Mechanisms of Immune-Checkpoint Blockade Resistance and Cancer Epigenetics

Subjects: Oncology

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Tumor evolution to evade immune surveillance is a hallmark of carcinogenesis, and the modulation of tumor immunogenicity has been a challenge to present therapeutic responses in immunotherapies alone for numerous cancers. By altering the cell phenotype and reshaping the tumor microenvironment, epigenetic modifications enable tumor cells to overcome immune surveillance as a mechanism of cancer progression and immunotherapy resistance. Immune-checkpoint blockade (ICB) therapies targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4/CD152), programmed cell death protein 1 (PD-1/CD279), and programmed death-ligand 1 (PD-L1) have presented unprecedented responses in significant percentages of cancer patients. Even then, efficacy and response rates vary according to cancer types and particular ICB regimens. Researchers have therefore since attempted to find ways to optimize immunotherapy and overcome immune checkpoint inhibitor resistance.

breast cancer epigenetics methylation

1. Introduction

Over the past decade, advancements in immunotherapy as an anticancer therapy have revolutionized patient responsiveness to treatment. To date, immune-checkpoint blockade (ICB) therapies targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4/CD152), programmed cell death protein 1 (PD-1/CD279), and programmed death-ligand 1 (PD-L1) have presented unprecedented responses in significant percentages of cancer patients [1]. Even then, efficacy and response rates vary according to cancer types and particular ICB regimens. Researchers have therefore since attempted to find ways to optimize immunotherapy and overcome immune checkpoint inhibitor resistance. Of note, only a minority of breast cancer patients clinically benefited from ICBs, with a relatively low overall response rate [2].

It is now established that epigenetic dysregulation can be involved in the pathogenesis and development of cancers. Defects in chromatin modifiers have been described in hematological and solid malignancies, where there has been increasing evidence of a correlation between the role of aberrant epigenetics and cancer etiology [3][4][5]. More importantly, the reconfiguration of immune cell chromatin landscapes in conjunction with the extensive modification of tumor cell epigenome can modulate and enhance antitumor immunity or immunotherapy responses to improve overall disease outcomes [6]. In the promising field of new drug discovery in epigenetic enzyme-targeted therapy, extensive research works to date have also demonstrated that histone deacetylases (HDAC) and DNA methyltransferases (DNMT) are druggable targets in cancer therapeutics. Nevertheless, active clinical trial

investigations on histone methyltransferases and lysine demethylase inhibitors are being evaluated as the latest potential group of epi-drugs [7].

2. Mechanisms of Immune-Checkpoint Blockade (ICB) Resistance and Cancer Epigenetics

2.1. Immune-Checkpoint Blockade (ICB) Therapies

Many decades ago in 1968, reactivity seen in isolated lymphocytes from cancer patients against cancer cells gave rise to the potential of cancer immunotherapy [8]. While chemotherapy, radiotherapy, and surgery have long been considered the basis of cancer treatment, the first successful FDA-approved ICB drug in 2011—the anti-CTLA-4 monoclonal antibody ipilimumab [9]—revolutionized immunotherapy as a new pillar of cancer therapy. Contrary to traditional cytotoxic therapies, ICB drugs function to augment durable host immune responses with less toxicity.

Inhibitory immune checkpoints that are well-described include CTLA-4, PD-1, and PD-L1 [10][11]. CTLA-4 molecule is overexpressed on the active T cell surface, preventing excessive T cell receptor (TCR) stimulation via competitive binding with CD28 co-stimulatory receptor, to bind against its ligands (B7-1/CD80, B7-2/CD86). Similarly, PD-1 is upregulated on activated T cells and binds to its PD-L1 ligand—limiting T cell activation. Overall, a specific blockade on the aforementioned molecules sustains anti-tumor responses [10][12]. Years later, other ICB agents targeting PD-1 (nivolumab, pembrozulimab, cemiplimab, dostarlimab) and PD-L1 (atezolizumab, avelumab, durvalumab) were discovered and approved for clinical use against solid malignancies [13][14]. While continual clinical development of ICBs and understanding of tumor immunology show great promise, only a small percentage of patients achieve a response to monotherapy. Hence, further research efforts to optimize immunotherapy options and exploration of new molecules in the application of ICB therapy are required. In particular, the identification of established factors that can influence patient treatment outcomes is necessary as well. One such mechanism is epigenetic remodeling, which is involved and essential in reprogramming enhanced antitumor immune response. Several recent studies have demonstrated that epigenetic modifiers (SETDB1, lysine-specific demethylase 1 (LSD1)) can regulate tumor cell-intrinsic immunity and T-cell exhaustion [15][16][17]—shedding new light on leveraging the potential of epitherapy to specifically improve the effectiveness of immunotherapies.

