

线粒体动力学:炎症微环境中 Th17/Treg 细胞平衡调控机制的新视角

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【摘要】 辅助性T淋巴细胞17(Th17)与调节性T淋巴细胞(Treg)的功能失衡是引起多种炎症性疾病的核心机制。尽管二者同源于CD4⁺T细胞,其免疫效应却截然相反:Th17介导促炎反应,而Treg维持免疫稳态。因此,深入解析炎症微环境中Th17/Treg平衡的调控机制,对开发靶向治疗策略具有重要意义。本文聚焦线粒体动力学(线粒体分裂/融合的动态过程)这一新兴调控维度,整合近年相关研究,探讨Th17/Treg的线粒体形态学特征及其与代谢重编程的关联,旨在为炎症性疾病提供“代谢-免疫”交互调控的创新理论框架,为靶向线粒体动力学纠正免疫失衡提供转化策略。

【关键词】 线粒体动力学; 辅助性T淋巴细胞17; 调节性T淋巴细胞; 细胞代谢

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Mitochondrial dynamics: A novel mechanistic insight into Th17/Treg balance regulation in inflammatory microenvironments

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【Abstract】 The functional imbalance between T helper 17 (Th17) and regulatory T cells (Treg) serves as a pivotal

mechanism underlying multiple inflammatory disorders. Although both subsets originate from CD4⁺T cells, they exhibit antagonistic immunological effects: Th17 drives pro-inflammatory responses while Treg maintains immune homeostasis. Deciphering the regulatory mechanisms governing Th17/Treg balance within inflammatory microenvironments is crucial for developing targeted therapeutic strategies. This review focuses on mitochondrial dynamics - the dynamic processes of fission and fusion - as an emerging regulatory dimension. By integrating recent advancements, we examine mitochondrial morphological signatures in Th17/Treg subsets and their interplay with metabolic reprogramming. Our findings establish an innovative "metabolism - immunity" interplay framework for inflammatory diseases and propose translational strategies targeting mitochondrial dynamics to rectify immune imbalance.

【Key words】 Mitochondrial dynamics; T helper cell 17; Regulatory T cell; Cellular metabolism

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辅助性T淋巴细胞17(T helper cell 17, Th17)和调节性T淋巴细胞(regulatory T cell, Treg)作为CD4⁺T细胞分化产生的关键效应亚群,在免疫应答中发挥功能拮抗作用。Th17以产生白细胞介素(interleukin, IL)-17A为特征,同时还分泌IL-8、IL-17F、IL-21、IL-22、IL-26和肿瘤坏死因子 α 等促炎因子^[1]。其分化过程受信号转导和转录激活因子3(signal transducer and activator of transcription 3, STAT3)和视黄酸相关孤儿受体 γ t(retinoic acid-related orphan receptor γ t, ROR γ t)等关键转录因子调控^[2]。生理状态下,IL-17在宿主抵御外来感染中发挥关键作用。然而,病理状态下其过度表达可诱发组织炎症与自身免疫损伤^[3]。

与之相反,Treg分泌IL-10、IL-35和转化生长因

子 $\beta 1$ (transforming growth factor- $\beta 1$, TGF- $\beta 1$)等抗炎因子^[4],并依赖其特异性表达的转录因子叉头盒P3(forkhead box P3, FoxP3)、细胞表面分子CD25和细胞毒性T淋巴细胞相关蛋白4(cytotoxic T-lymphocyte-associated protein-4, CTLA-4)^[5],在维持免疫耐受与稳态中扮演不可或缺的角色^[6]。

Th17/Treg平衡对于多种炎症和自身免疫性疾病具有至关重要的意义。大量研究报道,在多发性硬化症、类风湿关节炎、银屑病和牙周炎等多种疾病中,普遍存在Treg数量减少、Th17数量增加,以及Th17/Treg细胞失衡状态^[7-8],表明这些疾病可能具有以系统性炎症为特征的共同病理、生理过程^[9],而Th17/Treg细胞失衡可能是疾病的关键驱动因素。

线粒体作为细胞的“动力工厂”,不仅是三磷酸腺苷(adenosine triphosphate, ATP)合成的主要场所,更是调节细胞代谢、自噬、细胞死亡和分化等复杂信号网络的核心枢纽。线粒体通过持续地分裂与融合动态重塑其网络形态(线粒体动力学)以适应相应的功能需求。研究表明,线粒体融合与氧化磷酸化(oxidative phosphorylation, OXPHOS)增强有关,而线粒体分裂则常伴随糖酵解代谢活跃^[10-11]。

