Applying PERK/ERO1α inhibitors to modulate T cell metabolism to augment cancer immunotherapy

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Technology description

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A MUSC researcher has identified a novel immune-based therapy to treat cancer by targeting the PERK pathway using ERO1α antagonists combined with immune checkpoint blockade or Adoptive T-Cell (ACT) therapies. Data gathered demonstrates that either a PERK or ERO1α inhibitor combined with anti-PD-1 or ACT has a superior therapeutic effect than either treatment alone.

The inventors have demonstrated that PD-1+ Tumor Infiltrating Leukocytes (TILs) experienced mitochondrial exhaustion and oxidative stress, which leads to the function loss of T cells. By treating with the PERK inhibitor for 7 days, mitochondrial ROS (mtROS) was reduced in PD-1+ TILs in a sarcoma mouse model. In addition, the researchers found that using an ERO1α or PERK inhibitor reduced mtROS in effector T cells (data not shown). Further, in vivo PERK inhibitor treatment significantly augmented anti-PD-1 therapy, demonstrated by combination therapy-treated mice achieving complete response compared to anti-PD-1 therapy alone (Figure 1). Combination therapy-treated mice also exhibited 100% survival compared with ~28% survival in the anti-PD-1 therapy condition (Figure 1). The inventors also showed that treating mice-bearing pathogenic B16F10 melanomas with pmel-1 T cells conditioned ex vivo with an ERO1α inhibitor reduced the tumor size, indicating the increased efficacy of ERO1α inhibitor in combination with ACT (Figure 2). Hence, this invention suggests that the PERK/ERO1α inhibitors may be used as a combination treatment alone with immune checkpoint blockade and ACT therapies.

Overview

According to the report published by Zion, global immuno-oncology therapy market was valued at approximately USD 42.97 billion in 2016 and is expected to generate revenue of around USD 97.34 billion by 2022. Immune checkpoint blockade and ACT therapies for cancer have shown promising clinical results in recent decades. However, in some cancers and patients, the efficacy of the treatment is still limited. To improve the outcomes, the combination treatments are still necessary. The present invention using PERK/ERO1a inhibitors showed the reduction of energy and function loss of PD-1+ tumor-infiltrating lymphocytes (TILs). The PERK pathway mediates the terminal unfolded protein response (UPR) through regulation of transcription factors activating transcription factor 4 (ATF4) and C/EBPa homologous protein (CHOP), which induce downstream target ER oxidoreductase 1 (ERO1α Inhibiting the PERK pathway, blunts the energy reduction and effector function of TILs). In addition, the

combination treatment along with anti-PD-1 or ACT therapies showed high efficacy of tumor suppression in an animal model, indicating that the technology has a high potential impact on the current market.

Key Words:immune checkpoint blockade, adoptive cells therapy (ACT), anti-PD-1, anti-PD-L1, PERK inhibitor, ERO1α inhibitor, tumor, cancer, immunotherapy

Publication:Katie E. Hurst et al.” Endoplasmic Reticulum Stress Contributes to Mitochondrial Exhaustion of CD8+ T Cells ” Cancer Immunol Res. 2019 Jan 18

Application area

Enhance the efficacy of tumor suppression in combination with adoptive cellular therapy and immune checkpoint blockade therapy.

Superior ability to regress tumors

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