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Special Article – Spontaneous Remission

Spontaneous Remission of Cancer and Wounds Healing

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Abstract

The associativity of the spontaneous cancer remission with surgical trauma is considering in term of the competition of healing process outside the tumor for circulating morphogenic cells, providing proliferation in any tissues with high cells renewing, malignant preferably. The proposed competitive mechanism of Spontaneous cancer Remission phenomenon (SR) assumes the partial distraction the trophic supply from tumor to offside tissues priorities, like extremely high fetus growth, wound healing after incomplete resection, fight with infections, reparation of a multitude of non-malignant cells injured sub lethally by cytotoxic agents, and other kinds of an extra-consumption the host lymphopoietic resource mainly in the conditions of its current deficit. The definition of a reduction of tumor morphogenesis discusses as preferable instead of the activation of anticancer immunity. Pending further developments, it assumes that the nature of the SR phenomenon is similar to the rough exhaustion of lymphopoiesis at conventional cytotoxic therapy. The main task for future investigations for more reproducible SR is to elucidate of the phase of a cyclic lymphopoietic process that is optimal for surgery outside the tumor as well as for other activities, provoked morphogenesis in surrounding tissues.

Keywords: Spontaneous remission; Cancer; Surgery lymphocytes; Feeder cells; Morphogenesis; Lymphopoiesis

Abbreviation

SR: Spontaneous Remission; GR: Growth/Repair factors; HIV: Human Immunodeficiency Virus; TDT: Terminal Deoxynucleotidyl Transferase (marker of lymphoid stem cells); HSC: Hematopoietic Stem Cells; CD34: Marker of Hematopoietic Stem Cells

Introduction

An explanation of the majority of cancer problem consists of sophisticated schemes of cells immunity that are ignoring the current state of lymphopoiesis as the system at large. This trend creates many contradictions at the level of the path physiology of malignant growth and its treatment [1]. Partially, the long-term follow up studies confirm a decrease of an incidence, mortality, and prevalence of cancer in older people [2], as well as a trend toward cancer' spontaneous remission in adulthood [3] in parallel with decreasing immunity by age. However, conventional surgery, chemotherapy, radiation therapy are generally ineffective at both advanced age and advanced cancer, and these patients need some non-aggressive end-of-life care [4,5]. In this mini-review, we discuss the unclear Spontaneous Regression/Remission (SR) of cancer as a path physiological phenomenon perspective for the development of a precisive therapy of cancer patients with a terminal status of health and argue new, non-immunological explanation of SR.

Two separate regenerative processes can compete for morphogenic/feeding/trophic resource of lymphopoiesis at its deficit.

Recently some authors consider cancer as a persistent wound, which provokes gene activation to heal itself via recruited circulating cells secreted the Growth/Repair factors (GR) [6,7]. Residual cancer, after surgery inside the tumor during the curable phase of the process, progresses [8,9], proving its growths analogy with wound healing. But proposal to cure cancer with an excess of GR [7] is illogical because an excess cancer incidence and excess cancer mortality among individuals are inverse to age, being 9-4 fold higher at age 16 in comparing with advanced age 80 [10], where tissue growth near to minimal. In oppose to immune defence against cancer, conventional chemotherapy and radiation therapy are effective mostly when they provoke myelosuppression manifested by lymphocytopenia and aging of patients [1]. These data have confirmed again that the main factor of weakening of cancer activity is an age-dependent reducing both lymphopoiesis and related to it morphogenesis. Weak lymphopoiesis accompanies SR phenomenon also.

A rare (1:60000 or 1:100000) 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 is seen sporadically in every type of cancer of large volume accompanied by immune paralysis. Immunologists explain it that once, the paralyzed immune system would readjust itself and remove malignant growth. The expected spontaneous readjusting of anti-cancer immunity seems questionable at conditions of an advanced deadly disease with exhausted lymphopoiesis treated by cytotoxic agents many times already. Moreover, the SR phenomenon has multiple reasons. It notes at concomitant severe local infection with streptococci, measles, viral hepatitis, herpes zoster or chickenpox, during peritonitis, pneumonia, myocardial infarction, artificial graft versus processes, at long-term HIV-compromised T-cell immunity, and even the so-called psychoneuroimmunological reactions [11-19]. Around 40 percent of cases of SR can be related to operative trauma at the conditions of deficit of morphogenesis in the host [20]. For cases of SR is possible to see the concomitant surgical components in tissues outside of tumor such as a large resection with blood flow disorders [21], ample excision of abdominal wall, exploratory laparotomy for a

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perforated ulcer with peritonitis [17], colectomy, thoracotomy, bypass surgery with intestine, bowel, hernia, followed by a second surgical exploration, postoperative fever, pneumonia, prolonged healing of postoperative wounds [22]. A SR phenomenon may be a hidden consequence of conservative surgery for histopathological estimation of normal tissue margin around the tumor in the tumor excision specimens. The volume of such conservative activity and its distance from biological margin of cancer seem crucial parameters for reliable SR provocation. They may be the reasons for often equal effectiveness of radical cancer surgery and alternative surgery in which as much as possible of a part or structure is retained [23,24]. The cases of SR noted for non-malignant diseases also [3,25]. All mentioned conditions lead to light amortization of lymphocytopoiesis of different grade.

