PERK is a critical metabolic hub for immunosuppressive function in macrophages

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Nat Immunol **23**, pages431–445 (2022).

Date: 2022.10.14 Speaker: Tsen Hsuan Yen Advisor: Dr. Michael Chan

1. 簡述論文概要與重大發現

巨噬細胞 (macrophage) 是先天免疫系統的一部分，會根據不同 cytokine 的刺激導致分化，並執行不同類型的功能，例如促進免疫反應、對抗病原的 M1 巨噬細胞以及抑制免疫反應、促進組織修復的 M2 巨噬細胞。然而，目前對於 cytokine 是如何導致巨噬細胞分化的機制尚未清楚，因此作者透過表觀基因 (epigenetics)以及 immunometabolism 來研究其中的機制。

本篇研究以內質網上的 unfolded protein response (UPR) 作為切入點，探討主要的 PERK pathway，發現將 PERK knock out 之後會抑制巨噬細胞往 M2 macrophage 分化並促進免疫反應，接著探討 PERK knock out 後 metabolic pathway 的變化，進一步研究是下游 amino acid related pathway 影響巨噬細胞的分化，也發現 serine biosynthesis pathway 影響了粒線體的活性。作者接下來探討 serine biosynthesis pathway，發現其與 α-Ketoglutarate 合成息息相關，而 α-Ketoglutarate 亦與 epigenetic 的 demethylation 有關，可以得知巨噬細胞的分化也能透過表觀基因來調控。

藉由內質網上的 UPR 可以調控不同的 pathway，其中包含了巨噬細胞分化相關的 pathway，發現 PERK pathway 會影響 IL-4 induce 巨噬細胞分化的能力，其中 PERK pathway 影響的 serine biosynthesis pathway 會與 α-Ketoglutarate 合成有關，也直接影響巨噬細胞的分化。

2. 對論文內容的疑問:

Serine biosynthesis 會透過 fatty acid oxidation 影響粒線體活性並影響巨噬細胞分化，然而是否活性較差的粒線體會導致往 M2 巨噬細胞分化，亦或者只是影響其分化效率?

3. 論文的缺點、評論:

本篇研究以 UPR 進行研究，探討在 IL-4 cytokine 刺激下如何影響巨噬細胞分化，細部研究 PERK pathway 如何影響 macrophage，因此，藉由抑制此路徑便可以促進免疫反應，抑制腫瘤生長。然而，對於抑制 M2 巨噬細胞是否會導致自體免疫也需要被加以探討。

nature immunology

ARTICLES

https://doi.org/10.1038/s41590-022-01145-x

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Chronic inflammation triggers compensatory immunosuppression to stop inflammation and minimize tissue damage. Studies have demonstrated that endoplasmic reticulum (ER) stress augments the suppressive phenotypes of immune cells; however, the molecular mechanisms underpinning this process and how it links to the metabolic reprogramming of immunosuppressive macrophages remain elusive. In the present study, we report that the helper T cell 2 cytokine interleukin-4 and the tumor microenvironment increase the activity of a protein kinase RNA-like ER kinase (PERK)-signaling cascade in macrophages and promote immunosuppressive M2 activation and proliferation. Loss of PERK signaling impeded mitochondrial respiration and lipid oxidation critical for M2 macrophages. PERK activation mediated the upregulation of phosphoserine aminotransferase 1 (PSAT1) and serine biosynthesis via the downstream transcription factor ATF-4. Increased serine biosynthesis resulted in enhanced mitochondrial function and α-ketoglutarate production required for JMJD3-dependent epigenetic modification. Inhibition of PERK suppressed macrophage immunosuppressive activity and could enhance the efficacy of immune checkpoint programmed cell death protein 1 inhibition in melanoma. Our findings delineate a previously undescribed connection between PERK signaling and PSAT1-mediated serine metabolism critical for promoting immunosuppressive function in M2 macrophages.

Macrophages, a critical component of the innate immune system, are a group of heterogeneous cells present in all tissues. Due to this wide distribution, macrophages are uniquely poised to exert essential processes for human health—from pathogen clearance, tissue repair and maintenance of homeostasis[1,2]. The ability of macrophages to serve these functions reflects their ability to execute disparate cellular programs in response to distinct extracellular cues. As a result, immunosuppressive (M2) and proinflammatory (M1) macrophages represent two distinct polarization phenotypes in response to either tumor and helminthic insults or bacterial and viral infection[3]. Moreover, the revitalization of immunometabolism and epigenetics research has uncovered new insights into these polarization phenotypes, revealing major and largely nonoverlapping alterations in gene expression that are closely associated with distinctive metabolic pathways[4,5].

These distinct phenotypes are dependent on cues from the surrounding microenvironment, and inflammatory milieus are known to impose stress signals that affect the energetic demands and cellular fitness of infiltrating immune cells[6,7]. However, to induce phenotypic changes, these signals must be incorporated and translated intracellularly. The major organelle responsible for coordinating extrinsic challenges and intrinsic cellular demands is the ER where the progression of inflammatory diseases can provoke the unfolded protein response (UPR). The UPR is commonly associated with the maintenance of proteostasis; however, recent findings show that activation of the UPR is linked to the development and function of immune cells[8–10], including dendritic cells[11,12], myeloid cell-driven immunosuppressive cells (MDSCs)[13] and also T cells[14,15]. The UPR signaling cascade is primarily initiated by the type I transmembrane kinase, inositol-requiring enzyme-1α (IRE1α), the type II transmembrane protein, activating transcription factor (ATF) 6 and PERK (encoded by *Eif2ak3*)[16]. Recent studies have suggested that IRE1α-mediated, X-box-binding protein (XBP1) signaling plays a crucial role in macrophages during inflammatory diseases[17,18]. Yet, these findings have reached inconclusive and/or contradictory conclusions. This raises an important question about whether other arms of the UPR contribute to the metabolic adaptation necessary to support the immunosuppressive characteristics of macrophages.

Activated PERK phosphorylates the downstream mediator eukaryotic translation initiation factor 2α (eIF2α)[16], leading to the induction of stress-responsive ATF-4 activation[19]. PERK signaling induces mitochondrial function[20], whereas ATF-4 activation has been suggested to upregulate a set of targets involved in amino acid anabolism[21]. In the present study, we show that the PERK arm of the UPR is uniquely upregulated in macrophages responding to the helper T cell 2 (T_H2) cytokine interleukin-4 (IL-4) and also the tumor microenvironment (TME). This PERK signaling modality promotes mitochondrial respiration to fulfill cellular energy requirements while also signaling through ATF-4 to regulate PSAT1 activity to mediate the serine biosynthesis pathway. The process of PSAT1-mediated serine synthesis, in addition to supporting mitochondrial fitness, balances the production of α-ketoglutarate (α-KG) necessary for JMJD3-dependent histone demethylation and reinforces immunosuppressive M2 activation and cell expansion.

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