Immunity or morphogenesis in cancer development and treatment

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Abstract

Non-selective cytotoxic therapy of cancer is effective, acting harmfully for a host. Legal deep lymphocytopenia at conventional cytotoxic therapy, high risk of new malignancies after it, spreading of malignant cells through favourite lymph nodes, a restriction of immunocytes activity inside tumor at anti-angiogenic treatment does not feet the idea of host immune defense against spontaneous cancer. To understand these theoretical inconsistencies we discussed the development of a tumor and its microvessels, gradual exhaustion of hematopoietic stem cell number in blood and arising of cancer cachexia, ratio of infectious morbidity and cancer mortality in their interrelation, using an experimental, clinical data and population statistics. We concluded, that mentioned above and other principal discrepancies would become regularities, if the cells renewing in both malignant and normal tissues were taken as a result of the recently discovered morphogenesis activity of circulating mononuclear cells, originated from the bone marrow and presented by tissue's committed stem cells and some subsets of morpho-angiogenic lymphocytes.

Introduction

Invariable difficulties in rejection of a tumor and retention of an allograft exist in the theoretical sphere of cellular immunity, where these two tasks are united. The strategy of immunotherapy demands to reduce of regulatory T cells—suppressors—in cases of cancer, but extend them in case of allograft [1]. It is not clear, why such opposite immune reactions expected, if both malignant tissue and allograft, in the case being non-self, can provoke a uniform anti-allogeneic response. It is not clear also, why the practice of therapy both of cases leads to a uniform lymphocytopenia. Similarly, why the age-related decline in immunity associates with decreased survival of recipients of the liver allograft [2], but follows by improvement of mortality, incidence, and prevalence of malignancy among old cancer patients [3]. The “favourite” paths of the tumor cells dissemination, namely blood, and lymph nodes, are the very location of supposed “protective” cells. The modern anti-angiogenic therapy [4,5] prevents circulating lymphocytes interaction with tumor cells. The idea of non-selective cytotoxic therapy as the stimulator of immune defense against tumor dominates despite the main antineoplastic agents are carcinogenic, toxic, mutagenic, clastogenic, teratogenic [6] and treated cancer survivors have increasing risk of developing new malignancies by 14% compared with the general population [7]. The idea for tumor deception of immune protection is popular, in spite of the lowest limit of lymphocytopenia permitted at cancer therapy [8] and this level is comparable with such for survivors after nuclear bombing [9].

Alternatively, multi-annual practice [8] assumes that lymphocytopenia, induced by anti-cancer therapy, relates somehow to a positive result. Some scientists concluded earlier that mononuclear cells have the global morphogenesis function because they transfer regenerative information to purpose-oriented normal and malignant tissues on the distributive base [10-19]. However, overly pediatric belief towards the existence of the anti-neoplastic immunity did not cause comprehensive public discussion of the idea of spontaneous tumors belonging to tissues, which do not provoke any protective reactions of the host [20-23].

At present, the new facts of involvement of hematopoietic stem cells into tissues regeneration challenge again the traditional interpretation of lymphocytopenia, induced by cancer therapy, as annoying adverse effect or side effect. Its role continues to be far from well-defined and demands the reconsideration. We attempt to fill this gap using data for morphogenesis properties of primitive cells of the hematopoietic system, which were not known 20-30 years ago and should not be ignored further in palliative treatment of cancer. The experimental and clinical data, including population statistics for cancer patient’s vitality, will be considered as the most reliable criterion to prove the practical significance of morphogenesis function of circulating hematopoietic stem cells and lymphocytes.

The following data illustrates the involvement of specific circulating mononuclear cells in the nutrient supply and development of both the normal and malignant tissues.