值得注意的是, T细胞在激活和分化过程中会经历代谢重编程。不同的T细胞亚群,尤其是Th17与Treg,具有独特的代谢过程和线粒体动力学特征以支持其特定功能^[12]。在炎症微环境中,营养状态改变及氧化应激等信号可通过重塑线粒体动力学影响Th17与Treg的分化及功能状态,进而破坏免疫平衡并促进疾病进展^[13]。尽管,现有综述已阐明T细胞代谢重编程对Th17/Treg分化的调控作用,但是线粒体动力学如何决定免疫细胞代谢功能及炎症微环境中线粒体分裂/融合的时空调控机制与免疫失衡的因果关联缺乏系统解析。因此,本文将从线粒体动力学的角度,系统阐述Th17/Treg的线粒体形态学特征及其与代谢重编程的关联,旨在为深入理解炎症相关疾病的发病机制及发掘潜在治疗靶点提供新的理论依据。

一、Th17与Treg的生物学及代谢特征

T细胞是适应性免疫的重要组成部分,在细胞免疫和体液免疫中发挥重要作用。初始T细胞在受到特异性抗原刺激后开始活化增殖,最终分化为效应T细胞进而发挥功能。在这个过程中, T细胞从静息状态到活化状态的转变伴随能量需求剧增,因此代谢状态发生改变以满足不同阶段的能量需求,

这一过程被称为T细胞代谢重编程^[14]。T细胞代谢重编程不仅是T细胞发挥功能的能量基石,更是连接信号通路和细胞功能的关键枢纽^[15]。线粒体作为重要的细胞代谢中心,是T细胞代谢重编程的基础,线粒体形态、质量和功能状态的动态变化决定了T细胞的分化方向和功能活性。

1. Th17细胞:在代谢重编程过程中,细胞能量代谢从依赖OXPHOS转向依赖糖酵解,这一过程被称为Warburg效应,是代谢重编程的核心环节^[16]。初始T细胞受到抗原刺激后,可分化成不同亚型的T细胞,其中Th17是CD4⁺ T细胞的关键亚群。相较于初始T细胞, Th17细胞更依赖糖酵解^[17]。糖酵解不仅能为T细胞增殖分化快速提供能量,其中间产物如丙酮酸和乳酸对Th17的分化和功能也至关重要^[18]。T细胞受体(T cell receptor, TCR)激活后,糖酵解可以在不依赖转录、翻译、共刺激分子CD28,以及丝氨酸和苏氨酸激酶(serine/threonine kinase, Akt)信号通路的情况下迅速被诱导^[19]。随着糖酵解激活, Th17中糖酵解相关基因持续高表达,伴随葡萄糖摄入增加^[20]。有学者发现,葡萄糖转运蛋白抑制剂可通过抑制T细胞糖酵解进而抑制Th17细胞分化^[21],同时糖酵解抑制剂也能显著降低Th17的比例^[22-23]。此外,有研究发现在炎症性疾病中CD4⁺ T细胞内哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)信号异常活化会促进Th17分化^[24]。一方面,活化的mTOR通过直接激活葡萄糖转运蛋白1(glucose transporter 1, GLUT1)增强葡萄糖摄取与代谢,从而促进Th17分化^[25];另一方面, mTOR还可通过上调缺氧诱导因子1 α (hypoxia-inducible factor alpha, HIF-1 α)增强糖酵解从而促进Th17细胞分化^[26]。以上研究均提示糖酵解代谢对Th17分化至关重要。

Th17的分化与功能维持还受到OXPHOS^[27]、谷氨酰胺代谢^[28]及脂质代谢^[17]的影响。下调OXPHOS可抑制Th17分化并减缓相关疾病的发展^[27,29],这可能是由于OXPHOS产生的生物大分子如柠檬酸等可以维持Th17的代谢和功能^[30]。在无谷氨酰胺的培养基中,初始CD4⁺ T细胞向Th17细胞分化的能力减弱,而恢复谷氨酰胺后Th17细胞分化能力提高^[31]。T细胞内谷氨酰胺代谢合成还原型谷胱甘肽,在Th17分化过程中起到抗氧化作用,从而促进Th17分化^[32]。此外, Th17细胞分化过程需要上调乙酰辅酶A羧化酶1(acetyl-CoA carboxylase1, ACC1)和脂

肪酸合酶(fatty acid synthase, FAS)以合成脂肪酸产生细胞膜所需的磷脂。有学者使用FAS抑制剂处理T细胞,发现Th17的分化比例显著降低^[17]。高脂饮食也可通过增强编码ACC1的基因*Acaca*的表达促进Th17的分化^[33]。

2. Treg细胞:Th17和Treg的分化和功能依赖于独立且互补的代谢途径。与初始T细胞相比,Treg表现出更高的基础糖酵解水平;但与其他效应T细胞相比,Treg细胞的糖酵解活性最低^[34]。Treg的分化不依赖于糖酵解,相反,抑制糖酵解可以促进Treg分化^[35]。研究表明,TGF- β 1可通过降低Treg细胞内GLUT1、己糖激酶2(hexokinase 2, HK2)和烯醇化酶1(enolase 1, ENO1)的表达水平抑制糖酵解,进而促进Treg分化。Treg的特征性转录因子FoxP3可通过抑制糖酵解重新编程T细胞代谢^[36]。然而,葡萄糖激酶(glucokinase, GCK)依赖的糖酵解对Treg的迁移至关重要。GCK可通过与肌动蛋白结合,促进Treg细胞骨架重排从而介导Treg迁移^[37]。