2.2. Tumor Resistance to Immune Checkpoint Inhibition

A major challenge in ICB therapy is overcoming immune checkpoint inhibitor (ICI) tumor resistance [18]. Clinical progression on ICIs is broadly categorized into (i) primary resistance (irresponsive to checkpoint inhibition), (ii) adaptive resistance (functional antitumor response limited by immunosuppression), and (iii) acquired resistance (initial response followed by eventual disease progression or relapse) [19][20].

Primary and adaptive resistance to immunotherapy can be attributed to both tumor cell-intrinsic and/or tumor cell-extrinsic factors. Multiple tumor-intrinsic mechanisms that lead to primary and/or adaptive resistance include the lack of T cell responses due to loss of tumor antigen recognition/expression/presentation, as well as the expression

and repression of certain genes/pathways within tumor cells that limit the immune function within the tumor microenvironment (TME) [20]. The presence of such mechanisms could exist at the time of initial presentation (termed “primary resistance mechanisms”) or may potentially evolve later (termed “adaptive resistance mechanisms”). Meanwhile, tumor cell-extrinsic mechanisms that contribute to the inhibition of antitumor immune responses involve non-tumor cell components within the microenvironment such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), M2 macrophages, and other inhibitory immune checkpoints [20]. Other potential mechanisms of disease relapse and progression upon the brief therapeutic response seen in certain patients include the loss of T cell functional phenotype, downregulation of tumor antigen presentation, and development of escape mutation variants [20].

In the PD-1 checkpoint pathway, the PD-1 inhibitory receptor has roles in T cell dysfunction during cancer development where studies have proven PD-1 expression in exhausted T cells is driven by demethylation of the PD-1 promoter [21]. The degree of epigenetic program stability can limit the maintenance of long-term effector function and memory development by T cells following PD-1 blockade [22], and thus present a potential explanatory role of epigenetic fate inflexibility on refractory disease observed in anti-PD-1 and/or anti-PD-L1 treated patients. More importantly, selective targeting in a subset of exhausted CD8 T cells may sufficiently enhance sustained effector function and durable antitumor responses in future clinical studies [23].

2.3. T Cell Dysfunction

T cell dysfunction refers to the cytotoxic T cells within the TME that have turned ineffective or immunotolerant, thereby conferring both primary and acquired resistance. Prolonged signaling to T cell receptors, due to persistent antigen exposure, increases the expression of inhibitory immune checkpoint receptors, which in turn drives “T cell dysfunction” [24]. Chronic antigen stimuli also influence the increased level of PD-1 expression through the NFAT cytoplasmic 1 (NFATc1)-mediated pathway, which is involved in the maintenance of exhausted phenotype [25][26]. Moreover, simultaneous expression of inhibitory co-receptors (such as PD-1, CTLA-4, TIM-3) is correlated with increased T cell dysfunction in cancer and disease progression [27]. With an increasing proportion of T cells co-expressing such receptors or on tumor-infiltrating lymphocytes (TILs), the functionality of T cells decreases and ultimately leads to tumor progression [27].

2.4. T-Cell Exhaustion

Characterized by sustained upregulation of multiple checkpoint proteins (PD-1, TIM-3, CTLA-4, LAG-3), exhausted T cells are a distinct group of dysfunctional T cells with poor effector function that arise in response to chronic viral infections and cancer [24]. This process is driven by persistent antigen exposure in the TME, alongside other early events that initiate T cell activation, which is critical for the reprogramming of exhaustion in the tumor [28]. In addition, Pauken et al. [22] found out that long-term blockade of the PD-1 pathway eventually led to T cell “re-exhaustion”, as well as observed altered transcriptional programs in such exhausted T cells [29][30]. Furthermore, epigenetic changes (DNA methylation, histone modifications) are essential processes known to drive the differentiation of T cells, and therefore, exhausted T cells are often found to have altered epigenomes compared to

normal functioning T cells [31]. As such, elevated lysine-specific demethylase 1 (LSD1) levels are reported to be a major contributor to the exhausted T cell phenotype [32], where targeting LSD1 in exhausted T cells of immunotherapy-resistant mice noticed increased T cell effector functionality (corresponding to elevated IFN levels and greater T cell infiltration).

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