先天淋巴样细胞的代谢特征及其在人类重大疾病治疗中的潜在干预策略

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摘要: 先天淋巴样细胞 (innate lymphoid cells, ILCs) 主要包括自然杀伤细胞 (natural killer cell, NK细胞)、I型先天淋巴样细胞 (type I innate lymphoid cell, ILC1)、II型先天淋巴样细胞 (type II innate lymphoid cell, ILC2)、III型先天淋巴样细胞 (type III innate lymphoid cell, ILC3), 具有快速响应病原体和肿瘤细胞的能力。NK细胞通过细胞毒作用、细胞因子分泌以及抗体依赖性细胞介导的细胞毒性 (antibody-dependent cell-mediated cytotoxicity, ADCC) 发挥抗肿瘤和抗病毒功能, 而ILC1、2、3则主要在组织微环境中参与免疫调节和炎症反应。近年来研究发现, 代谢调控在ILCs发育、活化及功能中具有重要作用, 通过精准调控糖、氨基酸、脂类等物质的代谢流向, 可实现从ILCs静息态到效应态的功能转换, 而代谢失衡则会直接导致其效应功能异常。本文综述了NK细胞和其他ILCs的代谢特征与关键分子机制, 及其在肥胖、肿瘤和慢性病毒感染等病理状态下的代谢失调机制及潜在干预策略, 阐述了基于NK细胞和其他ILCs代谢调控的免疫治疗新策略, 并讨论了该领域内一些悬而未决的问题, 为研发基于NK细胞和其他ILCs的新型免疫治疗提供了理论基础。

关键词: 先天淋巴样细胞; 自然杀伤细胞; 代谢调节; 免疫治疗; 肿瘤微环境

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Metabolic signatures of innate lymphoid cells and their potential therapeutic interventions in human diseases

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Abstract: Innate lymphoid cells (ILCs) mainly consist of natural killer (NK) cells, type 1 ILC (ILC1), type 2 ILC (ILC2), and type 3 ILC (ILC3), all exhibiting rapid responsiveness to pathogens and tumor cells. NK cells execute antitumor and antiviral functions through cytotoxic activity, cytokine secretion, and antibody-dependent cell-mediated cytotoxicity (ADCC), whereas ILC1, ILC2, and ILC3 modulate immune regulation and inflammatory responses within tissue microenvironments. Emerging evidence highlights the pivotal role of metabolic reprogramming in the development, activation, and effector functions of ILCs. Recent studies have further revealed that metabolic pathways are the core link regulating the development, maturation, activation and functional

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execution of ILCs. By precisely regulating the metabolic flux of substances such as glucose, amino acids and lipids, ILCs can achieve functional transition from a quiescent state to an effector state, while metabolic imbalance directly leads to abnormalities in their immune effects. This review systematically summarizes the metabolic characteristics of NK cells and other ILC subsets, and also discusses their underlying molecular mechanisms. Furthermore, we discuss how metabolic dysregulation in NK cells and ILCs contributes to pathological conditions such as obesity, cancer, and chronic viral infections, alongside potential therapeutic interventions. Finally, we elaborate on novel immunotherapeutic strategies targeting the metabolic reprogramming of ILCs, addressing unresolved questions in this rapidly evolving field. These insights establish a theoretical framework for developing next-generation ILC-based immunotherapies.

Key words: innate lymphoid cell; natural killer cell; metabolic regulation; immunotherapy; tumor microenvironment

先天免疫系统作为机体抵御病原体入侵和肿瘤发生的第一道防线, 具有快速响应病原体和肿瘤细胞的能力。先天淋巴样细胞 (innate lymphoid cells, ILCs) 是先天免疫系统关键成员, 主要包括自然杀伤细胞 (natural killer cell, NK细胞)、I型先天淋巴样细胞 (type I innate lymphoid cell, ILC1)、II型先天淋巴样细胞 (type II innate lymphoid cell, ILC2)、III型先天淋巴样细胞 (type III innate lymphoid cell, ILC3)。ILC发育始于骨髓多能造血干细胞 (hematopoietic stem cell, HSC), 经共同淋巴样祖细胞 (common lymphoid progenitor, CLP) 进一步分化形成共同先天淋巴祖细胞 (common innate lymphoid progenitor, CILP)。CILP可分化为NK祖细胞或共同辅助样先天淋巴祖细胞 (common helper innate lymphoid progenitor, CHILP), NK祖细胞进一步分化为NK细胞而后者进而分化为ILC1、ILC2和ILC3[1,2]。NK细胞主要介导对病毒感染细胞和肿瘤细胞的直接杀伤作用, 并通过分泌干扰素γ (interferon-γ, IFN-γ) 等细胞因子调节免疫应答。ILC1与1型辅助性T细胞 (helper T cell 1, Th1) 类似, 通过分泌IFN-γ对抗胞内病原体; ILC2响应寄生虫和过敏原, 产生IL-4、IL-5、IL-13等细胞因子; ILC3依赖IL-17、IL-22等细胞因子, 维持黏膜屏障并抵御胞外菌, 部分亚群还具抗原提呈功能 (图1)[3]。近年来, 研究发现人体ILC1和ILC2在某些特定条件下也具备细胞杀伤能力, 并参与肿瘤清除[4,5]。

