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Cancer Uses the Common Morphogenesis Source of the Host

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Abstract

Trophic properties of hematopoietic stem cells can influence the malignant growth alternatively to immune control. The annual growth of the body mass by age in adult populations of welfare countries used as the most common criterion of metabolic and proliferative tissue activity, and these data compared with death' rate for malignant and somatic diseases in different age-groups of the same countries. The rate of physiologic involution of different cell populations in the lymphoid lineage by age also involved in correlations between the above parameters. A decrease in death rate for cancer and increase it's for non-malignant diseases found in 60+ populations, which have the lowest physiological temp of renewal of lymphocytes number and mass of the body. The lack of both the thymus gland volume and proliferative activity of naive lymphocytes reduces physiological body mass renewal as well as the cancer death rate but enhances somatic death rate, opposing to anticancer immunity at large. A protumor character of the lymphopoietic system's relation with malignancy seems more realistic than defending one.

Keywords

Rate of Death, Body Weight, Cancer, Non-Cancer Diseases, Age, Limphocytopoiesis, Moprphogenesis, Survival, Populations

1. Introduction

Though cancer-immune model has reached 12 types of immune cells, 13 types of cytokines, and 107 interaction links nowadays, the complexity of the model considers underestimated yet [1] [2], partly because the practical input of immuno-oncology is scanty. As for autonomous cancer immunotherapy, endless attempts at the clinical level remain just promising until now [3]. During the long

dominated story of the doctrine of immune defense against cancer, it has been ignoring numerous pro-tumor phenomena or finds additional arguments for immune defense inconsistency via sophisticated ad-hocs. The suppressor-helper cell antagonism, regulatory cells, immunoediting, an escape a tumor by deceiving of immunity, the assumption that cytotoxic chemotherapeutic agents, as well as radiotherapy, are stimulators of the anticancer immune system and on belong to them [4].

One of the main obscure phenomena is a reduce in the prevalence, incidence, and mortality rates of cancer at an advanced age [5] [6] when the risk of frailty and disability begins to increase rapidly [7], and the immunity at 60+ age cannot be more effective than at youngers [8]. A decrease in fat-free mass and an increase in percent body fat with the aging of healthy subjects [9] also are associated with alterations in lymphoid tissue architecture and detrimental effect on immunity [10]. Nevertheless, the average world cancer prevalence increases from 27.6% among 15 - 49 olds to 41.7% among 50 - 69 olds but declines to 23.8% among 70+ olds, covering a period 1990-2017 [11]. Thus, an association of advanced age with preventable chronic conditions, avoidable exposures, and modifiable health habits that are causally associated with cancer, are the only vague arguments for an age-related weakening of cancer activity [6].

The increasing risk of cancer at the start of the adult age and then decreasing it slightly up to death [5] [6] has never been discussing as a result of the parallel natural tissue renewal in the growing and aging organism. However, bone marrow has a unique capability to proliferate and differentiate into unspecified lineage of all types of cells of the body and its transplantation has increased health span and life-span and showed great potential towards the recovery from age-related diseases. With advancing age, bone marrow and stem cells are inefficient to maintain the homeostasis for the delivery of new cells, because of alterations in bone marrow [12].

The changes in mean body weight (BW) are the simplest and most reliable parameter of the current metabolic energy' state of an integrative renewing tissue in organism [13] [14] In the review, we compared together with the body weight, the cancer death rate, the death rate for non-malignant diseases, and lymphopoiesis by age and sex for human populations of countries with well socio-economy conditions, using complete and modern databases to provide most general conclusions for starting. We chose for investigating the open statistics for UK and US since the income' range between these countries is typical for Canada, Australia, Iceland Germany, Netherland, Denmark, Finland, France, and Ireland, according to data in [11].