研究表明,Treg优先通过线粒体OXPHOS而非糖酵解产生ATP,FoxP3可通过上调电子传递复合体组分及增强复合体活性促进OXPHOS为细胞供能。此外,脂肪酸氧化(fatty acid oxidation, FAO)也是Treg的重要供能途径^[38],是维持Treg免疫抑制功能的关键环节。PPAR γ 通过CD36/CPT1途径增强FAO从而调控Treg细胞功能^[39]。芳基羟受体激活可通过Skp2/K63-泛素化途径增强肝激酶B1(liver kinase B1, LKB1)介导的FAO,从而促进Treg细胞分化^[40]。AMPK激活可通过促进脂肪酸摄取与维持线粒体膜电位为FAO提供物质和场所,进而促进Treg细胞分化。此外,脂肪酸结合蛋白5(fatty acid-binding protein 5, FABP5)作为脂质转运枢纽,其缺失会导致脂质摄取障碍及Treg功能受损^[41]。因此,Treg依赖OXPHOS和FAO维持细胞分化与功能,与Th17拥有互补的代谢途径,共同构成免疫平衡的代谢基础。

3. Th17/Treg平衡:代谢组学研究表明,Th17富集糖酵解和戊糖磷酸途径中间产物,而Treg则显著累积FAO相关代谢产物^[20],揭示了两者的不同代谢模式,为调控Th17/Treg稳态提供了靶向代谢干预靶点。研究发现,使用2-脱氧葡萄糖抑制T细胞糖酵解可打破Th17/Treg的平衡,显著抑制促炎的Th17细胞分化,同时促进抑炎的Treg细胞分化^[17,42]。糖酵解抑制后,AMPK激活通过促进FAO为Treg分

化提供能量^[43]。在稳态和炎症条件下,T细胞内ACC1的缺乏阻断脂肪酸合成会抑制Th17细胞分化,并促进Treg分化^[44]。他汀类药物抑制胆固醇的生物合成使促炎性的Th17转向抗炎性的Treg^[45]。此外,谷氨酰胺代谢产物2-羟基戊二酸能够抑制FoxP3的转录,并促进Th17的分化^[28]。因此,调控T细胞的糖酵解、OXPHOS、脂质合成及谷氨酰胺分解等代谢节点,可有效调控Th17/Treg平衡。

二、Th17与Treg的线粒体形态学特征

初始T细胞能量需求低,主要依赖OXPHOS,而Th1、Th2和Th17等效应T细胞需支持细胞因子分泌与增殖,更依赖增强的有氧糖酵解^[9,20]。不同T细胞亚群的代谢特征与其线粒体结构高度关联:效应T细胞通常呈现碎片化、分散的线粒体,而记忆T细胞则具有致密且高度融合的管状线粒体^[46]。

与其他效应T细胞相比,Th17线粒体融合程度更高,嵴紧密排列,且长型视神经萎缩蛋白1(long-optic atrophy 1, L-OPA1)水平升高。OPA1是线粒体融合的核心调控蛋白,主要位于线粒体内膜,通过调控线粒体膜结构的动态变化维持线粒体功能。OPA1切割成L-OPA1将促进线粒体内膜融合,对维持IL-17分泌及Th17功能至关重要,提示线粒体融合状态是Th17效应功能的必要条件^[47]。Treg细胞分化过程中,线粒体也呈现出嵴延长的融合状态,是调控T细胞代谢重编程转为FAO的关键环节。值得注意的是,尽管Th17与Treg均呈现线粒体融合表型,但其代谢基础截然不同:Th17依赖糖酵解支持促炎功能,而Treg需线粒体融合驱动FAO以维持抑制炎症功能。

三、Th17与Treg的线粒体动力学

线粒体形态通过持续地分裂与融合动态重塑,以响应细胞代谢状态变化。这一过程主要由Dynamin GTP酶超家族介导,通过水解三磷酸鸟苷(guanosine triphosphate, GTP)实现对线粒体膜结构的调控与重塑^[48]。

线粒体融合是一个受严格调控的多步骤过程,涉及线粒体内外膜的协同重构。首先,两个相邻线粒体通过膜接触位点建立紧密连接,线粒体融合蛋白1/2(mitofusin1/2, MFN1/2)通过其GTP酶结构域介导外膜脂质双层融合。随后,OPA1通过介导心磷脂依赖性膜重构实现内膜融合^[49]。