细胞代谢通路受内源性和外源性信号调控, 以满足其生长、存活及执行特定功能所需的能量及生物合成需求。糖酵解和线粒体氧化磷酸化 (oxidative phosphorylation, OXPHOS) 是ATP生成的主要代谢途径[6], 葡萄糖为主要碳源。葡萄糖通过糖酵解转化为丙酮酸, 丙酮酸在胞质内代谢为乳酸或转运至线粒体, 进一步代谢为乙酰辅酶A (acetyl-CoA), 进而进入三羧酸 (tricarboxylic acid, TCA) 循环进行OXPHOS。谷氨酰胺和游离脂肪酸 (fatty acids, FAs) 可分别通过谷氨酰胺分解和脂肪酸氧化 (fatty acid oxidation, FAO) 为OXPHOS提供原料。一分子葡萄糖通过糖酵解途径产生两分子ATP, 而通过OXPHOS途径可获得多达36分子ATP。尽管糖酵解供能效率较低, 但其速率较快, 并可提供生物合成前体, 从而支持快速增殖细胞的存活[7,8]。免疫细胞需要进行适当的代谢改变以保障其高效的免疫反应[9]。近年来研究发现, NK细胞和其他ILCs均遵循“静息低代谢−活化重编程”的共性规律, 以糖酵解和OXPHOS为核心供能基础, 但亚群间存在特化路径: NK细胞与ILC1依赖柠檬酸−苹果酸穿梭 (citrate-malate shuttle, CMS) 优化糖酵解效率, 保障IFN-γ分泌与细胞毒性[10]; ILC2侧重FAO, 与精氨酸代谢协同[11]; ILC3则通过mTORC1-HIF-1α轴调控有氧糖酵解与脂质合成, 支撑IL-17/IL-22的高效分泌[12]。近年来研究发现, 代谢途径不仅为ILCs提供能量和物质基础, 更深度调控其发育、激活和命运抉择, 而其代谢异常与肿瘤、自身免疫病等疾病的发生、发展密切相关[13,14]。本文将围绕NK细胞与其他ILC的发育起源、激活机制及代谢特征, 系统综述其代谢调控的分子机制、病理状态下的代谢失调, 并探讨可能的靶向干预策略。

1 NK细胞的代谢特征

作为ILCs家族中兼具细胞毒性和免疫调节功能的独特成员, NK细胞主要通过两类机制发挥抗肿瘤和抗病毒作用。一是依赖接触依赖性的细胞毒性途径, 通过表面膜结合型FAS配体 (membrane-bound FAS ligand, mFASL) 与靶细胞表面FAS受体结合、释放穿孔素/颗粒酶或表达TRAIL, 启动靶细胞凋亡或坏死程序; 二是通过分泌IFN-γ、肿瘤坏死因子α (tumor necrosis factor α, TNFα) 等细胞因子, 调控免疫微环境并抑制病原体复制[1,2] (图1), 其功能受细胞因子微环境及靶细胞激活或抑制信号的整合调控[15,16]。在静息