Presently, there are no doubts that Hematopoietic Stem Cells (HSC) and young lymphocytes can promote cancer growth in their attempt to repair what they perceive as a wound or other tissue injuries including cancer itself [26]. In all such situations, the inflammatory phase of wound healing is initiated with the high infiltration of circulating morphogenic cells at the wound site, including the earliest hematopoietic progenitor γδ T-cells with CD34, Terminal Deoxynucleotidyl Transferase (TDT) markers, angiogenic and regulatory lymphocytes [27-29]. Importantly, the priority in similar morphogenic service belongs to cancer as an embryonic-like tissue in organism [30]. The priority realizes typically via initial attraction the circulating morphogenic cells to the tumor from normally renewing non-malignant tissues with following body weight loss and cachexia. High resting energy expenditure in cancer patients due to both initial hyper metabolism and repeated courses of cytotoxic/ mielosuppressive treatment increase the consumption of limited morphogenesis resource first and then exhausts it faster in comparing with physiological growth only. The cachexia in cancer is a result of the gradual exhaustion of morphogenesis processes [31] that confirmed by loss of body weight and lowering of overall survival [32].

As the physiology of wound healing is similar to that of malignant tissue [6,7,33], the processes of reparation/regeneration outside the tumor could reduce its growth /aggressiveness at the conditions of deficit of lymphopoietic function. In some cases, forced regeneration of non-malignant tissues restricts the vascularisation processes in the residual tumor and results in further SR [34,35]. The survival of patients who had physical trauma after cancer diagnosis was better versus those that had physical trauma before the cancer diagnosis, showing the importance of simultaneousness separate regenerative processes for damping influencing one onto another [36]. Such type influencing is more probable at the condition of deficit of lymphopoietic activity in patients [9]. Different mechanical modulations of morphogenesis are known either for restriction of tumor development [37] or to affect the circulating lymphocytes interaction with injured non-malignant tissues [38]. According to such type of competition, even physiological proliferation at pregnancy can provoke temporary exhaustion of lymphopoiesis followed by SR as it observed for a carcinoid tumor [39]. At the late period of gestation near to delivery, the number of circulating CD34+HSC reduces significantly to half in pregnancies complicated by preeclampsia [40]. Significant long-term maternal breast cancer protection associates with only late pregnancies lasting 34 weeks or longer [41]. Thus, the SR phenomenon relates to extreme proliferation/regeneration of large biomasses of the fetus in parallel to cancer development. In this view, any traumatic activity outside of tumor without specific cytotoxic properties can indirectly control the growth of cancer via provoking renewing processes in non-malignant tissues, such as a spontaneous engraftment of partially separated skin flaps [35]. The expected mode of tumor control in light of this 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 [22].

The simplest explanation of "competitive" relation of non-malignant and malignant growth processes is possible on the base of the morphogenetic function of hematopoietic stem cells and feeding lymphocytes in the condition of their deficit, but not excess. In oppose to cells immunity, the proposed competitive scheme fits at the level of physiological system the described cases of SR and some other obscure clinical phenomena such as the cases of long-term tumor dormancy, exceptional treatment-related survival after total-body irradiation of cancer patients with low, non-tumoricidal doses, as well, as results of cytotoxic chemotherapy [42], or radiation hormesis [43-45]. It seems that the benefit of such competitive kind of treatment is possible mostly at light cachexia [46] with a deficit of lymphopoiesis, but not complete exhausting of the poietic system. The data pointed on the crucial importance of the volume of injured non-malignant tissues for the successful triggering of morphogenic supply from the tumor to the newly induced injuries outside of it. Direct association between the density of lymphoid structures in tumor tissue and late recurrence after surgery [47] prove the dependence biological stage of cancer from its local growth support by feeding lymphocytes, as well as conjugacy of deep dumping of lymphopoiesis after conventional cytotoxic chemotherapy with its benefit [1,48]. However, a precise lymphopoiesis damping is harder to perform during its weakness, where the clinical practice of conventional cytotoxic therapy is not as large as for earlier stages with abundant lymphocytosis [49]. The problem is that weak lymphopoiesis at advanced cancer acts in abnormal symmetric regime with synphase fluctuations both SC production and rate of patient's death [50,51]. It increases the risks of an overdose a weak lymphopoiesis with affected (therapeutic) factor, followed the boost of deadly exhaustion of patient's viability. This is at least one reason for rare SR incidence. Thus, enigmatic lymphocyte aggregates in tumor and peripheral tissues, which arise in response to any form of unspecific, antigen-independent tissue injury, followed by non-resolving inflammation [52] may contribute to the non-immune pathogenic nature of SR and offer a window for further therapeutic interventions.

Conclusion

The competitive mechanism assumes the partial distraction the trophic supply from tumor to offside tissues priorities, like extremely high fetus growth, wound healing after incomplete resection, fight with infections, reparation of a multitude of non-malignant cells injured sub lethally by cytotoxic agents, and other kinds of an extra-consumption the host lymphopoietic resource mainly in the conditions of its current deficit. The definition an activation of anticancer immunity is better to replace on definition a reduction of tumor morphogenesis. Pending further developments, we assume that the nature of the SR phenomenon is similar to the rough

exhaustion of lymphopoiesis at conventional cytotoxic therapy. The main task for future investigations for more reproducible SR is to elucidate of the phase of a cyclic lymphopoietic process that is optimal for surgery outside the tumor as well as for other activities, provoked morphogenesis in surrounding tissues.

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