggravating cancerous cachexy.

The development of this state is induced by the primordial existence in the afflicted organism of a population of xenogeneic symbiotic cells. The population exists inside of afflicted organism like a sponger. It develops intensively at the expense of both the structures (proteins, lipids, saccharides) and functions (the supply with oxygen, nutritive substances and means for reproduction) owned by breadwinner's organism. The cells are able to produce molecular agents specifically targeted on the enzymatic splitting of muscle proteins. Beside cancerous cells are able to secrete lipolytic enzymes which functions make substantial investment in the creation of cancerous cachexia.

When a cancerous host dies from cancer, it is mostly because its tumors have exhausted its life supporting stuffs and intoxicated its life supporting organs. Unfortunately, the discovery of molecular origin of cancerous intoxication is now only at the beginning of its way. The development of either solitary or associated malignant tumors inevitable lead to the death of the cancer's breadwinner far before of genetically predetermined limit of its longevity. The possession by cancer of so specialized and undoubtedly wholesome toxins and nutritive factors evidenced evolutionary origin of cancerous marauding.

Genesis of cancer epidemic spread

Natural selection in cancer evolution

This time of cancer development is characterized by the complex of trades necessary appropriate for providing the breadwinner's ability to transmit cancerous genes to relevant gametes, execute multifold acts of fertilization, perform the breed of descendants to the stage that is usually named as complete maturity. The absence of any of the abilities diminished sharply the chances of cancerous genome to prolong its life in the genomes but the in the bodies of descendant generations

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Evolutionary-ecological prerequisites for cancer spread

Cancer belongs to the group of contagious diseases which exist thanks to the act of contagion - the communication of disease from one organism to another by direct or indirect contact. Beside cancer the infections and parasitic invasions are existed in the group. Like any other contagious disease cancer arises and exists as a result of natural ecological relations between two species in which the contageous one (the consumer) obtains the matters and energy for its life at the expense of substances composed of the consumed organism (the victim). The action of consument restricts the vitality of the victim, thus provoking the state of disease and a loss of its viability. Once filled with cancerous agents, the body of the affected victim serves as a source of contagion into new victims.

The intrusion of infectious agents inside the next victim's body is mainly carried out by means of the victim's ecological communications, through which the regular physiological functions are provided; for example, through feeding (as an alimentary intrusion), breathing (respiratory intrusion), as well as , through direct contact and self-reproduction (venereal intrusion). Of the three, the alimentary transfer of infectious agents functions most widely and effectively (Burgasov and Rumyantsev, 1974).

The spread of cancer trough direct transfer of cancerous cells from one organism to another is known among Tasmanian devils (Murchison EP, 2008), sea turtles, sea lion, dogs and so all (McAloose and Newton, 2009; Welsh, 2011). The canine transmissible venereal

tumor is spread during sexual intercourse between dogs. The possibility of such direct transmission of cancerous cells among humans is yet under question. Beside, tumor cells can be transferred from mother to fetus as well as by laboratory manipulations of animals or, occasionally, by organ transplation. And at last, concerning the predominant kind of human cancer is presumed and argued the transfer by means of genome intrusions over xenogamous self-reproduction. (Rumyantsev, 2009b; Rumyantsev, 2010b). At any of the cases we have concern with multicellular parasites that are belonging to the class of Mammalians. The parasites live inside of the bodies of higher mammalians using oxygen, nutrients and other supplies for their life and self-reproduction at the expense of substances composed of the victim organism.

The application of above explored scheme of cancer pathogenesis (section 3.3.) to cancer epidemiology can help to explain the leading propelling causes of current epidemic progression of this cancer prevalence. According to the above performed analysis of cancer pathogenesis, the carcinogenic functions of genome mutations possess important roles in the pathogenesis of any forms of the disease. Regretfully, none of such mutations by themselves are able to explain the pandemic spread of cancer. None mutations could be widely disseminated in the humankind because their rarity, randomness, and to the counteraction of natural selection. Thus, the undoubted existence of mutative carcinogenesis cannot be used for the explanation of the moving forces of current pandemic spread of malignancy.