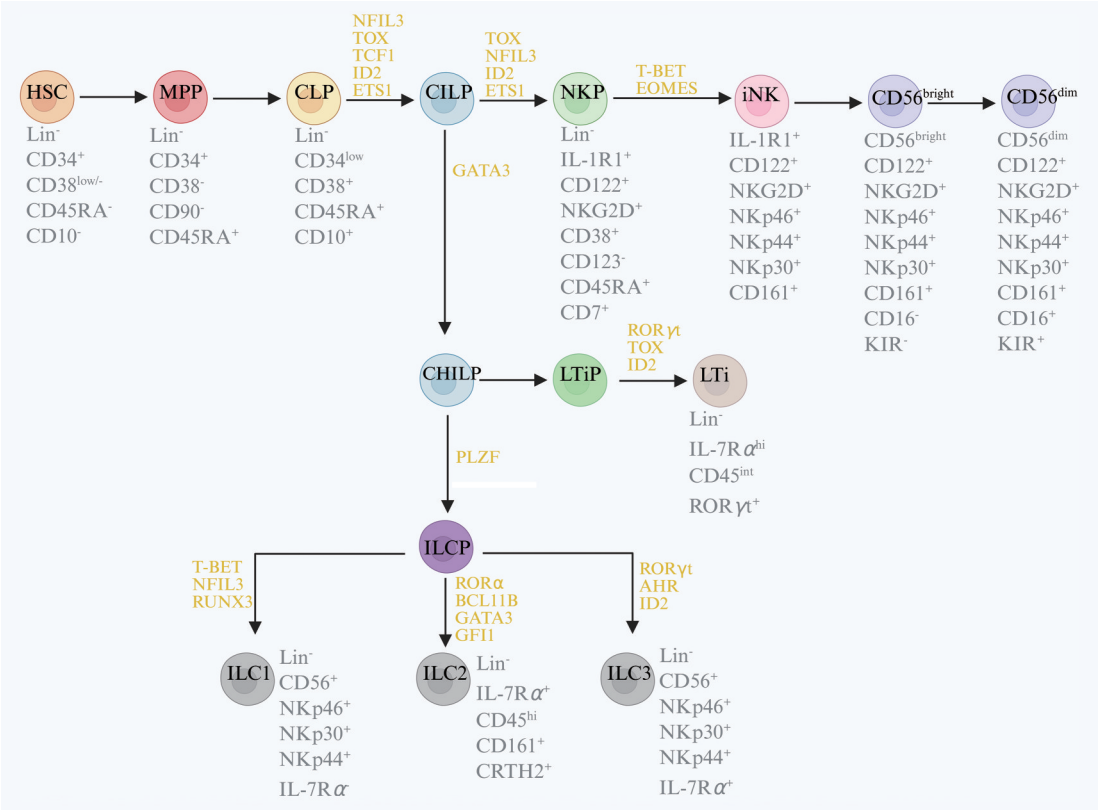


Figure 1 Innate lymphoid cell (ILC) development in humans. Hematopoietic stem cell (HSC) differentiate into multipotent progenitor (MPP) and subsequently into common lymphoid progenitor (CLP). CLPs further differentiate into common innate lymphoid progenitor (CILP). CILP can differentiate into natural killer cell progenitor (NKP) or common helper innate lymphoid progenitor (CHILP). CHILP could further differentiate into lymphoid tissue inducer progenitor (LTiP) and innate lymphoid cell progenitor (ILCP). LTiP differentiate into lymphoid tissue inducer (LTi) cell, and ILCP give rise to ILC1, ILC2, and ILC3. Each stage of differentiation is dependent on the expression of the indicated transcription factors: NFIL3 (nuclear factor, interleukin 3 regulated), ID2 (inhibitor of DNA binding 2), TOX (thymocyte selection-associated high mobility group box protein), TCF-1 (transcription factor 7), ETS1 (ETS proto-oncogene 1), GATA3 (GATA binding protein 3), PLZF (promyelocytic leukemia zinc finger), T-BET (TBX21, T-box transcription factor 21), EOMES (eomesodermin), RUNX3 (RUNX family transcription factor 3), RORα (RAR related orphan receptor A), BCL11B (BCL11 transcription factor B), GFI1 (growth factor independent 1 transcriptional repressor), RORγt (RAR related orphan receptor C), and AHR (aryl hydrocarbon receptor). Current evidence suggests that in humans, some ILC1 subsets may originate from precursors other than ILCP, though these remain unidentified. +: Positive expression; -: Negative expression; hi: High expression; low: Low expression

状态下, 小鼠和人NK细胞均表现出低水平的糖酵解和OXPHOS水平, 以维持基础生理功能, 与初始T细胞类似。NK细胞的分化成熟依赖转录因子Eomes和T-bet的层级调控: Eomes主导NK细胞毒性程序 (如穿孔素、颗粒酶B基因表达) 的建立, T-bet则协同IL-15信号调控IFN-γ分泌相关通路, 且RUNX3可增强T-bet的转录活性, 进一步强化NK细胞的效应功能。然而, NK细胞要获得完整的效应功能需要经历显著的代谢重编程, 且不同激活信号可引发不同的代谢变化。其中, 受体介导的激活比细胞因子活化更依赖代谢重编程过程[17]。在IL-2、IL-12等细胞因子激活条件下, NK细胞的糖酵解、OXPHOS、葡萄糖摄取和脂质合成均会增强[10]。葡萄糖是驱动此类激活NK细胞代谢增强的主要燃料。细胞因子激活NK细胞后, 葡萄糖先经糖酵解转化为丙酮酸, 部分丙酮酸被还原为乳酸。与其他淋巴细胞不同, NK细胞极少将丙酮酸导入TCA循环, 主要是通过CMS途径将丙酮酸代谢为胞质柠檬酸 (citrate)。具体而言, CMS途径首先丙酮酸先转化为线粒体乙酰-CoA, 后者与草酰乙酸 (oxaloacetate) 结合形成线粒体柠檬酸盐 (citrate); 线粒体柠檬酸盐通过柠檬酸–苹果酸逆向转运蛋白SLC25A1 (solute carrier family 25 member 1) 转运至胞质中进而被ATP柠檬酸裂解酶 (ATP-citrate lyase, ACLY) 分解为乙酰-CoA和草酰乙酸。细胞质中的草酰乙酸在氧化NADH为NAD^+的反应中转化为苹果酸 (malate), 而苹果酸可通过SLC25A1重新进入线粒体, 再次转化为草酰乙酸并