The average physiological body weight, death' rates for all malignant and all non-malignant somatic diseases were extracted from an openly accessible national database of US, UK, and Germany by age as starting sources for further analysis, together with chosen published date for age-dependency of physiological lymphopoiesis in human. The basal method of analysis of generated curves was their exponential approximation inside age periods under statistical control

of maximal validity by Excel program. Each part of the curve described by the exponential equation: $S = Ae^{\lambda t}$, where S is the current value, t is elapsed time in years, A is the initial value at $t = 0$, and λ is the constant exponential rate of changes per year for the given period It (λ) can be positive (+) or negative (¬). It was suitable for comparing periods because λ-value is independent of value A and is constant throughout of whole period. The maximal coefficient of determination R^2 used for the goodness of fitting of the function to the data. The p-value for $R \pm mR$ calculated according to the equation for Student's t-test [15]:

$$t = R^2 \times (n-2) \times (1-R^2) \quad (1)$$

2. Natural Tissue Growth and Lymphopoiesis

Phisiological body wight [16] [17], probability of survival [18], and basic metabolic rate (BMR) [19] present by age and sex in **Figure 1**.

After speed growth of the young's body (left ascendant line on **Figure 1**) with highest exponential growth rate $\lambda = 0.114$ for young males and 0.107 per year for young females [20] [21], the growth first slows down (λ_1 = 0.0045, 0.0046, 0.0028, 0.0026) and then it changes to loss (λ_2 = ¬0.005, ¬0.006, ¬0.008, ¬0.005). The dynamic of mean BW by age, similar to that on **Figure 1**, we calculated for the Germany population too, using data extracted from [20]. The rise and decline of mean BW exponential rate (λ) were 0.0035 and ¬0.005 for adult males, and 0.0032 and ¬0.004 per year for adult females (not shown).

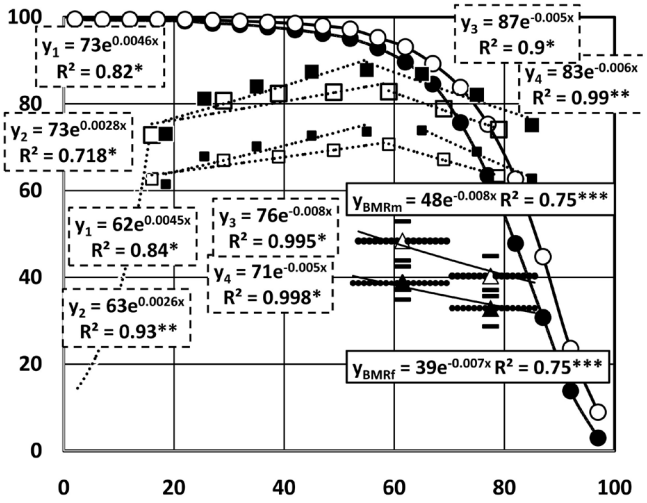

Figure 1. Mean BW (kg, dotted lines), survival (%, solid lines), and basal metabolic rate (BMR, kj/min × 10, solid lines) by age and sex. Abscissa: age, years; Ordinate: survival, %; body weight, kg; basic metabolic rate BMR, kj/min × 10; Circles-survival for England and Wails population. Squares-mean BW: big—for the US, small—for UK. Triangles—BMR for 139 French and Italian volunteers. Black symbols-male, white-female. Equations for BMR are in solid boxes, equations for BW are in dotted boxes. Equations $y = Ae^{\lambda x}$, where y are BMR or BW. A is y at the start of the age-periods (period 1: from 16 - 19 to 55 - 59 years old; p2: from 55 - 59 to 80 - 85 years old). λ is an exponential rate, per year. x is age, year. Probability p ≤ 0.05, ≤0.01, and ≤0.001 marks with asterisks *, **, and ***correspondently.

The highest exponential growth rate for young males and females, according to [20] [21], correspond to speed body weight growth from ≈2 kg to 73 - 60 kg.