In contrast, the distributive potencies of xenogamous carcinogenesis are fare more productive. The currently observed increasing incidence of most diseases (American Cancer Society, 2009) depends on the intensity of the genetic admixture within ethnically mixed populations (Rumyantsev, 2008). Causative function of xenogamy in the origin, individual manifestations and course of malignant diseases is also evidenced by a plethora of epidemiological and clinical observations and investigations (Rumyantsev SN, 2010b). African-Americans are more likely to die from cancer than any other racial or ethnic population. In contrast, Hispanics, Asian Americans and Pacific Islanders have lower incidence rates than Whites for the most common cancers (American Cancer Society, 2009).

The frequency of any site of cancer varies around the world. Colorectal site of malignancy is common in the Western world and is rare in Asia and Africa (American Cancer Society, 2009). Although only one cancerous clone usually exists in an affected body, the presence of a number of cancerous clones has also been documented. In a population of a developed country with high survival rates, multiple cancers often comprise two or more primary cancers occurring in an individual that originate in a primary site or tissue and are neither an extension, nor a recurrence or metastasis

(Soerjomataram I and Coebergh, 2009).

Xenogamous forces of cancer genesis and distribution could begin to function among humankind at the earliest steps of its evolution. Any evolutionary process is performed by two main propelling forces: mutative diversification and subsequent natural selection. In addition to spontaneous mutations the genetic diversity can be enriched by interbreeding with related populations and species. For instance, the hybridization and exchange of genes between mutual ancestors of chimps and humans may have occurred over period of just a few million years. Also they may have interbred for a long time after their two lineages began to split apart evolutionarily (Patterson et al., 2006). Considerable admixture between genomes of Neanderthals and early modern Europeans happened near 30,000 years ago (Soficaru et al., 2006). Cancer possesses a set of constitutional adaptive traits that could be thought to be a result of evolution that can be accounted by many millennia. The date of its initiation could be referred, for instance, to the epoch of intercourse of *Homo sapiens* with *Homo neandertelensis*.

The exodus out of African savannah and subsequent dispersion around the world over the last 60,000 - 70,000 years has resulted in a wide biological diversification of human species and a strong self-segregation of its tribes from each other. Some tribes moved back to tropical South Africa, the homeland of their predecessors. Other groups migrated in the Euro-Asian or South-Asian ways. Their further evolution was performed by the forces, which propelled biological and social diversification of the species over its dispersion around the world. Inhabiting ecologically disparate geographical areas, migrants continued to evolve independently into five anatomically different races and a multiplicity of segregated ethnic groups (Rumyantsev, 2010a). These new ways of life did not favor a xenogamous epidemic spread of cancer, except when segregation was broken forcedly, for instance, by aggressive tribes. In contrast, the influence of xenogamy on the distribution of cancer among the members of separated ethnic groups was restricted.

Social prerequisites for cancer epidemics

Today, the situation is becoming the opposite. Thanks to growing industrialization, urbanization, globalization, and migration, most urban populations became ethnically mixed. The genomes of modern urbanized humans become the mosaics composed of genetic segments inherited from a extensive row of ancestors has been ethnically segregated before for very long time. The spread of cancer became pandemic, intensified by the growing expansion of xenogamy, the reproductive intercourses between ethnoses, which proceeded at different environmental conditions for previous evolution. The currently observed increasing incidence of cancer,

as well as many other diseases, depends on the intensity of the population's genetic admixture promoted within ethnically mixed populations. This kind of pathology is now more characteristic of any mixed population. The current pandemic spread of cancer is intensified by the growing expansion of xenogamy.

CONCLUSION

The article was devoted to further development of principally new paradigm of cancer origin, pathogenesis and epidemic spread based on the hypothesis of carcinogenic transformation of reproductive genomes. The newly performed updates to the paradigm were based on multidisciplinary integrative reassessment and re-sensing of both well known and recent data about cancer genetics, epidemiology, pathogenesis and clinical manifestations from the viewpoint of up-to-date all-pathological, immunological, genetic, anthropological and evolutionary discoveries. The above-presented results of reconsideration of the actual data regarding cancer from the viewpoint of recent all-pathological, epidemiological, immunological, clinical, genetic, and evolutionary discoveries allowed a new integrative paradigm – the hypothesis of genome intrusion - about the origin and pandemic spread of the disease to be formed. The revealed set of evidence allowed state that

1) The existence of cancer diseases was predetermined by genome transformations have created, in evolution, inter-ethnic differences in molecular constitution of inherent physiological systems responsible for regulation of cell dividing and tissue growth.