产生另一分子NADH, 形成循环往复的穿梭过程。CMS的核心价值在于通过上述穿梭机制, 同时实现两大关键功能: ① 提供再生糖酵解必需的NAD^+, 满足甘油醛-3-磷酸脱氢酶GAPDH的需求; ② 通过柠檬酸的生成与裂解、苹果酸的中间角色以及丙酮酸的回补, 实现乙酰CoA的跨膜运输并伴随还原力的平衡, 为细胞内乙酰化反应、脂肪酸合成等提供碳源与能量 (图2)。因此, 抑制糖酵解或CMS会显著减少NK细胞IFN-γ和颗粒酶B等效应分子的表达[10]。这一独特代谢模式的核心逻辑, 本质是满足先天免疫“快速效应与微环境适应”的功能需求。作为需要瞬时释放穿孔素、颗粒酶或分泌IFN-γ的响应细胞, NK细胞优先通过糖酵解快速供能[18]。内源性丙酮酸仅少量进入TCA循环, 其余多数转化为乳酸并再生糖酵解必需的NAD^+[10]。CMS则通过转运线粒体柠檬酸至胞质, 分解为乙酰-CoA, 为细胞毒性颗粒组装所需脂肪酸合成提供关键碳源, 同时完成NAD^+的再生, 由此构成糖酵解、CMS与NAD^+再生的代谢闭环[19]。此外, 限制丙酮酸进入TCA循环可减少线粒体NADH过度积累引发的电子泄漏, 使线粒体ROS (mtROS) 生成量显著低于TCA循环主导模式。外源性丙酮酸还能通过特定转运体进入线粒体补充TCA循环底物, 维持线粒体膜电位稳定 (波动幅度仅为T细胞的1/3)[20,21]。在葡萄糖匮乏的肿瘤微环境中, NK细胞通过CMS整合谷氨酰胺代谢, 让谷氨酰胺衍生的α-酮戊二酸既补全TCA循环又生成NADPH抗氧化[22,23]。研究发现, 外源性丙酮酸可使NK细胞杀伤效率维持到正常水平的80%, 未添加组仅为正常水平的30%, 而$CD8^+$ T细胞在添加丙酮酸组的