This speed growth of the young accompanies by speed waist of a thymus size and basal metabolism after their short overshoot to 2 - 4 years age [22]. The decline of thymus size is titled lymphoid type of postnatal growth of the organs of human body because only lymphoid tissue reveals involution during adolescence. This unique lymphoid tissue involution and concomitant fast increasing in wight of the fat-free body during adolescence might be considered as result of lymphopoietic resource' consumption for growth of the other tissues. The highest basal metabolism and the highest rate of its followed spending $\lambda = \neg 0.016$ and ¬0.023 for boys and girls [23] confirm such opportunity. In oppose, the cells of the adult body reproduce themselves for a while as necessary to substitute the defective or dying cells during 17 - 55/60 years and then stop gradually growing and dividing in 60+ old in parallel with basal metabolism' decline with $\lambda = \neg 0.003$ per year for males and females, that is much slower than in a growing young's [23].

The described regularities are compared with age-dependent lymphopoiesis. The human longevity depends on lymphopoietic system injury, according to classic radiobiologic term—hematopoietic syndrome [24] [25] [26] [27]. **Figure 2** shows a natural age-dependence of the main lymphopoietic features for cell immunity of healthy people both combined sexes.

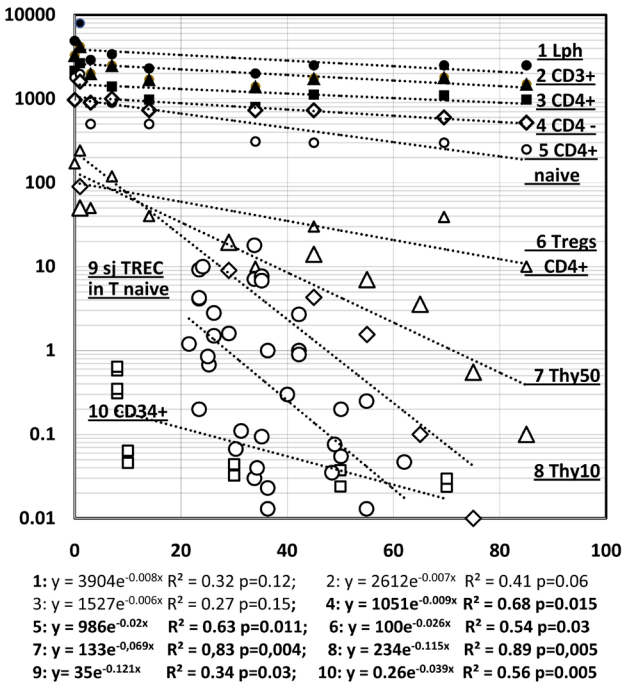

Figure 2. Exponential decline of humans lymphopoiesis parameters (y) by natural age (x), according to the equation: $y = Ae^{-\lambda x}$. Data for curves 1 - 6 extracted from [28]. Data for size of solid thymic glands both types: with ≥50% (curve 7) and ≥90% of active parenchyma (curve 8) extracted from [29]. Data for sjTREC molecules number per naïve T cell extracted from [30]. Data for CD34 + HSC per 1 ml of BM extracted from [31] and [32].

Figure 2 confirms a pillar of biology "Hayflick limit". According it a germ, stem, somatic, and cancer cells have individual replicative and reparative limits [33] [34]. Rates of declining per year, ¬λ, for total lymphocytes (1-Lph), total T-lymphocytes (2-CD3+), and total CD4+ lymphocytes (3-CD4+) are lowest and not significant (black symbols in Figure 2). They cannot represent longevity directly. Significant declining rates ¬λ (white symbols) increase as a range: ¬0.009 for total CD4 negative (curve 4, p = 0.015), ¬0.02 for CD4+ naive (curve 5, p = 0.011), ¬0.026 for CD4+ Treg (curve 6, p = 0.03), ¬0.039 for CD34+ hematopoietic stem cells (HSC, curve 10, p = 0.005), ¬0.069 for thymus volume with fat ≤ 50% (curve 7, p = 0.004), ¬0.094 for thymus volume with fat ≤ 10% (p = 0.006) and ¬0.121 for number of sjTREC molecules in naive T cells (curve 9, p = 0.008).

