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Review Article (Invited)

A battle between two biological singularities: Immune response vs. cancer

Tomoya Katakai[1], Taku Okazaki[2]

[1] *Department of Immunology, Niigata University Graduate School of Medical and Dental Sciences, Niigata 950-8510, Japan*
[2] *Laboratory of Molecular Immunology, Institute for Quantitative Biosciences, The University of Tokyo, Tokyo, 113-0032, Japan*

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In a post-growth multicellular organism, the phenomenon in which a small number of rare cells can be the starting point for inducing a dramatic change in the entire system is considered a "biological singularity." The immune response and cancer can be regarded as singularity phenomena in mammals, but their nature is fundamentally different. The immune response is considered a "programmed" singularity, whereas cancer is an "unprogrammed" singularity. These two systems perpetually engage in a cycle of attack and defense within the organism. The outcome is depending on the wining system, which determines whether the individual experiences a state resembling light or darkness. However, the overall mechanism of the competition remains unclear and is expected to be elucidated with future innovations in bioimaging technologies. Immune checkpoint blockade therapy is a means by which the two singularity balances can be artificially manipulated; therefore, mechanistic insight is necessary for cancer treatment strategies. Altogether, these findings provide a different perspective crucial for understanding the behavior of dynamic cell populations in multicellular organisms.

Key words: adaptive immune response, antigen, immunosuppressive environment, lymphocytes, tumor

Significance

The adaptive immune response and cancer/tumorigenesis show the properties of "biological singularity." Both systems compete in the body, with the winner manifesting as a singularity. This viewpoint is crucial for prospective live imaging endeavors, aiming to provide a more comprehensive understanding of the intricacies of this phenomenon. Additionally, it holds significance for advancing cancer immunotherapy by deliberately adjusting the equilibrium between the two singularities.

Introduction

Robust homeostasis maintains a relatively stable physiological state [1,2]. However, occasional fluctuations and changes can lead to a considerably different state. Additionally, it is likely to occur in response to strong environmental stresses or pathological conditions. In a multicellular system, the phenomenon in which only a single cell or an extremely small fraction of rare cells triggers a dramatic change in the state of tissues, organs, or even the whole body can be regarded as

Corresponding author: Tomoya Katakai, Department of Immunology, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Chuo-ku, Niigata 950-8510, Japan. ORCID iD: https://orcid.org/0000-0002-4290-7028, e-mail: katakai@med.niigata-u.ac.jp

a “biological singularity” [3]. In mammals, the immune response and cancer are phenomena that fit this criterion. In each case, only one or a small number of cells can proliferate dramatically in a relatively short period and become influential enough to change the entire body system. However, the underlying nature and processes differ, resulting in opposite outcomes.

During the immune response, dramatic changes are triggered by a small number of immune cells to eliminate foreign substances, and the state of the body after the response is not identical to that before [4,5]. Thus, the immune response meets the criteria for a singularity phenomenon and can be called a "programmed singularity" since it follows a predictable course to a certain degree as a “homeostatic” system. In contrast, cancer originates from an accidentally emerging aberrant cell that ignores the rules of the body system and multiplies endlessly, eventually leading to the death of the individual [6,7]. Cancer can be considered an “unprogrammed singularity” because it is uncontrollable and unpredictable in natural systems. A perpetual dynamic interplay exists between these two physiological and pathological systems within the organism, yielding divergent consequences contingent upon the prevailing side. When the immune system prevails, it sustains life; if cancer emerges victorious, it precipitates the cessation of vital processes.

In this paper, we discuss aspects of adaptive immune response and cancer/tumorigenesis as singularity phenomena. The detailed process of competition between the two systems, its significance, and medical interventions are addressed.