Haematopoiesis and tissues function

Haematopoiesis and normal tissues

Most of the primitive mononuclear cells in the bone marrow and blood of adults represented by markers CD133+CD34−, CD133+CD34+, CD133−CD34+, and marker CD133 is ancestral to...
CD34. Strongly proliferating CD133+ cells are able to differentiate into cells with characteristics of mesoderm, endoderm and neuroderm layers: endothelial progenitor cells, neural progenitor-like cells, astrocytes, oligodendrocytes, cells of kidney proximal tubules, cells of lactiferous ducts of the mammary gland, cells of the prostate gland, skin, lung, intestine, hepatocyte-like cells and skeletal muscle-like cells, expressed primary tissue- associated proteins [13,24]. The primitive cells of bone marrow migrate through the blood into different tissues and organs, especially after their injury [25]. The many examples of enhancing nonmalignant tissue regeneration via primitive bone marrow cells stimulation or their injection into the organism [26-28] confirm the idea, that bone marrow is a source of circulating tissue-committed morphogenetic stem cells [13,24]. The vascular endothelium is renewed with the help of circulating CD133+ progenitor cells of bone marrow origin [29]. Even if primitive bone marrow cells do not transdifferentiate, as some suggest, but only fuse with target host cells or excrete of some cytokines and nutrients [30] they thus support the regeneration of target tissues. A steady-state of cell proliferation in different tissues of the body is supposed to be maintained, by T-lymphocytes too [31]. Most early memory lymphocytes, as well as mononuclear stem and progenitor cells penetrate through capillary walls into the interstitium of non-lymphoid tissues like the skin, muscle, liver, small and large intestine and the central nervous system to exert most of their protective and homeostatic activities under a noninflammatory steady-state conditions [32]. They sacrifice themselves in support of the lives of the surrounding cells. The TdT+ prollymphocytes, y6-T cells (CD4–CD8–) [33] and CD3+CD31+CXCR4+ angiogenic T-lymphocytes [34] participate directly in tissue repair through the production of the growth factors, nutrients, and acceleration of the processes of angiogenesis. All these cells seem a trophocytes, feeding lymphocytes, rather than immunocytes, according to Fidler’s prediction [35].

**Spontaneous cancer is likely self-tissue and rather fed by the host**

A candidate for a feeding system for cancer is hematopoiesis, which supports the viability of an organism as a whole by the mechanism more universal, than immunity [23]. The well-studied phenomenon of total aplasia of the thymus in the middle age shows the applicability of morphogenesis function of circulating cells to cancer supply. The event of thymus aplasia is accompanied by the dislocation of the T-cell production from the gland to the bone marrow, by the temporary decrease in the number of immature CD4+CD62L+, CD8+CD 122+ lymphocytes in the blood [36,37] and by the temporary retardation of age-specific reduction of length of lymphocytes’ telomeres [38]. The expected in this connection maximum of all chronic non-malignant illnesses at middle age confirmed for population of eight countries of Northern Europe [39]. The maximum of the non-malignant morbidity rate is registered at middle age for a restricted group (n=14,448) of Chernobyl’s clean-up workers too [36]. Moreover, a relative risk of complications of influenza (such as hospitalizations and/or deaths) increased from age 20 to age 49, according to natural thymus functions involution, and then slowly declines again to age 60-69, as is shown for 43,345 adults populated Ontario state and aged ≥20 [40]. To the contrary, the lowest rates of death and the highest 3-10 year survival of adult cancer patients correspond to the middle age region of around 50 years according to SEER database (Surveillance, Epidemiology, and End Results; National Cancer Institute, USA) [41-43]. The described infectious/ malignant age relation is not explainable by intensifying of cancer immunity, as raise of infectious morbidity contradicts to this. In contrast, a universal ability of primitive cells in blood to support the cellular renewal in many tissues of the organism is quite acceptable for the explanation of the mentioned relation. The temporary shortage of tissue renewal may reduce both tumor aggressiveness and a non-malignant somatic resistance toward infection. Thus, well-established morphogenesis properties of circulating cells can be combined with real pathogenic processes, explaining some principal discrepancies at the level of populations.