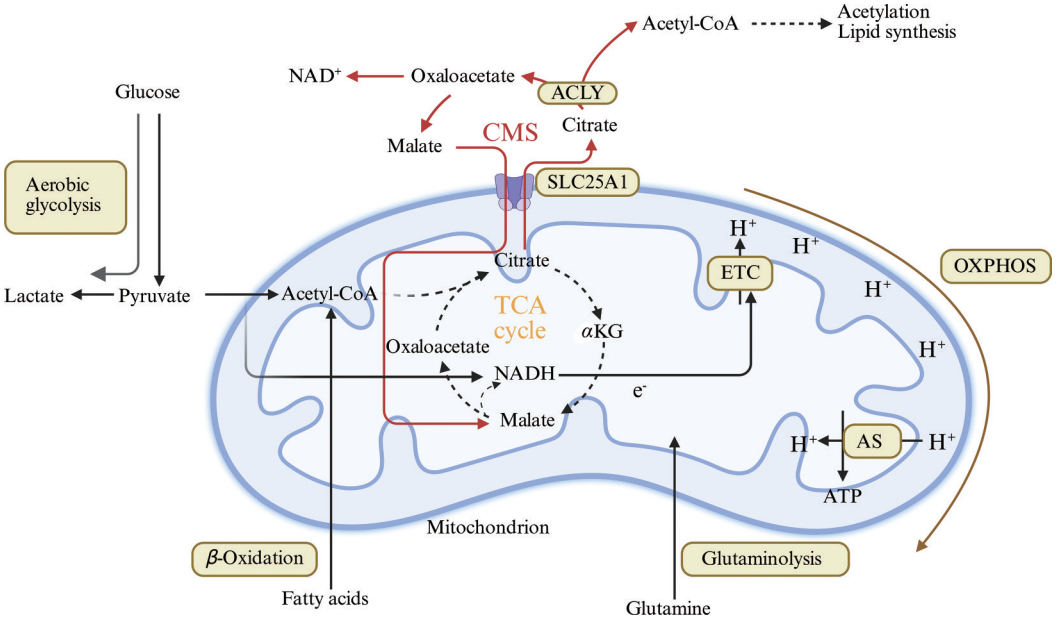


Figure 2 Metabolism characteristics of natural killer (NK) cells. Cellular metabolism can be configured to efficiently generate energy in the form of adenosine triphosphate (ATP). Glucose is metabolized to pyruvate *via* glycolysis, and pyruvate can further be used to drive oxidative phosphorylation (OXPHOS). In the cell's mitochondria, pyruvate is converted to acetyl-CoA, which fuels the metabolic cycle and generates reducing equivalents (NADH and $FADH_2$) to power OXPHOS. Notably, upon activation, NK cells rarely direct a large amount of pyruvate into the TCA cycle; instead, they mainly mediate pyruvate metabolism *via* the citrate-malate shuttle (CMS) pathway to generate cytosolic citrate, which supports energy supply and biosynthesis. Fatty acids produce acetyl-CoA in mitochondria through a catabolic process called β-oxidation, among which carnitine palmitoyltransferase 1A (CPT1A), the rate-limiting enzyme of fatty acid oxidation (FAO), can promote the transport of fatty acids into mitochondria for oxidation, which is crucial for maintaining mitochondrial homeostasis and cytotoxicity of NK cells. Glutamine can also serve as a fuel for mitochondrial OXPHOS, and in the glucose-deficient tumor microenvironment, NK cells can integrate glutamine metabolism through the CMS pathway. The α-ketoglutarate derived from glutamine can not only complement the TCA cycle but also generate NADPH to resist oxidative stress. Beyond powering ATP synthesis, glucose and glutamine can be metabolized to support biosynthetic processes. Metabolic intermediates can be shunted into pathways that generate biosynthetic precursors essential for the synthesis of lipids, nucleotides, and proteins. Glucose can also be diverted to the pentose phosphate pathway (PPP), which is critical for nucleotide synthesis and the production of NADPH. NADPH acts as a key cofactor in biosynthetic pathways and is used for the reduction of glutathione—glutathione can scavenge reactive oxygen species (ROS) to maintain cellular redox homeostasis, which plays an important role in helping NK cells avoid ROS-mediated functional impairment and ensuring the normal synthesis and release of effector molecules such as perforin and granzyme B. Created by BioRender.com

条件下仅达到正常水平的25%[20,21]。

从进化适应与功能优势视角看, 该模式与T细胞、B细胞形成显著差异: 进化上, NK细胞的非特异性即时防御功能, 仰赖于其低耗能的CMS状态及外源性丙酮酸利用机制, 以此实现高效、快速的免疫应答, 它既不似T细胞般依赖三羧酸循环产生核苷酸前体以支持增殖, 也无需如B细胞般大量利用三羧酸循环衍生的氨基酸以合成免疫球蛋白, 从而维系了其快速应答的代谢基础[20]。肿瘤微环境中NK细胞可通过CMS维持糖酵解进程, 且该过程不依赖内源性丙酮酸, 因此乳酸对其乳酸脱氢酶 (LDHA) 抑制率仅为T细胞的1/2, 其杀伤效率仅下降20%且耗竭标志物TIM-3表达量也比T细胞低60%; 与之相反, T细胞因内源性丙酮酸生成不足、mtROS大量积累, 导致杀伤效率下降75%并伴随功能耗竭, 而B细胞则难以适应此类应激环境[22,24-27]。综上, 这一模式是先天免疫与适应性免疫进化分工的直接体现, 保障NK细胞在应激微环境中的抗耗竭优势与快速效应功能。

尽管脂质合成对效应T细胞代谢重编程至关重要, 但抑制脂质合成通路对NK细胞效应功能和增殖的影响甚微[10,28]。高血脂、肥胖等背景下造成的细胞外FAs反而会抑制其代谢与功能[14]。谷氨酰胺虽非激活NK细胞OXPHOS的直接燃料, 但其通过介导的必需氨基酸摄取对NK细胞功能维持有重要作用[19]。因此, NK细胞形成了以葡萄糖为核心燃料的代谢模式, 通过糖酵解和CMS为IFN-γ、颗粒酶B等效应分子的合成及免疫突触的形成提供能量[14]。