Figure 2 shows the most specific influence of the naïve lymphocytes in BM and thymus (curves 7 and 8) and molecular witness of their proliferation-circularized DNA elements (sjTREC) [35]—on age. These cells originate in BM, migrate in blood and thymus during intensive growth of the body mass up to 17 - 18 age. Comparison of Figure 1 and Figure 2 identifies young lymphoid descendant of HSC as the most responsible cells for natural viability. During the period from 18 to 60 age, the thymus has involuted completely, providing slow BW growth 10 - 12 kg only at the lowest exponential growth rates λ = 0.0026 - 0.0046 per year (Figure 1). The final period of life 60+ accompanied with scanty generation of TdT+ lymphoid stem cells in BM only [36]. This deficit accompanies by loss of the BW (with negative λ) and accelerated loss of survival with λ = ¬0.1 (males) and ¬0.06 (females) in comparing with ¬0.0001 and ¬0.0008 before 60+ age. More than 90% death of the population aged 60+ (Figure 1) associate with a deficit of T reg cells as well, as HSC and naïve lymphoid cells (Figure 2), and the association points on their universal property to promote the regeneration of different tissue.

That function of lymphoid cells is defined earlier as morphogenic/trophic/feeding property. It associates partly with the marker of lymphoid stem cells-terminal deoxynucleotidyl transferase (TdT). This Na-dependent enzyme, in extracellular media, polymerizes free deoxynucleotides into oligonucleotides. The TdT appears in the media by apoptosis of young lymphocytes and facilitates the DNA reparation/regeneration' processes by nonsense-DNA fragments, produced by the enzyme. They re-utilize by target cells via pinocytosis much easy than single deoxynucleotides charged negatively [37] [38] [39]. Later the TdT enzyme discussed as one of three markers for the lymphoblasts, namely CD34 and CD133 markers [40], and as a component of proliferation in different tissues [41] [42]. The TREC and TdT enzyme both marks newly generated thymocytes in the cortex of the thymus gland [43], and part of these cells have a CD31 marker [43] that is typical for angiogenic properties [45]. Their deficit reduced angiogenesis and suggested as a probable reason for tumorigenesis inhibition by age [5]. This suggestion is in concordance with higher survival patients with lower presence of vascular endothelial growth factor (VEGF) in a growing tumor of early stages T1-2 [46]. The young lymphoid descendants may be committed

(aimed) also toward injured tissues needed for reparation [47] [48]. The specificity of lymphopoietic lineage of feeding elements (curves 7, 8, and 9) accentuates by their speeder decline in comparison with the multilineage ancestor CD34+ HSC (curve 10). Thus, the strong suppression in the progenitor pool of lymphocytes and a moderate decrease in a bulk cells number discredit the remodeling matured CD4+ and CD4− cells as an only reason the weakening of tumorigenesis in advanced age supposed by [5]. The small size cells with surface markers CD133+, CD34+ have a real stem nature and a lymphocyte-like appearanceas well as their descendants. The presence of more young, smallest embryonic-like stem cells (VSELs) in adult tissues and their morphogenic properties is a substantial challenge also to the dominated dogma of cellular immune defense from cancer [49].

3. Is the Age-Dependent Exhaustion of an Immunity Protumor or Anti-Tumor?

Figure 3 compares how a deficit of feeding cells influence the mortality rate from cancer and somatic diseases in 60+ populations. Data for Figure 3 extracted from United States Cancer Statistics 1999-2015 [50], UK Cancer Statistics 2015-2017 [51], United States National Center of Health Statistics 1999-2015 [52] and Dataset Deaths registered in England and Wales 2009-2018 [53].