**Blood supply is vital for tumor development but not its regression**

The rate of cancer progression depends obviously on microvessels density of the tumor tissue. The local regrowth a tumor after temporary arrest of its mitotic activity starts from the peripheral, most vascularized zones only, but not from central hypoxic ones with a deficit of immunocytes in them. The hypoxic conditions provoke the massive emigration of malignant cells to the new, more vascularized areas in the organism, provide the start of metastases and paralyze the effectiveness of chemotherapy [44]. The metastases appear only during the slow (quasi-linear) phase of the primary tumor growth, which replaces the previous fast (logarithmic) phase with highest microvessels density [45]. This sequence of events confirmed by a lack of hypoxia marker MCT4 expression in tumors of breast cancer patients with the high 10-year survival rate (mostly local development) and the high level of marker expression at the low survival rates (early spreading) [46]. Therefore, sufficient interaction of circulating blood with cancer cells promotes their local development and vice versa. Thus, a key to a local tumor proliferation is a feeding function of blood vessels even if they deliver supposed "protective" cells. The development of modern antiangiogenic therapy [4] supports this priority of blood supply for local growth of malignant tissue. In parallel, the CD133 hematopoietic stem cells are a universal angiogenic agent in non-malignant tissues [47].

**Hematopoiesis and tumor tissues**

There are no doubts today that similarity in collaboration between morphogenesis cells of the hematopoietic system and malignant tissues exists. CD133-positive cells found in the carcinomas of the liver, lung, colon, skin, prostate, nervous and muscular tissues are called as cancer stem cells (CSC) [48]. Nevertheless, cancer can be developed from CD133 - negative cells also [49]. Moreover, misleading intercellular transfer of a CD133 marker into a tumor cell is possible due to simple cellular fusion [50]. CD34+ stem cells migrate from the bone marrow into tumors of the lung, stomach, prostate, liver, and skin too. The increasing number of circulating primitive CD133+cells [51], as well as CD34 cells and young lymphocytes, is associated with a failing prognosis and survival of patients with cancer of the lung, ovary, colon, breast [35,52]. Thus, migration of morphogenesis cells or trophocytes into a tumor can support viability of malignant tissue via reutilization of debris [53,54-56], fusion with them [50,57], microvessels development [14,17,58,59].

As early as last century Gutman M. with coauthors stated, that therapeutic myelosuppression may result at least in inhibition of host cell-induced tumor angiogenesis, which is not an immune process.

The sectional case of updating vascular endothelium by CD133+ endothelial precursors and angiogenic T lymphocytes (CD3+, CD31+, and CXCR4+) may be at least a quite acceptable example of such a morphogenesis mechanism. Angiogenesis of tumor, being a principal cause of its progression and more intensive than that in a histologically identical normal tissue, is the main target of antiangiogenic therapy [4]. The rate of capillary networks formation and local growth of tumors
Shoutko AN (2019) Immunity or morphogenesis in cancer development and treatment

Probability of cancer therapy success in case of individual patient

There is a little of discussion about the limitation of the natural lymphopoietic capacity of the organism along with life, diseases, and treatment, apart from well-known prognostic deterioration at declining universal of neutrophils /lymphocytes ratio (N/LR) for many diseases [68].

Results of modern therapy of advanced cancer often become disappointing. According to general immunological point of view, a fatal development of tumor happens either because of deception.
of defensive system by a surprisingly low number of malignant cells at the very beginning, or because of followed exhaustion of immune potency during the long struggle against the majority of abnormal cells. Then, an additional lymphocytopenia induced inevitably by conventional cytotoxic therapy looks harmful [8]. However, the same lymphocytopenia looks quite relevant if it to consider basing on morphogenic processes.

There are many reasons to divide the progress of cancer disease onto two phases at least [87]. Treatment usually continues until it has a chance to work but, in parallel, from cycle to cycle it exhausts regenerative capacity of lymphopoiesis, and induces serious complications, including incurability and a higher risk of death. People who are much older and have exhausted lymphopoiesis may not be able to tolerate intense treatment, which brings no benefit, despite its intensification [88].

