ACTA SCIENTIFIC CANCER BIOLOGY

Volume 3 Issue 12 December 2019

Mini Review

Mitochondrial Manipulation Improves Anti-Tumor Immunity

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Received: October 30, 2019; **Published:** November 15, 2019

Abstract

PD-1 blockade cancer immunotherapy has led to a paradigm shift in cancer treatment. Despite its tremendous clinical success rate over other cancer treatments, a significant fraction of patients remains unresponsive to PD - 1 blockade therapy. It is very important to identify predictive biomarker and understand the mechanism of unresponsiveness to enhance its efficacy further. Here, in this short review, we have discussed how mitochondrial manipulation improves anti-tumor immunity. Mitochondria, a power-house in the cell, not only provides energy in the cell, rather it regulates activation and differentiation of immune T cells as well. Skewing mitochondrial metabolism towards oxidative phosphorylation could enhance the anti-tumor immunity. During combination therapy of mitochondrial activation chemicals (e.g., bezafibrate) along with PD-1 blockade therapy, T cells preferentially get energy from oxidative phosphorylation than glycolytic pathway which reflects in their higher longevity compared to PD - 1 blockade therapy alone which reactivates T cells that are short-lived and rely on glycolytic energy only. These works would promote for the development of novel combinatorial therapies with PD -1 blockade.

Keywords: PD-1, T Cells, Combination Therapy, PGC-1α, Bezafibrate, PPAR

Abbreviations

CTLA4: Cytotoxic T Lymphocyte Antigen 4; PD-1: Programmed Death Protein 1; PPAR: Peroxisome Proliferator-Activated Receptors; PGC-1α: Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha (PGC-1α)

Introduction

Worldwide, every sixth person is dying because of cancer. Around 9 million cancer deaths and 18 million new cancer cases were reported only in 2018 as revealed by WHO report 2018 on cancer statistics. After surgery, radiation and chemotherapy, cancer immunotherapy is the fourth and latest modality of cancer treatment. The idea of cancer immunotherapy stems from the work of Thomas and Burnet who first proposed the concept of cancer immunosurveillance in 1957 and emphasizes the ability of immune cells in detecting and killing the cancer cells. Decades later, the seminal works by Prof. James P. Allison (USA) and Prof. Tasuku Honjo (Japan) who discovered CTLA4 and PD-1 respectively, laid the foundation of cancer immunotherapy for clinical uses. Both CTLA4 and PD-1 are immunoinhibitory receptors present on lymphocytes. Cancer immunotherapy (especially PD-1 blockade based) has led to a paradigm shift in cancer treatment. PD-1 blockade therapy revolutionized the cancer treatment owing to improved survival, no or less side effects and applicability to a wide range of tumors irrespective of their origin and type [1,2]. Cancer and some immune cells express ligands of PD-1 (PD-L1) and ligate them with PD-1 on T cells which gives negative signal to T cells. Blocking the PD-1/PD-L1 interaction by antagonistic antibody to either PD-1 or PD-L1 leads to reactivation of T cells. The success of clinical trials with PD-1/PD-L1 led the FDA to approve PD-1 blockade therapy for many cancers including Hodgkin's lymphoma, head and neck squamous cell carcinoma, renal cell carcinoma, non-small cell lung carcinoma (NSCLC), and squamous cell lung cancer. Most importantly, in 2017, FDA approved nivolumab (anti-PD-1 mAb) for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers that covers various late-stage cancers [3].

PD-1 blockade therapy: Current Issues

Though PD-1 blockade is the most impressive cancer treatment so far. However, it suffers with some glitches that hinders efficacy in treating all patients. There is lack of a predictive biomarker to distinguish responder and nonresponse cancer patients. In addition, around 40% patients still remain unresponsive to the PD-1 blockade therapy. To improve efficacy, it is of utmost importance to i) identify predictive biomarker and ii) understand the mechanism of unresponsiveness to PD-1 blockade therapy. The response to PD-1 blockade therapy regulated by both tumor and host's immune properties. The development of predictive biomarkers will help the clinicians in stratification of cancer patients into responder and non-responder, and will save precious time of patients, laborious efforts of doctors and cost of social welfare. Studying the regulation of both the host immunity as well as the tumor side would give insight in understanding the mechanism of unresponsiveness.