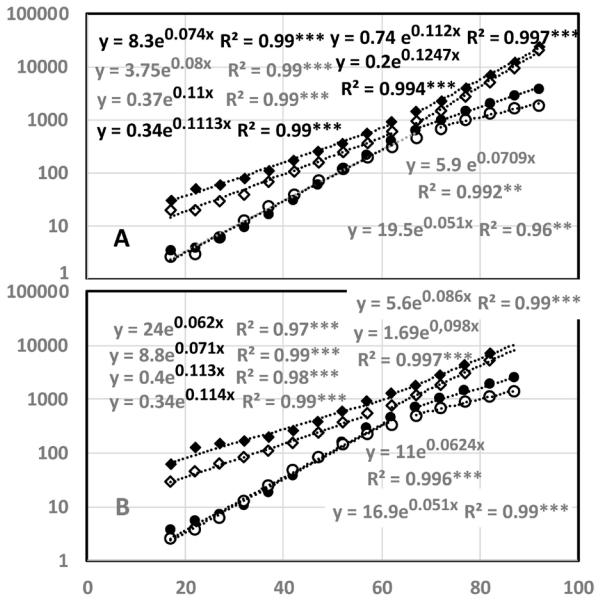

Figure 3. Rate of death (per 10^5 persons) for cancer and non-cancer diseases in the population of UK (A) and white population of US (B) by age and sex. Ordinate: rate of death per10^5persons. Abscissa: age, year; Rhombuses-non-malignant diseases. Circles-cancer; Black symbols-male and white symbols-females. Dotted lines correspond to equations $y = Ae^{\lambda x}$, where y is a rate of death per 10^5, λ-exponential rate, per year; x-age, year; A-the value of y at the start of each of two age-periods: the first from 16 - 19 to 62 - 65 and the second from 65 to 80 - 85 years old. The equations for the 16 - 65 period are in the left vertical columns, and these for period 65+ are in the right vertical columns. Each vertical range of equations corresponds to positions of the dotted line.

The changes in rates of death from cancer and non-cancer diseases are opposite in the same period of age for adults 55 - 62 years and more. They reflect a deficit of protumor activity of lymphopoiesis due to its physiological weakening rather than the popular of enhancing antitumor immunity expected traditionally. The increasing the death rate λ of all diseases from 0.062 - 0.080 to 0.086 - 0.125 per year after 60 age contradicts any enhance of immunity but agrees with the weakening of trophic function unmatured lymphoid cells toward both malignant and physiological tissue renewal. The concomitant reduction of the cancer death rate λ from 0.11 to 0.051 - 0.071 per year in 60 + populations proofs the trophic dependence of cancer activity from lymphopoietic function.

In view of this, we investigated more carefully whether the features of lymphopoiesis decline monotonously by age in adults, or accelerate the negative rate at some critical age point, like a body mass growth. The original data **Figure 2**, being transformed by sex, showed the bright age period 40 - 60 years, where the loss of lymphopoiesis accelerates nine times for females and three times for males, on average (**Figure 4**).

The fifth time's speed of declining of a loss CD34+ cells number per mkl of blood found in people both sexes, namely λ was ¬0/003 per year before 50 age, and later up to 80 age λ = ¬0.014 per year correspondently [54]. The similar increase in the rate of loss for HSC' subpopulations CD34+/CD133+, CD34+/CXCR4+,

