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Letter to Editor

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Lymphopenia-what is under the term

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Lymphopenia is a simple universal sign of the severity of pathologies like malignancy, somatic diseases, infectious diseases, including COVID 19. It is also a marker for natural tissue mass renewal at pregnancy, postnatal growth, or aging, as well as the toxicity of drugs, irradiation, and other agents that injured health. The dominant interpretation of lymphopenia in terms of immunity is enough for comprehension mentioned topics separately but not united, without contradictions and special reservations for them.

The last of many former controversies is the decrease in cancer death rate per 100,000 population *without* COVID 19 from 2017 to 2019, followed by a rise in 2020, which is the opposite of the 2017-2020's trend of death' rate from non-malignant somatic diseases among this population [1]. Compromised immunity cannot clarify such opposed trends. They rather point to competition malignant and normal tissues for some factors of the common lymphopoietic source of the host.

The second case, lymphopenia in a large population of cancer patients with Covid is associated with higher mortality [2,3], despite the accompanying specific depletion of Treg lymphocytes [4], which have to liberate anti-cancer immunity according to the dominant view on immune function of this cells' subset.

Several basic features of lymphopoiesis may provide a more suitable field for comprehension of the given examples and like these. These features usually become beyond of attention of immunologists because of concern to *unmatured* parts of the lymphocytes' pool.

First, the *trophic* (same as morphogenic/ mitogenic/ angiogenic/ regenerative/ reparative ones) capacity of the circulating unmatured lymphocytes seems more appropriate to solve the two mentioned cases.

Second, lymphopoietic tissues are the most vulnerable of those on which life depends, determining multi-organs syndromes. Organ-specific syndromes (myocardial dysfunction, respiratory symptoms, gastrointestinal symptoms, acute kidney injury, liver cell injury, neurological diseases, dermatological complications) result from the deficit of circulating tissue-committed trophic lymphocytes.

Third, the resource of lymphopoiesis given at the birth, spends during life irreversibly, as fast as renewal/regeneration of tissues demand. Its gradual depletion happens with every act of its natural or artificial tension at an early age with active bone marrow plus thymus, and at an advanced age with rest lymphopoietic function in bone marrow only, changing a regime of cells generation from natural -asymmetric to turbulent- symmetric one. Lymphopenia *seems* reversible, mainly at the early stage of *unidirectional* resource' exhaustion.

In view of this, the mentioned above case one means the increase of morphogenic activity in the *whole* 2020' population for *all* tissues independently of their origin (malignant or normal) [5].

The case second *confirms* the ability of unmatured Treg to participate in the tumor progression by fostering angiogenesis, as it suggested by Zheng X, *et al.* [6]. Indeed, a human "truly naıve" T cells are able to create the new vessels around artificial scaffolds, too far from the bone marrow and thymus [7,8]. They belongs to recent thymic emigrants with markers CD34, TdT and CD31, which are specific for stem, progenitor and immatured Tcells [9-12]. The reality is the progressive loss of lymphopoiesis' capacity to generate these naıve Tcells even with natural increasing age, nothing to say of Covid or cancer.

This short analysis may provide context for researchers to design prospective studies based on the dual function and non-homeostatic nature of T-cells lymphopoiesis.

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