Immune resilience in response to cancer therapy

Joanina K. Gicobi¹ · Whitney Barham¹ · Haidong Dong¹

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The dynamic relationship between the immune system and cancer has been a topic of interest for decades. In 1909, Paul Ehrlich was the first to propose the hypothesis that host defense may prevent cancers from forming. Lewis Thomas and Frank Burnet later formalized this idea into the “immune surveillance theory,” suggesting that it is the immune system that constantly recognizes and deletes potential cancer cells throughout the body. Dunn and Schreiber then expanded this theory into the framework of “cancer immunoediting,” stating that if mutated cells do make it past the initial immune surveillance, they continue to interact with immune cells, first in equilibrium, and then eventually escaping the immune system’s control altogether to become a true malignancy.

Tumor cells use multiple mechanisms to evade the host immune response such as secretion of immunosuppressive cytokines and recruitment of immunosuppressive cells. In addition, inhibitory molecule signaling and persistent antigen stimulation make tumor-reactive T cells dysfunctional or “exhausted” within the tumor microenvironment (TME). Exhausted T cells seem to abound within tumor tissues, having increased their inhibitory receptors, and decreased their cytokine production, proliferation, and effector molecule expression [1]. By the time a patient presents with a clinically detectable tumor, tumor surveillance has by definition failed and the original, effective, tumor-reactive immune cells can no longer be identified. They have become “invisible” [2].

However, the recent success of immune checkpoint inhibitor (ICI) therapy gives us a unique opportunity to re-visit the concept of “invisibility” of human tumor immunity. ICI therapy uses the patient’s own immunity to find and kill tumor cells, suggesting that there is still immune activity within the host that, if given the chance, can be extremely

effective. Thus, perhaps the invisible anti-tumor immune cells can be both identified and re-stimulated. This then leads to a critical question that remains unanswered with regard to ICI therapy: do checkpoint inhibitors work by resurrecting an immune response from once exhausted T cells? Or by expanding a remnant of effector T cells that never entered the exhausted state, but merely became suppressed and outnumbered? The answer to this question has significant implications for predicting the outcome of treatment, monitoring of clinical response, and for design of future combination therapies.

For many years, we have assumed that clinical responses to ICI therapy were due to successful reinvigoration of the exhausted T cells in tumor tissues [1]. Thus, characterizing exhausted T-cell states has been a major focus of the immunotherapy field. However, recent studies have provided strong evidence that this may not be the full story. Rather than directly rescuing the exhausted T cells, ICI can induce stem-like T cells to produce cytotoxic, effector progenies that can infiltrate the tumor and replace the exhausted cells [3, 4]. Furthermore, ICI can directly expand effector-like T cells that were never exhausted, but remained capable of tumor killing [5]. Therefore, it is possible that ICI therapy-responsive T cells arise from T cells already in a functional state and not only from those that are in a progressive state of exhaustion.

Indeed, effector-like T cells which are responsive to ICI therapy have recently been identified in humans and animal models [6–8]. They are characterized by highly cytotoxic state, proliferative activity, and migrative capacity in the peripheral blood of patients who respond to ICI therapy. They can withstand the pressure of chronic tumor antigen stimulation and TME suppression without becoming exhausted, and importantly, they quickly expand with full cytotoxic function upon ICI therapy [6–8]. Thus, we propose using the term “resilient T cells” (Trs) to describe these cells, highlighting their ability to quickly expand with full cytotoxic function upon ICI therapy and to distinguish them from exhausted T cells. The word “resilience” in Latin means “leaping back”, and describes a state of

✉ Haidong Dong
dong.haidong@mayo.edu

¹ Mayo Clinic College of Medicine and Science, Mayo Clinic, Rochester, MN, USA

being able to withstand or recover quickly from difficult or stressful conditions.

We submit that this new concept of “immune resilience” may help to explain why we have responders and non-responders following ICI therapy. Cancer is a fast-growing disease with rapid proliferation and dynamic evolution. Therefore, if immunotherapy is expanding a population of resilient T cells that are phenotypically primed to be highly proliferative and effective, then the cancer can be conquered and even eliminated (as in responders). However, if these resilient T cells are absent or outnumbered, tumor growth will continue to outpace T-cell activity and the patient will not respond.

This of course leads to many more questions: from where do Trs cells originate? Why do some patients have sufficient Trs, while others do not? It has been shown that the expanded effector T-cell pool is comprised of a diverse and disparate population of T cells even though they may have a common, single naive cell origin and the same TCR [9, 10]. Thus, the resilient T cells may have a transcriptionally distinct state that is controlled either intrinsically or extrinsically and endows these cells with a heightened capacity for long-term survival and resilience. Determining what factors lead to and influence the resilient state will be an important future direction for the field. Furthermore, releasing the anti-tumor power of Trs cells may not be limited to ICI therapy alone; chemotherapy, radiation therapy, and other therapeutic interventions which can induce immunogenic stimulation to Trs cells may also have the potential to induce their expansion.

Fig. 1 A theoretic sphere of cancer immunology and immunotherapy. The dynamic interaction of immune cells (green) and tumor cells (brown) determines the clinical outcome of cancer disease and how it can be re-shaped by cancer immunotherapy

Understanding immune resilience in response to immunotherapy would represent another major advance in human cancer treatment. The importance of this concept may not only be in cancer control, but also in prevention of immune related adverse effects that may be due to the “bounce back” of Trs cells that are self-antigen-specific. Finally, it may also speak to why certain autoimmune conditions fail to “burn out” over time, but instead continue to flare.

In summary, we propose a theoretic sphere of cancer immunology (Fig. 1): the immune surveillance theory describes the importance of immune cells in cancer prevention; cancer immunoediting provides a framework for how the immune system and tumor cells interact during cancer development; and immune resilience provides a new hypothesis for how the immune system responds to cancer immunotherapy.

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