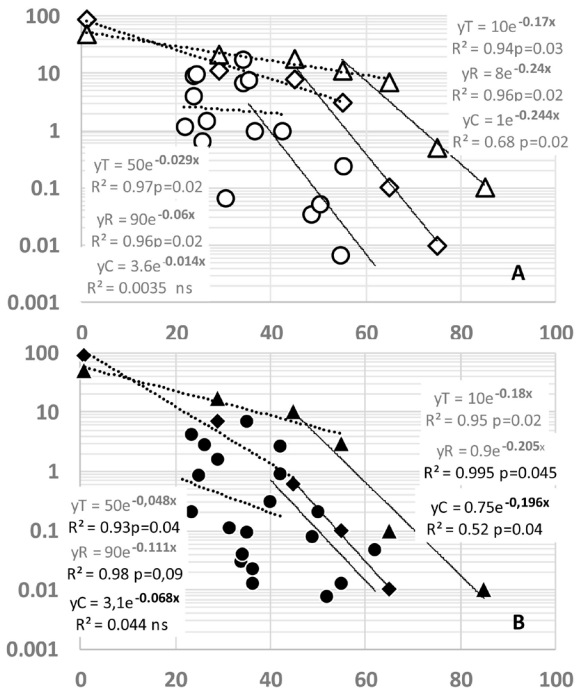

Figure 4. Two Exponential rates of lymphopoiesis exhaustion by age and sex. Whyte symbols-female; Black symbols-males. Size of solid thymic glands, %: with ≥50% of active parenchyma—triangles; with ≥90% of active parenchyma—rhombuses. The number of sjTREC molecules per naïve T cell-circles. Letters T, R, and C in the equations mean triangles, rhombuses, and circles. Equations in the left column—for dotted lines; right column—for solid lines.

and CD34+/CD133+/CXCR4+ with age registered later [55]. Simultaneously, a percentage of death from heart and cerebrovascular diseases among all non-cancer increases fifth times from 40 to 60 age, whereas the average percentage from 20 to 40 age did not change [56]. A six-seven times reduction of the average percentage of VSEL (very small embryonic-like) CD133+ stem cells in epicardium and endocardium of the heart was in people 40 - 60 age vs. 20 - 40 age. Transplantation of these cells after acute and chronic myocardial infarction demonstrated their therapeutic potential [57]. It was consistent with last world statistic. For example, in 2017 the cancer was a course of death for 1.05, 3.96 and 4.43 million of people in age groups 15 - 49, 50 - 69 and 70+, whereas the 2.36, 8.08 and 17.42 million died from non-malignant pathologies, including cardiovascular, respiratory, kidney digestive, diarrheal diseases, and lower respiratory infections [58]. A deficit of common morphogenic resource presented by angiogenic HSC and young lymphocytes seems to be the most logical reason for six-time reduction of world cancer death together with slight-in one and sixth tenths time-enhance of non-cancer death after 69 age. Relative excessive risks of cancer incidence and cancer mortality for a cohort of Russian Chernobyl emergency workers with mean age 33.9 years, at entry into the zone of recovery operations increased to 51 years old but to 59 years old mortality has lowered though the incidence continued to rise [59]. Thus, the best available justification for the sharp turn of curves in **Figure 3** is an abrupt deficit of lymphatic lineage of hematopoiesis between 40 - 60 age.

4. Discussion

Figure 5 summarizes the presented data.

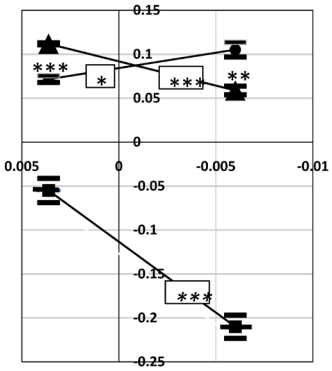

Figure 5. The relation of the bodyweight changes, the changes of malignant/non-malignant death rates, and the changes of lymphopoietic resources in adults by age. Abscissa: average exponential rate λ of the body mass during its evolution (left) and involution (right), per year. (Source: **Figure 1**). Ordinate: Average exponential rates λ of the death rate for malignant (triangles, source **Figure 3**), non-malignant diseases (circles, source **Figure 3**), and λ of an aggregate cumulative overall index of lymphopoietic resource (ILR, squares, source-**Figure 2**). ILR = average λ for the thymus sizes and sjTREC molecules. Bars-standard errors. Asterix: *p ≤ 0.05, **p ≤ 0.01, and ***p ≤ 0.001. Asterix in boxes—for p inside a parameter, without boxes—for p between parameters. All points are the average for white males and females according to US and UK national statistics.