Therefore, at phase 1, the growth of tumor forces the hematopoiesis to supply additional feeding cells. It is true, the higher lymphocytosis before cytotoxic treatment and more evident lymphocytopenia are after, the less mortality is [71,78,79,89]. In this phase, cytotoxic therapy interferes tropic supply of cancer tissue by course to course but depletes concomitantly sensitive lymphopoiesis until its complete exhaustion. Once injured by therapy, lymphopoiesis recovers spontaneously between courses and provides again cell renewing in privileged cancer tissues, bringing relapse of disease.

Eventually, over-production of stem cells in bone marrow, typical for phase 1, replaced by the weakened (turbulent) stem cells genesis phase 2, which, in turn, finishes with irreversible total somatic exhaustion/cachexia incompatible with life [90]. The hematopoietic turbulence of CD34+ cells content in blood at phase 2 is accompanied by synchronized fluctuations of monthly mortality of patients with advanced carcinomas during the final year of their life [71]. The found stem cells fluctuations in the blood are in agreement with replays of natural (asymmetric) type of bone marrow cells division on abnormal (symmetric) one in phase 2 [91].

As the turbulence provokes sooner or later a fatal deficit of the morphogenesis cells in somatic tissues, the chronic homeostatic imbalance between created and lost biomasses of the body has to follow. In spite of intensive treatment and unlimited food, cachexia affects nearly half of all cancer patients being the cause of one-third of cancer-specific deaths.

It is remarkable that one of the attempts to cure cachexia bases on the replenish hematopoietic stem cells in blood as they significantly contribute to tissue regeneration [92]. Consequently, the deep pretreatment lymphocytopenia in phase 2 is a poor personal characteristic of the patient and predicts the failure of conventional cytotoxic therapy [93]. The unstable proliferation in bone marrow in phase 2 is a course of prognostic instabilities some signs related to hematopoiesis. Contrary to phase 1, CD133 positive expression in advanced cholangiocarcinoma predicts a surprisingly favorable outcome of patients (14 months median survival), while negative CD133 expression correlates with poor prognosis (4 months median survival) [94]. This inversion reflects the general shortage of morphogenesis cells in the blood and tissues of terminal patients at the end of life with increased risk of death from common somatic frailty.

It is important to note, that this prognostic inversion compromises malignant origin of CD133+ cells called as cancer SC. Similarly, the preliminary exhausting of hematopoiesis by large field and high dose radiotherapy inverts expected mobilization of CD34+ host progenitor cells by G-CSF’s injection to super-exhaustion the bone marrow reproductive capacity, and increases risk of death, chiefly because of common somatic disability [95]. The attempts to replenish the poiesis in phase 2 cachexia with low doses of growth factor are remarkable since hematopoietic stem cells in the blood significantly contribute to tissue regeneration [92]. Thus, phase 2 reflects a victory of a quasi-embryonic malignant tissue over non-malignant ones in unequal competition for exploit of a naturally limited morphogenesis resource of cancer host’s hematopoiesis. The dividing of tumor’s development on phase 1 and phase 2 explains why the therapeutic lymphocytopenia coexists with beneficial results at forced proliferative potency of bone marrow but later, at its exhaustion, becomes dangerous for patients life.

Uncertainty of average results of therapy in group

Such tests as survival and average life span predictable by a distribution of the personal proliferative resources of the hematopoietic system among subjects inside the group before the action of injured factor [96]. Any real group always consists of patients with transitional characteristics of hematopoiesis between two, formally described above, phases 1 and 2. For the correct expectation of survival and average life span needs to know the ratio of patients with phase 1 and phase 2 in the untreated group. Most of the survivals curves are biexponential that confirm the mix type of studied groups consisted of persons with poiesis in phases 1 and 2. Considerable variability of individual life span in groups of cancer patients is persisting even if the group consists of members with uniform diagnosis and uniform treatment [87].