Adaptive Immune Response as a “Programmed Singularity”

The immune system, composed of various immune cells, plays a pivotal role in inducing an immune response to eliminate foreign substances and pathogens. The immune system also removes waste products, abnormal substances, and aberrant cells that emerge in the body [8–10]. The adaptive immune response is responsible for forming an immune memory with high specificity to targets, which is initiated when lymphocytes recognize non-self-antigens of foreign substances or pathogens (Figure 1). T cells are a type of lymphocyte-expressing antigen receptor (TCR) that can recognize diverse antigens by changing their structure via genomic recombination and mutation [11]. Thus, as a whole population, lymphocytes can adopt a myriad of repertoires that can recognize virtually any antigen. However, because each

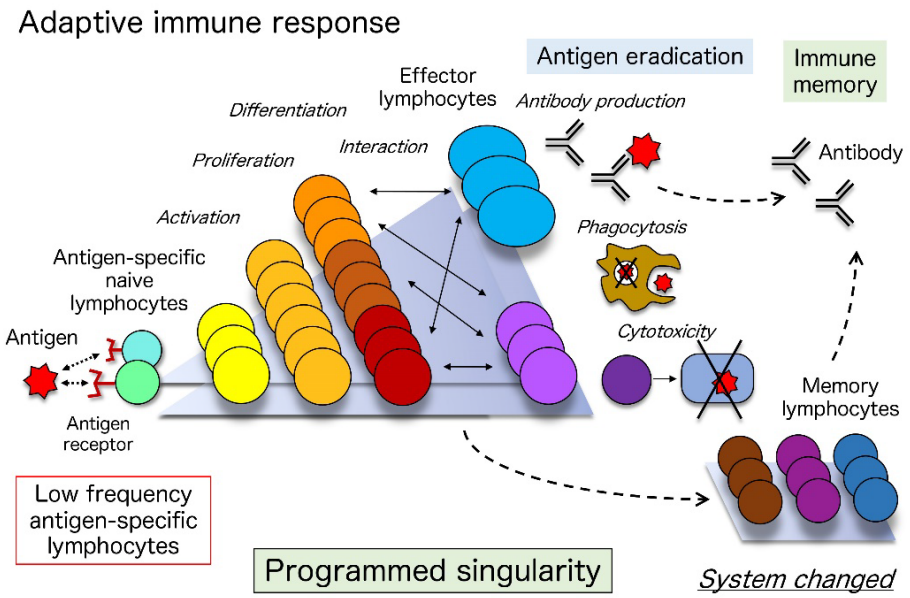

Figure 1 Adaptive immune response as a “programmed singularity.” Induction of adaptive immune response requires antigen recognition by rare antigen-specific lymphocytes. Once activated by the antigen, these rare lymphocytes rapidly proliferate, differentiate into a variety of effector cells, and interact with other effector cells to remove antigens. Effector functions include antibody production, phagocytosis, killing infected cells, among other functions. When the antigen is removed, the number of effector cells decreases as a result of apoptosis; however, a small fraction survives and becomes memory cells to prime for the subsequent entry and encounters with the same antigen. As the memory cells increase in quantity after the first response and become functionally distinct from their naive state, they can respond more rapidly and strongly during the subsequent response. This phenomenon can be termed as “programmed singularity,” as the adaptive immune response is a physiologically pre-determined process.

lymphocyte expresses a TCR with essentially a single antigen specificity, the frequency of T cells specific to a certain antigen is extremely low [12,13]. This implies that of all body lymphocytes, only a few cells must find a specific antigen to initiate an immune response.

In an adaptive immune response, antigen-specific lymphocytes are activated once they recognize a cognate antigen and rapidly proliferate, dramatically increasing their number [14]. This dynamic process occurs over a short period, ranging from a few days to a week. Simultaneously, they differentiate into effector cells with various properties that induce and regulate responses suitable for eliminating foreign substances and pathogens [15,16]. When the antigen is eradicated, the response converges, and most lymphocytes die by apoptosis. However, a small fraction survives as memory cells that can induce a more rapid and stronger response to the same antigen [16,17]. This phenomenon is called "immunity" or immune memory in the context of infectious diseases. Additionally, it elucidates the state wherein an individual who has recovered from an infectious disease is subsequently shielded from experiencing it again or manifests only mild symptoms upon subsequent encounters.