Data in **Figure 5** show the reduction of cancer mortality (triangles) in parallel with natural decreasing both tissue growth (abscissa) and lymphopoietic activity (squares) in the host's body by age of adults. Oppositely, non-malignant somatic mortality increases simultaneously in population. Thus, the lymphopoiesis prevents the non-malignant pathology but provides both cancer and physiologic morphogenesis. Data argued the identity of the feeding influence of lymphopoiesis on malignant growths and the physiological renewing of somatic tissues of the host without the need to involve immunity for an explanation. This vision agreeable with the perception of cancer development like a developing embryo. To recognize the immune defense paradigm insufficient would be quite logical if malignancy were a tissue used all growth resources of a host organism, as a tissue of fetus and childish teen body do during maximal reproductive potency of the thymic gland [60]. This proposal does not compromise the leading role of lymphopoiesis in providing all regenerative and cell' renewal processes in tissues with any genesis. Commonly, the morphogenic function of HSC has been widely discussing applying to somatic non-malignant tissues [48] [57] [61], but rare to malignant tissues growth [24] [47] [62] [63] [64] because of domination of immune defense dogma. Even simple bone marrow transplantation has increased health span and life-span, recovering from some age-related diseases, confirming the ability hematopoietic stem cells to support not immunity only but the different tissue renewal also. At the same time, the recurrent malignancy and secondary cancers consider as a leading cause of the late mortality after curative treatment with hematopoietic cell transplantation [65]. The irradiated dogs with normal hematopoiesis in comparison with those who had weakened function lived longer and generated more cancers or benign tumors during the first two-thirds of life. But dogs with limited hematopoietic function shoved relatively much more hematoblastoses during the same time [66]. The decrease in the rate of cancer death after 60 natural age (**Figure 3**) would be unexplainable if the activation of cancer after BM transplantation were due to the weakening of immune defense, as it is usually explained. Thus, our analysis shows/points on the dependence of both non-malignant and malignant tissues growth from the morphogenic function of young lymphocytes during the senescence of the host. Then, the generally harmful exhaustion of lymphopoiesis might be considered an anticarcinogen in the elderly. All kinds of systemic cytotoxic therapy of cancer have been doing the same by decades. The permitted -moderate-level of induced lymphopenia during cancer treatment 0.8 - 0.5 × 10^9/L [67] is comparable with that typical for acute radiation sickness grade 2 after exposure with doses 2 - 4 Sv, which is not guaranteed the fair prognosis even for healthy people [27] [68]. Moreover, basing on this similarity, we grounded the competition of cancer and host tissues for the trophic resource of lymphopoiesis, limited naturally. On this modern base, we proposed earlier new principles of competitive cancer therapy with conventional cytotoxic agents, explanation of cancer cachexia, and the matter of coming resistance of cancer to cytotoxic treatment [69].

5. Conclusion

Thus, a protumor character of the lymphopoietic system's relation with malignancy seems more realistic than defending one. We did not find reasons for supporting the stimulation of anticancer immunity by any cytotoxic treatment, including long time metronomic therapy with low doses of anticancer drugs, as argued by Calabrese EJ and followers [70]. Analysis of the phenomenon of radiation hormesis showed that it does not disprove a linear hypothesis, being a result of redirection of morphogenic potency of the host from cancer tissue' growth to reparation/regeneration of the multitude of sub-lethal injures in non-malignant tissues of the body [71]. Giving low doses of cytotoxic chemotherapy may act that indirect way, simulating direct inactivation of cancer cells due to insufficiency of tumor endothelial net renewal [72]. We support the actuality of the changing paradigm of tumor response to different kinds of cytotoxic agent also [72] [73]. With this review, we try to initiate the discussion, should the immune doctrine in oncology continue to elongate an endless range of new mechanisms at cellular and molecular levels, or attempt to re-evaluate and subdue them to general physiological phenomena at the level of the whole organism of the host.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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