Mitochondrial activation and T cell response

Mitochondria, a cellular organelle, not just produce energy, rather it plays important role in many functions as well. CD8+ T cells are major effector cells in tumor rejection by PD-1 blockade therapy and they become dysfunctional in unresponsive tumors [4]. It is reported that energy metabolism plays regulate the T cell function and differentiation [5,6]. In previous work from our group, we found mitochondrial activation associated genes were upregulated in lymphocytes from PD-1 KO mice compared to wild-type mice [4]. This result suggests blocking PD-1 signaling enhances mitochondrial activity and energy (ATP) production in T cells. Based on such preliminary findings, we compared the mitochondrial activation parameters and mitochondrial energy production of immune effector T cells from responsive and unresponsive tumor-bearing mice treated with PD-1 blockade therapy. The mitochondrial respiration can be measured by Seahorse analyzer which utilizes a series of chemicals (Oligomycin, FCCP, and Rotenone/Antimycin) to disturb the electron transport chain in a programmed manner to measure oxygen consumption rate (OCR; an indicator of mitochondrial respiration). We found T cells from mice with responsive tumor had higher mitochondrial activation (higher OCR values) after PD-1 blockade therapy over ctrl IgG treated while no significant enhancement was observed from unresponsive tumor bearing mice. These in vivo results demonstrated that mitochondrial activation parameters would serve as a potential biomarker to differentiate between responding and non-responding patients.

Augmenting PGC-1 α/PPAR axis: a common approach to enhance anti-tumor immunity

Blocking PD-1/PD-L1 axis releases T cells from inhibitory PD-1 signaling. T cells starts proliferation and become effector killer T cells destined for tumor clearance. During proliferation it utilizes energy from glycolysis which supports terminal differentiation of T cells. Effector T cells starts dying after few divisions and so even after initial response by PD-1 blockade therapy, the tumor again starts growing despite PD-1 blockade therapy because of short-lived effector T cells. Its reported that mitochondrial metabolism decides the fate of T cells. Effector T cells rely mainly on glycolysis while central memory T cells depends mainly on oxidative phosphorylation and fatty acid oxidation for energy demands.

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a transcriptional coactivator, is the master regulator of mitochondrial biogenesis. Recently, it is reported that the activation of PGC-1α leads to metabolic reprogramming and enhances T cell based antitumor immunity mediated [7]. PGC-1α interacts with nuclear transcription factors e.g., peroxisome proliferator-activated receptors (PPARs), nuclear respiratory factors (NRFs) and regulate expression of genes associated with mitochondrial biogenesis, fatty acid oxidation and oxidative phosphorylation. Bezafibrate (Bz; hereinafter), approved by FDA as a lipid-lowering agent, is a pan-PPAR agonist. Chowdhury et al. showed activation of PGC-1a/PPAR axis by bezafibrate along with PD-1 blockade enhances anti-immune response compared to PD-1 blockade alone [8]. The combination therapy showed better tumor suppression and host survival compared to PD-1 blockade monotherapy alone. Bezafibrate enhances the expression of carnitine palmitoyl transferase 1a (Cpt1a), an important enzyme for fatty acid metabolism and fatty acid oxidation. The combinatorial therapy with Bz enhances mitochondrial activation of T cells as evidenced by higher mitochondrial respiration and mitochondrial mass of T cells [8].

Conclusion

PD-1 blockade therapy alone causes T cells proliferation and differentiation into terminal effector T cells with short live. This is one of the reasons of unresponsiveness in some patients that monotherapy alone would not suffice for complete tumor clearance. Combination therapy for activation of PGC-1 α/PPAR causes mitochondrial biogenesis and enhances fatty acid oxidation and oxidative phosphorylation which have long live (Figure 1). The combination therapy with bezafibrate and modulators of PGC-1α/NRFs would be of great importance for clinical settings.

Figure 1: Hypothetical model of enhanced immune response by activation of PGC-1α/PPAR. PD-1 blockade alone causes proliferation of T cells and differentiate into terminal effector T cells with short-live which rely on glycolysis. Bezafibrate combination therapy skew T cells towards fatty acid oxidation and oxidative phosphorylation, a phenotype of central memory T cells with long-live.

Acknowledgements

I acknowledge the JSPS and Takeda Science Foundation for providing financial support.

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