Lymphocytes activated upon antigen recognition, i.e., effector or memory lymphocytes, show completely different properties from "naive" lymphocytes that have never been in contact with cognate antigens [5,16–18]. Moreover, a significant change is observed in terms of acquiring the ability to eliminate certain antigens. This implies that when an adaptive immune response is induced, the state and nature of the entire immune system are primarily altered. Therefore, the adaptive immune response can be regarded as a singularity phenomenon, as rare naive lymphocytes increase dramatically upon contact with target antigens, and the nature of the entire immune system differs from that of the previous one. The immune response can be considered a "programmed singularity" because it is strictly regulated according to certain rules as a physiological response of the body (Figure 1).

Cancer/Tumorigenesis as an "Unprogrammed or Accidental Singularity"

Cancer is composed of aberrant cells derived from normal cells, in which random genetic mutations lead to unusual growth deviations from the control of the multicellular tissue system (Figure 2) [6,7,19]. During proliferation, they accumulate mutations, accelerate abnormalities and malignancies, destroy surrounding normal tissues, and ultimately kill individuals. Cancer cells are thought to arise from various underlying factors, including environmental factors and genetic background [20]. A large cluster of proliferating cancer cells is called a tumor; a certain may retain many of the

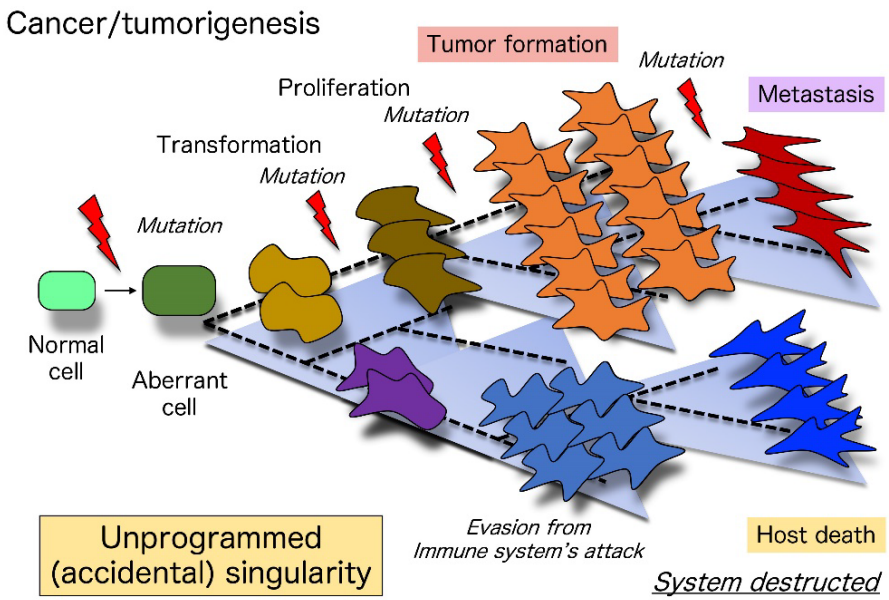

Figure 2 Cancer/tumorigenesis as a "unprogrammed singularity." Cancer occurs as a result of normal cells irreversibly changing to an abnormal state due to genomic mutations. Various stimuli can result in mutations that lead to production of aberrant cells which exhibit uncontrolled growth. Mutations could occur successively leading to the accumulation of changes and eventually forming a large tumor. Metastasis is a serious event, wherein cancer cells move from the primary site to distant secondary sites. This phenomenon can be called "unprogrammed singularity," given that cancer development and tumor formation are accidental and unpredictable processes.

characteristics of the original tissue, whereas others may show completely different characteristics. Accumulating mutations may proceed in a certain direction, reflecting the previous stage. However, mutations likely occur randomly because of genomic instability, making it difficult to predict future alterations [21]. The stochastic progression of such mutations leads to the coexistence of multiple clones within a tumor that have acquired different properties [7,22]. A few clones may acquire metastatic potential and migrate to and settle in other organs, where they proliferate to form metastatic tumors [6,19]. Such competitive selection pressure favors faster growth and more viable (malignant) clones, which is the same principle as the evolution of organisms.