上述代谢模式在不同NK细胞亚群中也呈现显著差异。与之相对, $CD56^{dim}CD16^{+}$ NK细胞在静息状态下即维持较高的基础糖酵解活性。这与其表面高表达的杀伤相关受体 (如NKG2D、NKp46) 功能储备相适配, 可快速响应靶细胞信号启动杀伤程序。当受到靶细胞刺激或抗体介导的CD16激活时, $CD56^{dim}$亚群会进一步上调己糖激酶2 (HK2)、LDHA等糖酵解关键酶的表达, 同时轻度增强OXPHOS效率, 这种“糖酵解主导、OXPHOS辅助”的代谢特征, 能在短时间内为穿孔素/颗粒酶的组装释放及免疫突触形成提供充足ATP, 完美匹配其作为主要杀伤性亚群的功能需求。而$CD56^{bright}$ NK细胞在IL-2或IL-12/IL-15刺激下, 优先上调转铁蛋白受体CD71、L型氨基酸转运体 (CD98) 及葡萄糖转运蛋白1 (GLUT1) 表达, 从而迅速增强葡萄糖摄取[29]。尽管抑制糖酵解对$CD56^{bright}$和$CD56^{dim}$两亚群的脱颗粒作用影响甚微, $CD56^{bright}$亚群的IFN-γ生成却被显著抑制, 反映其细胞因子分泌能力对糖酵解的高度依赖性[29]。这种代谢分工使$CD56^{bright}$亚群能够在免疫应答中快速释放大量细胞因子, 与其在次级淋巴组织中的免疫调节功能相匹配。

IL-15对NK细胞代谢的影响具有剂量依赖性。低浓度IL-15仅维持细胞存活, 不诱导代谢重编程, 而高浓度IL-15则驱动NK细胞糖酵解和OXPHOS协同上调。值得注意的是, 持续暴露于高剂量IL-15会通过抑制代谢通路而引发NK细胞耗竭, 提示临床应用中需精准调控IL-15剂量和给药频率[30]。在体内, 糖酵解对NK细胞清除小鼠巨细胞病毒 (MCMV) 的杀伤活性不可或缺, 但对IFN-γ分泌无显著影响, 提示代谢通路对NK细胞不同效应功能的差异调控机制[31]。此外, IL-15预刺激可通过代谢重编程降低杀伤功能对糖酵解的依赖性, 这一发现为临床场景提供了具体的新治疗方向: 面对病毒感染时, 免疫微环境常存在糖代谢限制, 且感染还会引发NK细胞代谢耗竭, 而通过上述代谢调控策略, 有望增强NK细胞抗病毒活性[31]。

2 NK细胞代谢调控关键分子

2.1 哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) mTOR是代谢调控的核心分子, 通过与不同蛋白亚基形成mTORC1 (mammalian target of rapamycin complex 1) 和mTORC2 (mammalian target of rapamycin complex 2) 两种复合体而发挥作用, 两者调控路径和靶点存在差异。其中, mTORC1活性对NK细胞发育、代谢重编程及效应功能至关重要, mTORC2则更多通过间接调控mTORC1而影响NK细胞代谢。在NK细胞发育阶段, mTORC1活性在$CD11b^{low}/CD27^{hi}$不成熟NK细胞中最高, 随成熟逐渐下降, 与营养转运体和代谢酶表达趋势一致。NK细胞特异性敲除mTOR或Raptor可导致骨髓中不成熟$CD11b^{low}$ NK细胞向成熟$CD11b^{hi}$NK细胞分化受阻[32]。成熟静息态NK细胞mTORC1活性低, 但经细胞因子刺激后显著增强, 且$CD56^{bright}$亚群激活强度高于$CD56^{dim}$[29]。$CD56^{bright}$凭借更高mTORC1活性, 快速启动糖酵解和OXPHOS以支持IFN-γ分泌[29]。mTORC2虽非主要代谢调控因子, 但对小鼠NK细胞发育和功能至关重要, 其通过抑制STAT5介导的L型氨基酸转运体SLC7A5 (solute carrier family 7 member 5) 表达负调控mTORC1活性, 从而避免NK细胞过度活化[32]。

2.2 c-MYC c-MYC作为NK细胞代谢与功能的核心转录调控因子, 通过多重机制驱动糖酵解和OXPHOS。c-MYC不仅调控葡萄糖转运体和糖酵解酶的表达以增强糖酵解, 还通过促进线粒体生物合成支持OXPHOS, 为NK细胞效应功能提供能量基础[19]。在调控机制上, c-MYC的表达呈现动态依赖性。IL-2、IL-12或IL-15刺激初期, 其上调部分依赖mTORC1信

号, 而数小时后其持续表达则依赖氨基酸的可及性[32,33]。谷氨酰胺通过SLC7A5进入细胞后, 可促进c-MYC mRNA的翻译过程以增加c-MYC蛋白合成, 部分抵消c-MYC蛋白的持续降解, 若阻断谷氨酰胺供给或抑制SLC7A5活性可导致c-MYC蛋白在数分钟内快速丢失, 进而降低糖酵解和OXPHOS速率[19]。此外, c-MYC还作为内质网压力传感器IRE1α-XBP1s轴的下游靶标, 通过IRE1α-XBP1s-c-MYC通路调控线粒体功能和OXPHOS速率, 在NK细胞增殖与活化中形成代谢−应激响应的交叉调控网络[34]。除代谢调控外, c-MYC还可通过直接上调NKG2D等激活性受体表达水平来增强NK细胞对靶细胞的识别与杀伤能力[35]。