线粒体分裂主要由线粒体动力相关蛋白1(dynamin-related protein 1, Drp1)介导,其过程分为

3个阶段^[50]。首先,胞质Drp1被转运至线粒体分裂位点,该位点富含分裂受体蛋白包括线粒体裂变因子(mitochondrial fission factor,MFF)、线粒体动力学蛋白49/51(mitochondrial dynamics protein of 49 and 51 kDa, MiD49/MiD51)、线粒体裂变蛋白1(mitochondrial fission protein 1,Fis1)。随后,Drp1在受体锚定位点组装成螺旋状超分子复合物^[51-52]。最后,通过GTP水解驱动Drp1构象变化,产生机械力收缩线粒体膜,最终完成分裂^[53-54]。

1. Th17细胞:Th17细胞分化及效应过程均依赖糖酵解功能。Th17细胞分化过程中,CD4⁺T细胞通过协同上调OXPHOS与糖酵解通量实现代谢重编程。在Th17分化的关键起始阶段,OXPHOS是支撑其分化的必要条件,通过调控早期转录事件主导Th17细胞分化。研究表明,与初始CD4⁺T细胞相比,在Th17分化条件下活化的CD4⁺T细胞展现出显著增强的基础及最大呼吸能力,并伴随ATP合成速率增加。其基础耗氧率(oxygen consumption rate, OCR)在活化后24 h开始升高,48 h达到峰值,72 h回落,提示线粒体OXPHOS可能是Th17分化早期关键事件;细胞外酸化率(extracellular acidification rate, ECAR)同样升高,提示糖酵解通量增强。有趣的是,抑制OXPHOS同时也导致ECAR的显著降低,表明在Th17分化期间糖酵解增强与分化早期线粒体OXPHOS升高密切相关。此外,实验证据表明抑制ATP合酶及OXPHOS将显著下调代谢相关基因表达(糖酵解基因*Hk1*、*Hk2*、*Eno1*和*Aldoa*;HIF通路基因*Ldha*、*Hif1a*;TCA循环基因*Idh1*、*Mdh1*、*Aco1*和*Aco2*),并诱导细胞转向FoxP3⁺Treg表型。

Th17分化早期高OXPHOS水平激活蛋白酶YME1L(YME1 Like 1 ATPase),YME1L是AAA家族ATP酶的主要成员,位于线粒体内膜,其对维持线粒体的形态、功能和可塑性至关重要。YME1L切割OPA1生成L-OPA1促进线粒体融合。因此,Th17呈现L-OPA1累积、线粒体融合态、嵴结构致密化的独特形态特征。反过来,线粒体融合通过增强线粒体嵴结构完整性与呼吸链超复合体组装促进OXPHOS效率,进一步激活Th17糖酵解代谢以维持分化^[55]。有研究表明,Th17需要L-OPA1维持线粒体嵴紧密状态、调控TCA循环,OPA1缺失导致线粒体嵴松散,进一步激活LKB1将放大谷氨酰胺氧化,导致NADH/NAD⁺平衡受损、TCA循环代谢物和2-羟基戊二酸的积累进一步影响表观遗传学,抑制IL-17表

达及Th17细胞分化^[47]。

2. Treg细胞:Treg的核心代谢特征表现为FAO,FAO与线粒体融合密切关联。高度融合的线粒体网络为脂肪酸摄取提供必需的结构基础,碎片化线粒体严重限制脂质转运效率。因此,Treg细胞分化依赖线粒体融合状态。研究表明,FABP5可通过促进心磷脂合成维持Treg线粒体完整性,其功能受损会导致线粒体嵴结构丧失、OXPHOS降低及脂质代谢受损,进而抑制Treg分化^[41]。Treg细胞分化过程中,其关键诱导因子TGF- β 1通过激活Smad2/3信号通路上调过氧化物酶体增殖物激活受体 γ 共激活因子1 α (peroxisome proliferator activated receptor γ coactivator-1 α , PGC-1 α)表达。PGC-1 α 可通过双重机制调控线粒体网络重构,一方面其可直接促进线粒体融合蛋白OPA1与MFN1/2的转录表达,增强线粒体融合^[56];另一方面PGC-1 α 可结合*Drp1*基因启动子抑制其转录,从而抑制线粒体分裂^[57]。

线粒体融合蛋白MFN1/MFN2可通过调控基础脂质代谢(包括表面活性磷脂与胆固醇合成)增强FAO效率,*Mfn1/Mfn2*双敲除模型可显著损害脂质代谢^[58]。线粒体去乙酰化酶SIRT4作为线粒体融合负调控因子,可通过抑制OPA1/MFN1表达抑制FAO。在Treg中,类似机制可能限制其代谢活性,进而抑制Treg细胞功能^[59]。同样的,线粒体载体同源物2作为线粒体外膜载体蛋白,通过感知脂质合成中间产物溶血磷脂酸也可激活线粒体融合^[60]。综上,线粒体动力学通过直接调控能量代谢,成为Treg细胞分化与功能的关键枢纽。线粒体融合促进高效FAO以满足Treg的高能量需求;而线粒体分裂导致的线粒体嵴碎片化状态则限制Treg细胞代谢及功能。