Since normal cells have various safety mechanisms, a single mutation rarely immediately leads to cancer [7,20]. Moreover, the immune system is thought to eliminate abnormal cells in a precancerous stage that may emerge daily in the body [9]. Therefore, the process by which cancer cells circumvent these mechanisms and grow sufficiently until the tumor is assumed to be stochastic and takes a relatively long period. However, once a cancer cell population "evolves" to overcome these restrictions, it accelerates proliferation, accumulates mutations, and destroys the individual body. Cancer begins with a single cellular mutation, and once it exceeds a certain threshold, it accelerates growth and forms malignant tumors that have a profound effect on the host. In this sense, cancer/tumorigenesis is a kind of singularity. However, it can be defined as an "unprogrammed" or "accidental" singularity in terms of being an uncontrolled and unpredictable phenomenon in a natural system (Figure 2).

Attack and Defense between the Adaptive Immune Response and Cancer/Tumorigenesis

The immune system detects and eliminates abnormal mutant cells that emerge daily. This is known as immunosurveillance (Figure 3) [9,23]. Cells in a precancerous aberrant state are first detected and removed by the innate immune system, which operates with low specificity [24,25]. For instance, in epithelial tissues, innate immune cells such as natural killer (NK) cells could directly contact with epithelial cells and detect their aberrant state by some activation receptors for elimination [24,26]. In addition to NK cells, innate lymphoid cells (ILCs) potentially restrict the expansion of transformed cells via secreting several cytokines [27]. In contrast, the adaptive immune system could recognize an altered protein sequence derived from a genetic mutation as "non-self," which triggers an eliminating response [23,28]. The antigenic products of these mutated genes are known as cancer neoantigens. However, they do not always efficiently induce adaptive immune responses [29]. In addition to the small changes in a small number of genes in originally normal autologous cells, these cancer antigens often escape recognition by adaptive immunity due to the subsequent loss of

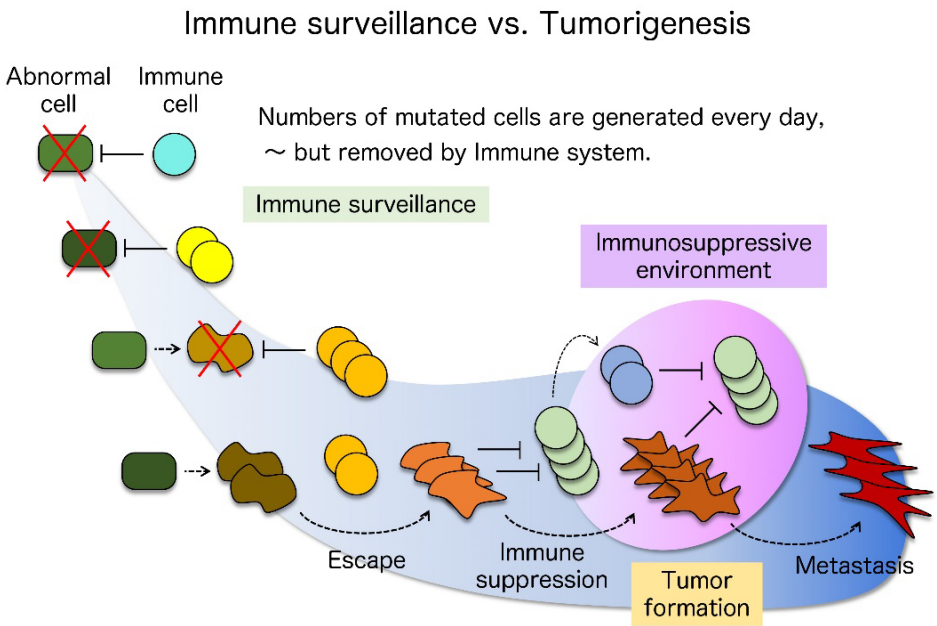

Figure 3 Immune surveillance versus tumorigenesis. Mutated cells are thought to be generated every day; however, immune cells quickly find out and remove them. Even if some aberrant cells emerge, immune cells can efficiently respond to eliminate them. In some rare cases, cancer cells could escape from immune surveillance and acquire the ability to suppress immune response by forming an immunosuppressive environment. Moreover, certain cancer cell clones begin to exhibit metastasizing ability.

expression or abortion of the antigen presentation machinery [30]. In addition, cancer cells frequently acquire the ability to suppress immune responses in various ways [9,23,24]. These, in turn, induce inhibitory subsets of immune cells and construct a defensive environment against cancer (an immunosuppressive environment) [31]. Cancer cells that acquire these abilities can survive and continue to proliferate, leading to tumor manifestations. The tumor, a large abnormal object in the body, could continue to grow without being eliminated because the immune system tolerates the cancer cells.