2) The development of individual cancer disease is initiated by the appearance in afflicted body of deviant cell clone (or clones) inherently immune to normal physiological regulators of cell growth and tissue formation. The cells of such inherently immune clones are able to grow independently of physiological control of normal cell replication. This clone is foreign (alien, non-self) for afflicted body with many of its traits.

3) The inherently immune clones appear in a body as a result of xenogamy (genetic admixture) performed over the crossbreeding between parental gametes owned partially different genotypes led to both the intrusion of offspring's genome with heterozygous genes and to the formation in the offspring's body of coexisting cell clones with opposite relation to the regulators of their growth. The currently observed increasing incidence of the disease depends on the intensity of xenogamous genetic admixture within ethnically mixed populations.

4) The emergence of cancerous clone and its dispersion around the body in the form of discrete micro-populations are performed before postnatal ontogeny in the manner used to dispose other embryonic tissues and organs. Thus the lymphatic system of individual adaptive immunity does not recognize the deposited cancer cells

as foreign and does not destroy them.

5) After the end of their disposition the subpopulations continue to reside at their stable places like cell masses of smallest but different sizes. Cancerous cell populations are subsisting on life supporting stuffs provided by intruded host. Any individual cancer disease arises and exists as a result of natural ecological relations between two organisms in which the xenogamous one (the consumer) obtains the stuffs and energy for its life at the expense of substances composed of the consumed organism (the victim or host). Cancer disease is a kind of parasitism.

6) The marauding way of life exploited by populations of cancerous cells performed mainly by their molecular enzymatic agents targeted either on the splitting of breadwinner's macromolecules or produced inhibition of the host cells.

7) At a relevant time of a breadwinner's life (mainly after 40 years of its age), the uncontrollably growth of such micro-subpopulations led them into sight in the form of detectable extra cells masses of cancerous tissue, the multiple malignant tumors. The initially largest one of subpopulations achieves detectable tumorous size far earlier in comparison to the initially smallest ones thus forming the first appeared cell mass usually called the 'primary' tumor.

8) The growth of all subpopulations of a cancerous clone is under control performed by their own united physiological mechanism which maintains the whole structure of cancer within its genetically predetermined size. The destruction of one or more tumors gives boost to growth of other sub-units of the clone.

9) Cancer possesses a set of constitutional adaptive traits that could be thought to be a result of evolution that can be accounted by many millennia. The date of its initiation could be referred, for instance, to the epoch of xenogamous intercourse of *Homo sapiens* with *Homo neandertelensis*.

10) The current pandemic spread of cancer is brought about growing expansion of interethnic admixture favored by growing industrialization, urbanization, globalization, and migration. Prevention of cancer could be achieved voluntary restriction of xenogamous fertilization as well by the launching of noncancerous genealogies.

.These new notions provides the framework and some initial landmarks for the location of genomic roots of cancer origin and should induce the appearance of new research ideas and proposals for cancer prevention and therapy. Beside, here remains fare much to be learned about this extraordinarily unique and extremely complex disease. According to the paradigm, the search for a coveted clue to the genomic roots of cancer would be oriented on the discovery of structural and functional differences between the genomes of cancerous and normal cells.

"Will our children develop cancer?" This tough question should be asked by each groom-and-bride couple before they have decided to marry. The genomes of expectant moms and dads must be tested for the risk of cancer in their potential children. Appropriate genomic tests must be performed before conception. This kind of protective parenting is now on its way to becoming a mainstream medical testing. The Unites States government is already starting to consider the possibility of searching the genome of every newborn baby by whole genome sequencing. The results can provide early warnings about some of the deadliest and most debilitating diseases including cancer, diabetes, obesity, Alzheimer's disease, dementia and other diseases that may not strike until adulthood. Those warnings can make people to be prepared to enable timely treatment, or at least allow them to elaborate plans about long-term care.

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