四、总结

Th17/Treg失衡是驱动多种炎症性及自身免疫性疾病的核心病理机制。现有治疗策略主要聚焦在直接调控T细胞数量方面(如IL-17A抑制剂brodalumab/ixekizumab在银屑病、脊柱关节炎中的临床应用),虽然证实其具有平衡恢复的治疗潜力,但是未能揭示靶向失衡的深层代谢根源^[61]。本文基于现有文献发现,Th17依赖“线粒体融合-糖酵解”驱动促炎效应,Treg依赖“线粒体融合-FAO”维持抑制功能(表1)。表明线粒体动力学是代谢-免疫交互调控的关键枢纽,细胞代谢与线粒体形态高度相关,T细胞代谢重编程直接受线粒体网络形态调控,并且众

表1 Th17与Treg细胞的生物学特征、代谢特性及线粒体动力学比较

项目	Th17细胞	Treg细胞
生物学功能	促进炎症	抑制炎症
核心代谢途径	糖酵解	FAO
线粒体形态特征	线粒体融合、嵴结构致密化	线粒体融合、嵴完整清晰
动力学调控因子	L-OPA1、YME1L等	PGC-1 α 、OPA1等
代谢-形态偶联机制	OXPHOS $\uparrow$ $\rightarrow$ YME1L激活 $\rightarrow$ L-OPA1 $\uparrow$ $\rightarrow$ 融合 $\uparrow$ $\rightarrow$ 糖酵解 $\uparrow$	TGF- β $\rightarrow$ PGC-1 α $\uparrow$ $\rightarrow$ OPA1/MFN2 $\uparrow$ $\rightarrow$ 融合 $\uparrow$ $\rightarrow$ FAO $\uparrow$

注:Th17为辅助性T淋巴细胞17;Treg为调节性T淋巴细胞;L-OPA1为长型视神经萎缩蛋白1;YME1L为YME1L蛋白酶;OXPHOS为氧化磷酸化;FAO为脂肪酸氧化;PGC-1 α 为过氧化物酶体增殖物激活受体 γ 共激活因子1 α ;OPA1为视神经萎缩蛋白1;TGF- β 为转化生长因子 β , MFN2为线粒体融合蛋白2。

多因素可通过重塑线粒体动力学驱动T细胞分化^[41,62],揭示了其潜在的临床应用价值。

未来相关研究应基于“代谢-免疫”交互理论框架,深入解析线粒体动力学影响Th17/Treg平衡的时空动态特征,利用活细胞成像等技术直接比较Th17/Treg线粒体网络实时重塑,绘制不同炎症微环境(如牙周炎、银屑病)中T细胞的特异性动力学图谱,开发调控OPA1/YME1L或Drp1/Fis1的小分子化合物并探索基于线粒体形态的细胞治疗改造(如增强Treg线粒体融合)等。总之,靶向线粒体动力学有望成为恢复Th17/Treg平衡的下一代治疗策略,但是其成功仍有赖于未来对代谢-形态-功能三维调控网络的深度解析。