The relationship between the immune system and cancer is outlined as follows: the two sides continue to play a tug-of-war under the influence of various factors, determining whether a tumor develops. If the immune system eliminates cancer cells in the early stages of development or before tumor formation, they cannot be clinically identified as cancer or tumors. In contrast, if cancer cells evade immune surveillance and establish an immunosuppressive environment, the tumor quickly grows to a catastrophic end. From a broad perspective, this is attack and defense in the preliminary stages of the two singularities. When one becomes dominant and exceeds a threshold, it manifests as a singularity phenomenon; the winning side succeeds as a singularity.

The Process of Anti-cancer Immune Response to the Win of Immune Singularity

The process by which the adaptive immune system detects and responds to cancer neoantigens can be inferred, to a certain extent, from a vast number of previous studies (Figure 4). When cancer cells die for various reasons, antigens are released and captured by dendritic cells (DCs) in the surrounding tissues [31–33]. DCs then enter lymphatic vessels, a vascular system for body fluid recovery, and migrate to the draining lymph nodes. Ingested cancer antigens in DCs are cleaved into short peptides during migration and loaded onto major histocompatibility complex (MHC) molecules on the cell surface [30]. Within the lymph node, DCs further migrate to the paracortical region where large numbers of T cells accumulate and migrate intensely, and contact with T cells one after another, searching for antigen-specific T cells [33]. Therefore, lymph nodes serve as a clever mechanism for increasing the efficiency of rare antigen detection by collecting antigen-bearing DCs and T cells within a confined spatial arrangement.

