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Cancer is not a guest

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ABSTRACT

In a recent article titled "Embracing Cancer Complexity: Hallmarks of Systemic Disease" published in Cell, Swaton et al. propose the idea of cancer as a guest that develops within a host. They discuss the possible causes and events of neoplastic cell dysregulations within an organism, highlighting events such as cachexia and thrombosis. However, we believe that to understand cancer-associated phenomena better, cancer cannot be considered a guest. In reality, cancer is born, develops, and spreads within its environment. It does not come from outside but instead uses the same system in which it lives to promote its death plan. Indeed, today we know that cancer not only causes local symptoms in the affected organ but also leads to systemic symptoms, which are evidence of inflammation associated with cancer. Inflammation is vital in controlling oncogenesis and neoplastic proliferation during the resistance phase, which is a critical moment for the immune system to demonstrate its effectiveness. However, if the immune system causes immunopathological damage, it may lead to necrosis and eventually to the tolerance phase, which can result in systemic symptoms. Understanding these phenomena thoroughly explains thrombophilia, anemia, sarcopenia, and iron metabolism disruption in advanced-stage neoplastic patients. The concept of the microenvironment takes on a different meaning in this context. The same cells that should oppose cancer in the tolerance phase now participate in a process that self-maintains, favoring the growth of the cancer and its death plan. The exact knowledge of these mechanisms is a more modern translational approach to treating cancer and its related symptoms.

We read with interest the recent article by Swaton et al. [1], *"Embracing cancer complexity: Hallmarks of systemic disease."* This manuscript reintroduces the concept of cancer as a guest who develops within a host and well discusses the possible causes and events of neoplastic cell dysregulations within an organism emphasizing systemic severe cancer-related conditions such as cachexia and thrombosis. In this regard, we would like to highlight that to make the most correct therapeutic choices and better understand cancer-associated phenomena, cancer cannot be considered a guest. According to the dictionary, *"a guest is someone who is invited or hosted by someone else in their home or another place. In ancient times, being a guest was considered a sacred privilege. People would welcome and look after their guests in their homes or countries for a few days"*. In reality, cancer is not a guest; instead, it is born, develops, and spreads within its environment. It does not come from outside but instead uses the same system in which it lives to promote its death plan. The concept of microenvironment needs to be redefined to reflect a different idea. The neoplastic cell moves away for various reasons from the initial project, as well explained in Swaton's manuscript [1]: it undergoes initiation (oncogenesis), growth, and diffusion in an absolutely familiar environment. In reality, he is not a guest but a member of the family who has ceased to comply with the general order of the organism to which he belongs for reasons still not entirely clear. This raises a fundamental philosophical question about the actual connection between cancer and fatality. Limiting the identification of appropriate therapy is possible without recent acquisitions in quantum physics and the links between mind and body [2]. Advancements in quantum physics are revolutionizing medical research, diagnosis, and treatment. Incorporating quantum mechanics into the study of medicine can enable efficient diagnosis before symptoms even appear, aiding in identifying various diseases. By applying mathematical structures that describe the transmission of neurons in the brain and mind at a quantum scale, we can gain a better understanding of the epigenetic mechanisms that may influence the development, spread, and treatment resistance of cancer. In fact, quantum theory may help

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explain subtle DNA changes and even shortened telomeres in cancer patients [2].

After conducting years of research on the causes and development of cancer-related weight loss, known as neoplastic cachexia, we recently decided to write a monograph [3]. This monograph emphasizes the critical role of the immune system and its phases of involvement in the progression of cancer. Understanding the phases of the immune response helps us comprehend not only oncogenesis but also the subsequent systemic symptoms linked to this condition [3]. Today, we know that cancer not only causes local symptoms in the affected organ but also leads to systemic symptoms, which are evidence of inflammation associated with cancer [3]. Inflammation is vital in controlling oncogenesis and neoplastic proliferation during the resistance phase. This is a critical moment for the immune system to demonstrate its effectiveness [4]. However, if the immune system causes immunopathological damage, it may lead to necrosis and eventually to the tolerance phase, which can result in systemic symptoms [3]. During this phase, the macrophages and other myeloid cells, such as neutrophils [5], play a crucial role. They produce cytokines, chemokines, and oxidative stress that not only promote immunosuppression and the growth of neoplastic cells but also cause systemic symptoms [3]. Understanding these "repair" phenomena thoroughly explains thrombophilia, anemia, sarcopenia, and iron metabolism disruption in advanced-stage neoplastic patients [6]. The concept of the microenvironment takes on a different meaning. The same cells that should oppose in the tolerance phase now participate in a process that self-maintains, favoring the growth of the cancer and its death plan. Cancer is primarily caused by various mutations, but it thrives and spreads within the body's own environment. It's not an outsider but rather an internal member who has somehow deviated from the body's natural order, disrupting the survival instinct. The exact reasons why this happens are not yet fully understood. There is a common misconception regarding the Warburg effect, which is believed to be a unique characteristic of cancer cells. However, the metabolic remodulation associated with the Warburg effect is also observed in M1 macrophages, which undergo this process before polarizing to escape death [7]. This suggests that the Warburg effect is not exclusively found in cancer cells, as most people consider it. The immune system is prepared to function effectively through the constant activation of checkpoint systems and the action of non-specific immunity. These systems help the activated immune system avoid developing myeloproliferative and autoimmune diseases. In other words, these pathways, once activated, act as an effector of immunosuppression [4]. It should be noted that cancer uses the same immune checkpoint pathways that the immune system uses to turn off its uncontrolled response, in a manner that is similar to macrophages. Indeed, both cancer cells and macrophages produce the PD-1 ligand.

Attempting to explain the mechanisms that are involved in the pathogenesis of cancer-related cachexia, back in 2000, we showed a strong link between the decline in nutritional status and the level of inflammation [8]. Later on, we conducted several studies using advanced ovarian cancer as a model. As this cancer is typically associated with cachexia, anemia, and thrombophilia, we were able to demonstrate a close correlation between these conditions and the levels of IL6 [9,10]. We conducted a study to define the events that occur in the microenvironment of ovarian carcinoma. Our findings revealed that macrophages in the microenvironment produce not only IL6 but also hepcidin [11]. This process regulates iron metabolism in an autocrine manner, leading to changes in energy metabolism and anemia. Of great importance is the correlation between the level of M1 macrophages and the response to chemotherapy [7]. As the tumor responds to platinum and its derivatives, the inflammation indices and cachexia regress until the patient's clinical conditions are entirely restored [3]. Starting from ovarian carcinoma and the immunopathological damage related to it, our recent review seeks to explain the disproportionate inflammatory reaction that emerged in COVID-19 [12]. The study conducted by Swaton et al. [1]. successfully explains the progression of neoplastic disease up to systemic multiorgan cachexia syndrome. However, we feel that it did not delve much into the contribution of the entire organism of cancer patients toward the symptoms and phenomena associated with this pathology. In light of current knowledge, we believe the term "host" should be eliminated from usage.

CRediT authorship contribution statement

Antonio Macciò: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Clelia Madeddu:** Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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