2.3 甾醇调节元件结合蛋白 (sterol regulatory element binding proteins, SREBP) SREBP作为mTORC1的下游靶基因, 是NK细胞代谢与功能的关键转录调控因子。传统上, SREBP被视为脂肪酸和胆固醇合成的主调控因子, 可诱导脂肪酸合酶 (fatty acid synthase, FASN)、低密度脂蛋白受体 (low density lipoprotein receptor, LDLR)、乙酰辅酶A羧化酶 (acetyl CoA carboxylase, ACC) 等脂质合成相关基因的表达[36,37]。但在NK细胞中, SREBP调控的脂肪酸和胆固醇合成并非主导功能, 而是通过全新机制参与代谢重编程。细胞因子刺激NK细胞后, SREBP的核心作用转向调控CMS代谢途径。通过诱导SLC25A1和ACLY的表达, 促使线粒体产生的柠檬酸转运至细胞质并裂解为乙酰辅酶A和草酰乙酸, 从而显著增强糖酵解和OXPHOS速率[10]。此外, SREBP还可通过调控c-MYC表达促进聚胺合成, 进一步上调糖酵解和OXPHOS水平, 协同增强IFN-γ分泌及颗粒酶B等效应分子表达, 最终提升NK细胞对靶细胞的杀伤能力[38]。实验证实, 无论是药物抑制还是敲除SREBP基因, 均会导致小鼠NK细胞糖酵解和OXPHOS显著下降, 伴随IFN-γ产生减少及细胞毒性受损[10]。值得注意的是, 这一调控机制在人NK细胞中同样关键。抑制SREBP激活会直接损害人NK细胞效应功能, 表现为IFN-γ分泌减少和颗粒酶B表达下调[10]。综上, SREBP通过整合脂质合成调控与代谢通路重编程, 成为NK细胞应对免疫激活的核心分子节点。

3 不同疾病背景下NK细胞代谢特征改变

3.1 肥胖 越来越多的研究证实, 代谢紊乱是肥胖、癌症等慢性疾病中NK细胞功能异常的关键驱动因素, 而肥胖对NK细胞的影响呈现显著的组织特异性。在外周循环与脾脏等系统免疫层面, 肥胖通过过氧化物酶体增殖物激活受体 (peroxisome proliferator-activated receptors, PPAR) 通路驱动NK细胞内脂质异常堆积, 从而抑制mTORC1和c-MYC信号通路活性, 进而导致糖酵解-OXPHOS代谢紊乱, 使得NK细胞无法响应细胞因子等刺激启动能量代谢, 表现为循环NK细胞数量减少、颗粒酶B/穿孔素表达下调、IFN-γ分泌不足及肿瘤靶细胞杀伤能力显著降低[14]。在脂肪组织局部微环境中, 肥胖诱导脂肪细胞高表达NK细胞激活受体NCR1 (也称NKp46) 的配体且脂肪组织巨噬细胞分泌IL-15。IL-15与NCR1配体对NK细胞的双重激活作用, 导致脂肪驻留NK细胞呈过度激活表型, 表现为增殖速率加快、IFN-γ和TNF分泌增加, 进而导致促炎性巨噬细胞极化, 损伤胰岛细胞, 进而加剧胰岛素抵抗和慢性炎症反应[39,40]。因此, 信号传导异常和代谢缺陷是肥胖人群NK细胞功能障碍的核心问题。

3.2 肿瘤 NK细胞在抑制肿瘤生长、侵袭和转移等进程中发挥关键控制作用。然而, 肿瘤细胞的快速增殖会引发肿瘤微环境内葡萄糖、谷氨酰胺及氧气等营养物质的匮乏, 同时伴随腺苷、乳酸等代谢产物的大量蓄积, 进而导致NK细胞出现代谢功能紊乱。研究显示, 肿瘤微环境中NK细胞的代谢异常可能是其功能受到抑制的重要因素之一。