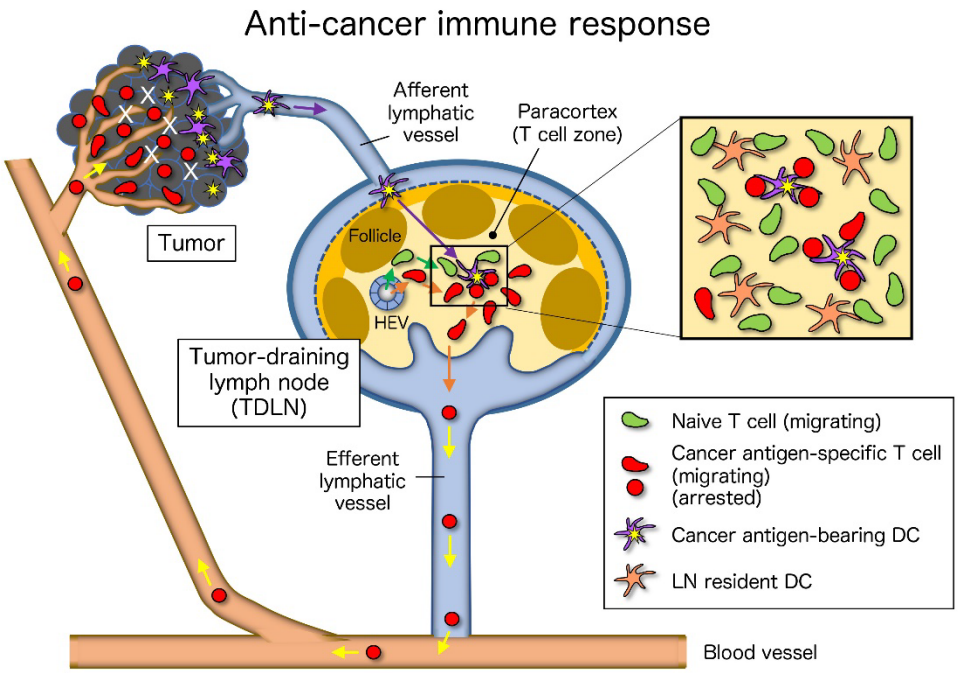

Figure 4 Immune cell trafficking in anti-cancer response. DCs, that internalize cancer antigens in primary tumor, migrate to tumor-draining lymph node (TDLN) via afferent lymphatic vessels. Tumor antigen-bearing DCs reach the TDLN and then enter the paracortical T zone. The naive T cells in the paracortex actively migrate to the interstitial spaces, and when antigen-specific T cells encounter the DCs displaying antigens on MHC, they stop migrating and become arrested on the DC surface. The motility of T cells gets restored when activated with sufficient TCR-dependent signaling. Activated/effector or memory T cells exit the TDLN via the efferent lymphatic vessel and circulate in the bloodstream. Cancer antigen-specific T cells migrate across blood vessels and infiltrate the tumor microenvironment, where the T cells kill tumor cells.

When antigen-specific T cells recognize the antigen peptide/MHC complex present on the DCs, they stop migrating and strongly adhere to the DCs. They then receive signals through TCR and other costimulatory molecules to become activated and begin proliferation [34]. Furthermore, T cells change their properties as they proliferate and differentiate into effector cells that acquire various functions in the immune response. Activated T cells that have increased in number leave the lymph nodes from the efferent lymphatic vessels, eventually return to the blood circulation, and spread throughout the body. A certain effector T cell enters the primary tumor, detecting and destroying cancer cells expressing antigens [23,33]. This process is performed by a T cell subset called cytotoxic (killer) T cells. If the adaptive immune response is strongly induced, cancer cells will be eradicated, or tumors will disappear, leading to the triumph of immune singularity.

Process of Cancer Singularity Winning over Immune Surveillance

The adaptive immune system monitors the entire body with high sensitivity to emerging non-self-antigens or neoplastic antigens. The mechanism by which cancer cells circumvent this strict surveillance and develop tumors remains unclear. However, recent studies have suggested that cancer cells make this possible in part by inducing an "immunosuppressive environment" in which the immune response is inhibited by various mechanisms (Figure 3) [31,35]. The immune system has a variety of safety mechanisms to suppress excessive responses; however, cancer cells take advantage of these mechanisms to create a favorable situation for themselves. Typical examples include attracting or activating regulatory T (Treg) cells and myeloid-derived suppressor cells (MDSCs), which can suppress immune responses [31]. Several factors produced by cancer cells have been implicated in this process. Cancer cells are known to express immunosuppressive cytokines, such as TGF-β and immune regulatory factors called immune checkpoint molecules, such as PD-L1, which may directly suppress the activity of immune cells [36]. Furthermore, cancer cells often lose MHC class I expression, preventing recognition and attack by antigen-specific killer T cells [30]. Under the strong pressure of immune surveillance, cancer cells that have gradually acquired immunosuppressive abilities are selected to survive, proliferate, and develop apparent tumors. In this situation, the cancer singularity wins over the immune system.

Challenges in Understanding the Attack and Defense of the Two Singularities

The scenarios described above are merely conjectures based on the indirect evidence obtained. However, it is unclear whether this happens in vivo and, if so, how it proceeds. An effective way to verify this is to directly observe the actual locations where events occur using live imaging techniques. However, there are a lot of technical obstacles. To comprehensively grasp the dynamic interplay between the adaptive immune response and cancer or tumorigenesis, it is necessary to elucidate both the perspective and intricate details of this enduring phenomenon. However, while most current live imaging techniques excel at observing relatively small areas in a short time, it is difficult to observe a wide area for a long period while maintaining single-cell resolution and covering three-dimensional structures in complex tissues [37,38]. In addition, it is more challenging to capture the moment and site at which cancer cells arise spontaneously. Real-time observation of the daily appearance of cancer cells and the immune attacks against them will require major technological innovations.

Currently, it is still possible to observe a 1–2 cm square area in mice transplanted with cancer cells, including the inoculation site and nearest draining lymph nodes, using a wide-field next-generation imaging system such as AMATERAS [39]. The outstanding hurdles still involve improving the spatial resolution for acquiring three-dimensional information within the tissue as well as the duration over which such resolution can be maintained.