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参 考 文 献

- [1] Medara N, Lenzo JC, Walsh KA, et al. A review of T helper 17 cell-related cytokines in serum and saliva in periodontitis [J]. Cytokine, 2021, 138: 155340. DOI: 10.1016/j.cyto.2020.155340.
- [2] Kumar R, Theiss AL, Venuprasad K. ROR γ t protein modifications and IL-17-mediated inflammation [J]. Trends Immunol, 2021, 42(11): 1037-1050. DOI: 10.1016/j.it.2021.09.005.
- [3] Akhter S, Tasnim FM, Islam MN, et al. Role of Th17 and IL-17 cytokines on inflammatory and auto-immune diseases [J]. Curr Pharm Des, 2023, 29(26): 2078-2090. DOI: 10.2174/1381612829666230904150808.
- [4] Lee GR. The balance of Th17 versus Treg cells in autoimmunity [J]. Int J Mol Sci, 2018, 19(3): 730. DOI: 10.3390/ijms19030730.
- [5] Göschl L, Scheinecker C, Bonelli M. Treg cells in autoimmunity: From identification to Treg-based therapies [J]. Semin Immunopathol, 2019, 41(3): 301-314. DOI: 10.1007/s00281-019-00741-8.
- [6] Ohkura N, Sakaguchi S. Transcriptional and epigenetic basis of Treg cell development and function: Its genetic anomalies or variations in autoimmune diseases [J]. Cell Res, 2020, 30(6): 465-474. DOI: 10.1038/s41422-020-0324-7.
- [7] Paradowska-Gorycka A, Wajda A, Romanowska-Próchnicka K, et al. Th17/Treg-related transcriptional factor expression and cytokine profile in patients with rheumatoid arthritis [J]. Front Immunol, 2020, 11: 572858. DOI: 10.3389/fimmu.2020.572858.
- [8] Li X, Jiang M, Chen X, et al. Etanercept alleviates psoriasis by reducing the Th17/Treg ratio and promoting M2 polarization of macrophages [J]. Immun Inflamm Dis, 2022, 10(12): e734. DOI: 10.1002/iid3.734.
- [9] Soriano-Baguet L, Brenner D. Metabolism and epigenetics at the heart of T cell function [J]. Trends Immunol, 2023, 44(3): 231-244. DOI: 10.1016/j.it.2023.01.002.
- [10] Yao CH, Wang R, Wang Y, et al. Mitochondrial fusion supports increased oxidative phosphorylation during cell proliferation [J]. Elife, 2019, 8: e41351. DOI: 10.7554/eLife.41351.
- [11] Gao T, Zhang X, Zhao J, et al. SIK2 promotes reprogramming of glucose metabolism through PI3K/AKT/HIF-1 α pathway and Drp1-mediated mitochondrial fission in ovarian cancer [J]. Cancer Lett, 2020, 469: 89-101. DOI: 10.1016/j.canlet.2019.10.029.
- [12] Bailis W, Shyer JA, Zhao J, et al. Distinct modes of mitochondrial metabolism uncouple T cell differentiation and function [J]. Nature, 2019, 571(7765): 403-407. DOI: 10.1038/s41586-019-1311-3.
- [13] Xie A, Robles RJ, Mukherjee S, et al. HIF-1 α -induced xenobiotic transporters promote Th17 responses in Crohn's disease [J]. J Autoimmun, 2018, 94: 122-133. DOI: 10.1016/j.jaut.2018.07.022.
- [14] Wang R, Green DR. Metabolic reprogramming and metabolic dependency in T cells [J]. Immunol Rev, 2012, 249(1): 14-26. DOI: 10.1111/j.1600-065X.2012.01155.x.
- [15] Buck MD, Sowell RT, Kaech SM, et al. Metabolic instruction of immunity [J]. Cell, 2017, 169(4): 570-586. DOI: 10.1016/j.cell.2017.04.004.
- [16] Xu K, Yin N, Peng M, et al. Glycolytic ATP fuels phosphoinositide 3-kinase signaling to support effector T helper 17 cell responses [J]. Immunity, 2021, 54(5): 976-987.e7. DOI: 10.1016/j.immuni.2021.04.008.
- [17] Cluxton D, Petrasca A, Moran B, et al. Differential regulation of human Treg and Th17 cells by fatty acid synthesis and glycolysis [J]. Front Immunol, 2019, 10: 115. DOI: 10.3389/fimmu.2019.00115.