Variability of an average life span at treated cancer diseases covers range around 1-25 years independently from age at diagnosis [42] and is comparable with the variation of “ideal” natural aging, which occupies period 80-110 years old. Analysis of natural survival curves by age for countries with high social status has shown specific rectangularity of the curve, which arises due to the strongly = 30 fold increasing the exponential rate of death at the last 20 - 25 years of life. [80,97]. Thus, the majority of untreated patients with malignant diseases were older, than their calendar age of diagnoses. Although their lifespan was increased by 5 - 10 years because of therapy, when diagnosed between 15 - 65 years of age, it will result in the concomitant loss of 55 - 5 years of active natural longevity [80]. Those treated in phase 2 of poiesis had the live span of 1-2 years, but those in phase 2 lived 7-10 times longer [87].

The randomized data of the surprisingly lowest (<3%) contribution of curative cytotoxic chemotherapy to 5-year survival of adult cancer patients from USA and Australia provoked recently chemotherapy disappointment [98].

The low percentage of complete responses to chemotherapy confirmed the disappointment later [99]. These results seem regular in the light of practical incurability of patients who start the treatment in phase 2 of the reproductive resource of their lymphocytepoiesis, and their domination in studied cohorts. Even the mild stimulation of exhausted lymphopoesis by natural growth factor leads to its deterioration [95] and no reason to expect stimulation phenomenon from cytotoxic drugs, originated from their historical ancestor in oncology – mustard gas. Thus, the curable part of the group/population of patients depends on the percentage of members with powerful lymphopoiesis in it, because of conventional cytotoxic therapy bases on the competitive principle restriction of the tumor’s feeding with trophic lymphoid cells [80,100]
The principle advantage of competition therapy based on the redirection of the morphogenetic lymphocytes from tumor to the multitude of slightly injured host tissues is the preservation of a limited lymphopoietic reserve, in contrast with all other kinds of cytotoxic therapy followed by deep lymphocytopenia. But the level of optimal reparable injury of non-malignant tissues, its origin and volume in every personal case are in obscure yet. However, it is a perspective field for the lymphopoietic system reappraisal, which will overcome and reconcile a theoretical inconsistency not attract the attention of modern science aimed presumably at the molecular level.

Phenomenon of spontaneous cancer regression is example of competitive tissues regeneration

The disappearance of all or at least some relevant parameters of a soundly diagnosed malignant disease without any medical treatment or inadequate treatment for the resulting regression defines as spontaneous regression (SR). The pathophysiology to spontaneous resolution of cancer is not well understood and requires further study. It is a rare (1:60000 or 1:100000), but exciting event in oncology, which is seen sporadically in every type of cancer and nowadays there are no more doubts on the validity of the observation [101-106]. The known offered explanation of SR due to severe local infection (with streptococci, measles, viral hepatitis, herpes zoster or chickenpox during peritonitis, pneumonia, artificial graft versus processes), and even the so-called psychoneuroimmunological reactions is doubtful as it based on parallel activation of anti-cancer immunity. SR observed among the patients with HIV-compromised T-cell immunity [107,108] and after an episode of myocardial infarction [106]. In rare cases, forced regeneration of non-malignant tissues restricts the vascularization processes in the residual tumor and results in further SR [109]. In most cases of well-documented SR are possible to see the concomitant surgical components in tissues aside tumor such as ample excision of abdominal wall, incomplete resection, thoracotomy, bypass surgery with intestine, bowel, hernia, followed by a second surgical exploration, postoperative fever, pneumonia, prolonged healing of postoperative wounds, and ctr. In all such situations the incomplete chronic regeneration of injured tissues is the real event which accompanies SR. Even extreme physiological conditions such as pregnancy can provoke temporary exhaustion of lymphocytopenia followed by spontaneous regression of a carcinoid tumor [110]. Therefore, SR, as well as the positive results of complementary medicine methods, deserve a more scientific systematic registry of cases and sophisticated scrutiny, because a deep understanding of such tumor control may lead to a new, unexpected, unusual therapeutic approach in oncology.