Manipulation of Singularity Balance by Immune Checkpoint Blockade

Identifying immune checkpoint molecules and their clinical applications has opened avenues for deliberate intervention and manipulation in the dynamics of attack and defense associated with the two singularities. Immune checkpoint molecules such as CTLA-4 and PD-1 are negative regulators of the immune response and serve as safety valves that prevent the excessive activation [33,34,40]. Immune checkpoint blockade (ICB) therapy in cancer enhances the overall activity of the immune system by administering inhibitory antibodies against these molecules to block negative regulatory pathways. An augmented response against cancer cells could lead to the regression and elimination of tumors [33,34,40,41]. The restoration of equilibrium through ICB is anticipated, shifting the dominance from the cancer singularity to the immune singularity. This can be characterized as an engineered adjustment of singularity balance (Figure 5). In other words, the ICB modulates the threshold of immune singularity. However, this approach does not selectively enhance the cancer antigen-specific responses, which carry the risk of various adverse effects [42]. Moreover, ICB efficiency is influenced by various factors, such as genetic background and environmental factors, and is often not

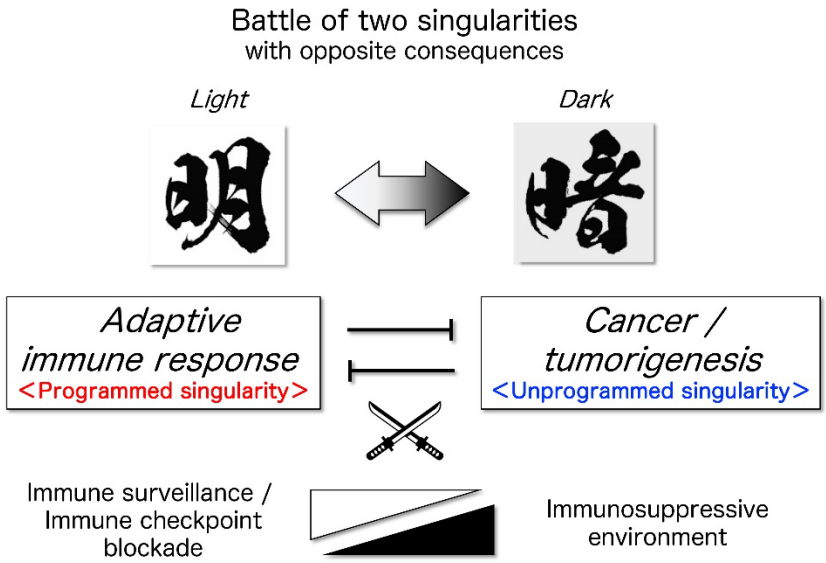

Figure 5 Battle of two singularities. Adaptive immune response behaves as a programmed singularity, while cancer/tumorigenesis shows a property of an unprogrammed or accidental singularity. Two systems constantly engage in a cycle of attack and defense; the immune system constantly works to suppress cancer through immune surveillance, while the cancer cells form an immunosuppressive environment to evade the attack of the immune system. Immune checkpoint blockade alters the balance of power between the two systems in the favor of the immune system side.

as effective as desired in the current situation [40]. In the future, ICB therapy should be improved by considering singularity balance in the local tissue environment.

Conclusions

The interaction between the adaptive immune response and cancer/tumorigenesis represents a dynamic interplay between two singularity phenomena observed in fully developed mammals. This interaction manifests as a tug-of-war, leading to distinct and contrasting outcomes akin to the juxtaposition of light and dark (Figure 5). However, the overall mechanism remains largely unclear, and future innovations in biological imaging technology are anticipated to further clarify it. The balance between the two singularities can be artificially manipulated by ICB therapy, and the underlying principle should be understood in detail as a key concept in therapeutic intervention. These are important perspectives for understanding the extremely dynamic behaviors of cell populations in multicellular organisms.

Conflict of Interest

The authors declare no conflict of financial interest.

Author Contributions

T. K. wrote the manuscript. T. O. provided expertise and edited the manuscript.

Data Availability

The evidence data generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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