- [18] Soto-Hereder G, Gómez de Las Heras MM, Gabandé-Rodríguez E, et al. Glycolysis: A key player in the inflammatory response [J]. FEBS J, 2020, 287 (16) : 3350-3369. DOI: 10.1111/febs.15327.
- [19] Menk AV, Scharping NE, Moreci RS, et al. Early TCR signaling induces rapid aerobic glycolysis enabling distinct acute T cell effector functions[J]. Cell Rep, 2018, 22(6) : 1509-1521. DOI: 10.1016/j.celrep.2018.01.040.
- [20] Gerriets VA, Kishton RJ, Nichols AG, et al. Metabolic programming and PDHK1 control CD4⁺ T cell subsets and inflammation [J]. J Clin Invest, 2015, 125(1) : 194-207. DOI: 10.1172/JCI76012.
- [21] Li W, Qu G, Choi SC, et al. Targeting T cell activation and lupus autoimmune phenotypes by inhibiting glucose transporters [J]. Front Immunol, 2019, 10: 833. DOI: 10.3389/fimmu.2019.00833.
- [22] Zhao L, Wu Q, Wang X, et al. Reversal of abnormal CD4⁺ T cell metabolism alleviates thyroiditis by deactivating the mTOR/HIF1 α /glycolysis pathway [J]. Front Endocrinol (Lausanne) , 2021, 12: 659738. DOI: 10.3389/fendo.2021.659738.
- [23] Xiao F, Rui K, Han M, et al. Artesunate suppresses Th17 response via inhibiting IRF4-mediated glycolysis and ameliorates Sjögren's syndrome [J]. Signal Transduct Target Ther, 2022, 7 (1) : 274. DOI: 10.1038/s41392-022-01103-x.
- [24] Shan J, Jin H, Xu Y. T cell metabolism: A new perspective on Th17/Treg cell imbalance in systemic lupus erythematosus [J]. Front Immunol, 2020, 11: 1027. DOI: 10.3389/fimmu.2020.01027.
- [25] Zeng H, Chi H. mTOR signaling in the differentiation and function of regulatory and effector T cells [J]. Curr Opin Immunol, 2017, 46: 103-111. DOI: 10.1016/j.coi.2017.04.005.
- [26] Liu Y, Zhang DT, Liu XG. mTOR signaling in T cell immunity and autoimmunity [J]. Int Rev Immunol, 2015, 34 (1) : 50-66. DOI: 10.3109/08830185.2014.933957.
- [27] Hong HS, Mbah NE, Shan M, et al. OXPHOS promotes apoptotic resistance and cellular persistence in TH17 cells in the periphery and tumor microenvironment[J]. Sci Immunol, 2022, 7 (77) : eabm8182. DOI: 10.1126/sciimmunol.abm8182.
- [28] Xu T, Stewart KM, Wang X, et al. Metabolic control of TH17 and induced Treg cell balance by an epigenetic mechanism [J]. Nature, 2017, 548(7666) : 228-233. DOI: 10.1038/nature23475.
- [29] Kaufmann U, Kahlfuss S, Yang J, et al. Calcium signaling controls pathogenic Th17 cell - mediated inflammation by regulating mitochondrial function [J]. Cell Metab, 2019, 29(5) : 1104-1118. e6. DOI: 10.1016/j.cmet.2019.01.019.
- [30] Soriano-Baguet L, Grusdat M, Kurniawan H, et al. Pyruvate dehydrogenase fuels a critical citrate pool that is essential for Th17 cell effector functions [J]. Cell Rep, 2023, 42(3) : 112153. DOI: 10.1016/j.celrep.2023.112153.
- [31] Johnson MO, Wolf MM, Madden MZ, et al. Distinct regulation of Th17 and Th1 cell differentiation by glutaminase - dependent metabolism [J]. Cell, 2018, 175 (7) : 1780-1795.e19. DOI: 10.1016/j.cell.2018.10.001.
- [32] Diaz-Vivancos P, de Simone A, Kiddle G, et al. Glutathione: Linking cell proliferation to oxidative stress [J]. Free Radic Biol Med, 2015, 89: 1154-1164. DOI: 10.1016/j.freeradbiomed.2015.09.023.
- [33] Endo Y, Asou HK, Matsugae N, et al. Obesity drives Th17 cell differentiation by inducing the lipid metabolic kinase, ACC1 [J]. Cell Rep, 2015, 12(6) : 1042-1055. DOI: 10.1016/j.celrep.2015.07.014.
- [34] Michalek RD, Gerriets VA, Jacobs SR, et al. Cutting edge: Distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4⁺ T cell subsets [J]. J Immunol, 2011, 186 (6) : 3299-3303. DOI: 10.4049/jimmunol.1003613.
- [35] Shi LZ, Wang R, Huang G, et al. HIF1 α -dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of Th17 and Treg cells [J]. J Exp Med, 2011, 208 (7) : 1367-1376. DOI: 10.1084/jem.20110278.
- [36] Chen X, Feng L, Li S, et al. TGF- β 1 maintains Foxp3 expression and inhibits glycolysis in natural regulatory T cells via PP2A - mediated suppression of mTOR signaling [J]. Immunol Lett, 2020, 226: 31-37. DOI: 10.1016/j.imlet.2020.06.016.
- [37] Yero A, Bouassa RM, Ancuta P, et al. Immuno-metabolic control of the balance between Th17 - polarized and regulatory T - cells during HIV infection [J]. Cytokine Growth Factor Rev, 2023, 69: 1-13. DOI: 10.1016/j.cytogfr.2023.01.001.
- [38] MacIver NJ, Michalek RD, Rathmell JC. Metabolic regulation of T lymphocytes [J]. Annu Rev Immunol, 2013, 31: 259-283. DOI: 10.1146/annurev-immunol-032712-095956.
- [39] Miao Y, Zhang C, Yang L, et al. The activation of PPAR γ enhances Treg responses through up - regulating CD36/CPT1 - mediated fatty acid oxidation and subsequent N-glycan branching of T β R II/IL-2R α [J]. Cell Commun Signal, 2022, 20 (1) : 48. DOI: 10.1186/s12964-022-00849-9.
- [40] Zhang Q, Zhu Y, Lv C, et al. AhR activation promotes Treg cell generation by enhancing Ikb1 - mediated fatty acid oxidation via the Skp2/K63 - ubiquitination pathway [J]. Immunology, 2023, 169(4) : 412-430. DOI: 10.1111/imm.13638.
- [41] Field CS, Baixauli F, Kyle RL, et al. Mitochondrial integrity regulated by lipid metabolism is a cell - intrinsic checkpoint for treg suppressive function [J]. Cell Metab, 2020, 31(2) : 422-437. DOI: 10.1016/j.cmet.2019.11.021.
- [42] Almeida L, Lochner M, Berod L, et al. Metabolic pathways in T cell activation and lineage differentiation [J]. Semin Immunol, 2016, 28(5) : 514-524. DOI: 10.1016/j.smim.2016.10.009.
- [43] Gualdoni GA, Mayer KA, Goschl L, et al. The AMP analog AICAR modulates the Treg/Th17 axis through enhancement of fatty acid oxidation [J]. Faseb J, 2016, 30(11) : 3800-3809. DOI: 10.1096/fj.201600522R.
- [44] Kao YS, Mamareli P, Dhillon-Labrooy A, et al. Targeting ACC1 in T cells ameliorates psoriatic skin inflammation [J]. J Mol Med