The simplest explanation of the SR phenomena for the cases of long-term tumor dormancy and exceptional treatment-related survival bases on the morphogenetic function of lymphocytes. Presently, there are no doubts that lymphocytes can promote cancer growth in their attempt to repair what they perceive as a wound or other tissue injuries including cancer itself [111]. The priority in morphogenenic service belongs to cancer as an embryonic-like tissue. The priority realizes via redistribution the morphogenetic cells to the tumor and following bodyweight loss and cachexia. A competitive mechanism assumes the inhibition of trophic supply in the residual tumor during the concomitant wound healing after incomplete resection, reparation of non-malignant cells injured sublethally by cytotoxic agents, supply the enormously high fetus growth and other processes, which consume the naturally limited proliferating resource of lymphocytopenia of the host. The simple competitive scheme explains described cases of SR and some other obscure clinical phenomena such as the positive results of total body irradiation of cancer patients with low, non-tumoroidal doses as well, as cytotoxic chemotherapy at large [79], or radiation hormesis [96,112,113].

In light of the ability of sublethally injured non-malignant tissues to compete with the tumor for the regenerative resource of circulating feeding (trophic) cells of bone marrow origin, the possible mode of tumor control could look like a crazy fantasy. For example, it could be the bone fracture followed by long-term slight mechanical stretching of the broken ends to delay the knit-like structure, as used to be done for surgical lengthening of bone with the cosmetic aim. Some other mechanical provocations of morphogenesis are known for either restriction of tumor development [114] or for improvement feeding of liver graft inside the holistic system called homeostasis [28]. Accordingly, any artificial activity aside tumor without specific cytotoxic properties can indirectly control the growth of cancer via provoking renewing processes in non-malignant tissues. But the regular therapeutic benefit is possible presumably in conditional phase 1 of lymphopoiesis, as the drug treatment results in a tumor burden debulking matched with mild cachexia [115]. High resting energy expenditure in cancer patients due to hypermetabolism and repeated courses of cytotoxic treatment both increase the consumption of limited morphogenesis resource and exhausts it faster in comparing with physiological growth only. The cachexia in cancer has different grades [116] and is result of exhaustion of morphogenesis processes that confirmed by loss of body weight and lowest median of overall survival [117]. So, in phase 2 of lymphopoiesis exhaustion the successive competitive treatment becomes less probable, if not reversed to negative [87,118]. Pending further developments, we assume that the nature of the SR phenomenon is similar to the exhaustion of lymphopoiesis at successful conventional cytotoxic therapy in phase 1 of lymphocytopenia. However, the probability of SR registration is much lower because it arises presumably in phase 2 of lymphopoiesis when the probability of competitive mechanism realization is very low or questionable as well.

Conclusion

The comparing of clinical cancer features in alternative terms of immunity or morphogenesis leads to recognition of the trophic contribution of hematopoietic cells into tumor development. Replacement of the immune pathogenesis of cancer on a feeding one eliminates global discrepancies described in the introduction and elucidates the questions, why circulating cells of the host take part in the creation of microvessels of malignant tissue, ignoring their supposed allogenic, and how cancer may “deceive” the host. This alternative is in agreement with bone marrow's potency to produce circulating subsets, which are committed to supporting regenerative processes in both non-malignant and malignant tissues. As tumor progression consumes an extra -number of such circulating cells, the hematopoiesis of the host becomes more intensive first and exhausted secondly. Therapeutic myelosuppression is the cause for indirect retardation of tumor progression at early stages only but becomes a threat to life later. That is the reason for the adaptation of cytotoxic therapy for a personal clonogenic resource of the hematopoietic system of a patient.

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