- (Berl), 2023, 101(9): 1153-1166. DOI: 10.1007/s00109-023-02349-w.
- [45] Al-Kuraishy HM, Al-Gareeb AI, Saad HM, et al. The potential therapeutic effect of statins in multiple sclerosis: Beneficial or detrimental effects [J]. *Inflammopharmacology*, 2023, 31(4): 1671-1682. DOI: 10.1007/s10787-023-01240-x.
- [46] Buck MD, O'Sullivan D, Klein Geltink RI, et al. Mitochondrial dynamics controls T cell fate through metabolic programming [J]. *Cell*, 2016, 166(1): 63-76. DOI: 10.1016/j.cell.2016.05.035.
- [47] Baixauli F, Piletic K, Puleston DJ, et al. An LKB1-mitochondria axis controls Th17 effector function [J]. *Nature*, 2022, 610(7932): 555-561. DOI: 10.1038/s41586-022-05264-1.
- [48] Chan DC. Mitochondrial dynamics and its involvement in disease [J]. *Annu Rev Pathol*, 2020, 15: 235-259. DOI: 10.1146/annurev-pathmechdis-012419-032711.
- [49] Meeusen S, McCaffery JM, Nunnari J. Mitochondrial fusion intermediates revealed *in vitro* [J]. *Science*, 2004, 305(5691): 1747-1752. DOI: 10.1126/science.1100612.
- [50] Quiles JM, Gustafsson AB. The role of mitochondrial fission in cardiovascular health and disease [J]. *Nat Rev Cardiol*, 2022, 19(11): 723-736. DOI: 10.1038/s41569-022-00703-y.
- [51] Chan DC. Fusion and fission: Interlinked processes critical for mitochondrial health [J]. *Annu Rev Genet*, 2012, 46: 265-287. DOI: 10.1146/annurev-genet-110410-132529.
- [52] Pernas L, Scorrano L. Mito-morphosis: Mitochondrial fusion, fission, and cristae remodeling as key mediators of cellular function [J]. *Annu Rev Physiol*, 2016, 78: 505-531. DOI: 10.1146/annurev-physiol-021115-105011.
- [53] van der Bliek AM, Shen Q, Kawajiri S. Mechanisms of mitochondrial fission and fusion [J]. *Cold Spring Harb Perspect Biol*, 2013, 5(6): a011072. DOI: 10.1101/cshperspect.a011072.
- [54] Kraus F, Roy K, Pucadyil TJ, et al. Function and regulation of the divisome for mitochondrial fission [J]. *Nature*, 2021, 590(7844): 57-66. DOI: 10.1038/s41586-021-03214-x.
- [55] Adebayo M, Singh S, Singh AP, et al. Mitochondrial fusion and fission: The fine-tune balance for cellular homeostasis [J]. *FASEB J*, 2021, 35(6): e21620. DOI: 10.1096/fj.202100067R.
- [56] Fang Y, Zhang Q, Lv C, et al. Mitochondrial fusion induced by transforming growth factor- β 1 serves as a switch that governs the metabolic reprogramming during differentiation of regulatory T cells [J]. *Redox Biol*, 2023, 62: 102709. DOI: 10.1016/j.redox.2023.102709.
- [57] Ding M, Feng N, Tang D, et al. Melatonin prevents Drp1-mediated mitochondrial fission in diabetic hearts through SIRT1-PGC1 α pathway [J]. *J Pineal Res*, 2018, 65(2): e12491. DOI: 10.1111/jpi.12491.
- [58] Chung KP, Hsu CL, Fan LC, et al. Mitofusins regulate lipid metabolism to mediate the development of lung fibrosis [J]. *Nat Commun*, 2019, 10(1): 3390. DOI: 10.1038/s41467-019-11327-1.
- [59] Noone J, Rochford KD, O'Sullivan F, et al. SIRT4 is a regulator of human skeletal muscle fatty acid metabolism influencing inner and outer mitochondrial membrane-mediated fusion [J]. *Cell Signal*, 2023, 112: 110931. DOI: 10.1016/j.cellsig.2023.110931.
- [60] Labbé K, Mookerjee S, le Vasseur M, et al. The modified mitochondrial outer membrane carrier MTCH2 links mitochondrial fusion to lipogenesis [J]. *J Cell Biol*, 2021, 220(11): e202103122. DOI: 10.1083/jcb.202103122.
- [61] Navarro-Compan V, Puig L, Vidal S, et al. The paradigm of IL-23-independent production of IL-17F and IL-17A and their role in chronic inflammatory diseases [J]. *Front Immunol*, 2023, 14: 1191782. DOI: 10.3389/fimmu.2023.1191782.
- [62] Wu B, Wan Y. Molecular control of pathogenic Th17 cells in autoimmune diseases [J]. *Int Immunopharmacol*, 2020, 80: 106187. DOI: 10.1016/j.intimp.2020.106187.

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