转化生长因子-β (transforming growth factor-β, TGF-β) 作为与多种肿瘤发生发展相关的多效性细胞因子, 可通过抑制细胞代谢显著诱导肿瘤微环境中NK细胞功能障碍[41]。在KRAS驱动的肺癌模型中, TGF-β可诱导NK细胞异常表达糖异生酶果糖-1,6-二磷酸酶 (FBP1), 其通过抑制糖酵解、损害细胞活力引发NK细胞功能障碍, 而药物抑制FBP1可恢复糖酵解及NK细胞效应功能[13]。在转移性乳腺癌患者中, 过高的TGF-β浓度使得外周血NK细胞出现mTORC1活性受损、线粒体形态改变、OXPHOS速率降低等代谢缺陷, 与IFN-γ产生减少、死亡配体TRAIL表达降低及肿瘤细胞杀伤能力减弱等现象密切相关[13]。而阻断TGF-β与其受体结合, 或体外阻断升高的TGF-β, 均可显著改善肿瘤微环境中NK细胞的代谢活性及效应功能[42,43]。多个临床前实验发现通过基因编辑的方式阻断TGF-β可显著增强嵌合抗原受体 (chimeric antigen receptor, CAR)-NK细胞对抗肿瘤的功能[44,45]。

肿瘤微环境中缺氧微环境对NK细胞功能产生显著双重影响。一方面, 通过mTOR-Drp1途径诱导NK细胞线粒体过度分裂和碎片化, 降低OXPHOS速率, 损伤其细胞毒活性并削弱存活能力[46]。如肝癌患者的肿瘤组织微环境中NK细胞因缺氧出现线粒体小型化、碎片化, 最终导致肿瘤免疫逃逸[46]。另一方面, NK细胞通过HIF通路应对缺氧环境, 短期缺氧诱导HIF-1α

表达, 其与IL-15协同驱动糖酵解基因表达以维持NK细胞功能[47]。而常氧条件下, HIF-1α缺失的NK细胞在IL-2和IL-12刺激下仍能保持正常代谢和功能, 提示HIF-1α的调节作用具有氧依赖性, 是NK细胞在缺氧微环境中存活和功能维持的关键[19]。尽管NK细胞主要依赖糖酵解和OXPHOS供能, 但肿瘤所致的葡萄糖限制是否通过诱导NK细胞异常表达糖异生关键酶FBP1抑制糖酵解, 以及谷氨酰胺缺乏是否通过影响c-MYC表达抑制NK细胞代谢, 仍需进一步研究验证。

肿瘤微环境中蓄积的乳酸是NK细胞效应功能和活力的强效抑制剂, 肿瘤细胞因"Warburg效应"以极高糖酵解速率摄取葡萄糖并产生大量乳酸[8]: 一方面阻碍NK细胞对葡萄糖的利用, 另一方面使肿瘤内pH值显著下调 (乳酸浓度 > 20 mmol·L^{-1}时尤为显著)。乳酸通过细胞内酸化抑制活化T细胞核因子 (nuclear factors of activated T cells, NFAT) 表达, 导致ATP合成受阻、IFN-γ生成减少, 并诱导线粒体活性氧蓄积, 引发肝驻留NK细胞凋亡[8]。胰腺癌细胞产生的乳酸还可通过下调NK细胞表面NKG2D、NKp46等活化性受体表达, 降低颗粒酶B、TNFα水平削弱其功能[27]。此外, 肿瘤微环境中的腺苷、前列腺素E_2 (PGE_2)、犬尿氨酸、吲哚胺2,3-二氧化酶 (IDO)、尿嘌呤等代谢物亦参与对NK细胞活性的抑制[48-52]。如腺苷通过抑制IL-12/IL-15介导的STAT5和mTOR通路活化而抑制糖酵解与OXPHOS[53]; 犬尿氨酸与尿嘌呤通过ROS诱导NK细胞凋亡[48]; IDO抑制NK细胞抗体依赖的细胞毒性作用 (ADCC) 效应[54]。最新研究还发现, 肿瘤细胞丝氨酸代谢失调可干扰NK细胞膜鞘磷脂合成, 阻碍免疫突触形成而使其丧失杀伤能力[55]。综上, 肿瘤微环境的代谢失衡通过多重机制系统性抑制NK细胞功能, 维持其代谢稳态对抗肿瘤免疫至关重要 (图3)。

3.3 病毒感染 在人类免疫缺陷病毒1 (HIV-1)、乙型肝炎病毒 (HBV) 等慢性感染中, 免疫系统无法清除病毒, 导致NK细胞长期暴露于持续性炎症环境, 逐渐出现效应功能耗竭, 表现为程序性细胞死亡蛋白-1 (PD-1)、NKG2A、Tim-3、LAG3、PD-L1等多种抑制性受体上调, 呈现类似$CD8^+$ T细胞耗竭的"免疫无能状态"[56-59]。慢性HIV-1感染会诱导NK细胞线粒体功能障碍, 包括OXPHOS受损、线粒体去极化加剧和碎片化, 使其在激活受体刺激下无法通过代谢重塑调动替代能源支持IFN-γ生成, 对CD16抗体刺激的反应减弱[60]。而IL-15预处理可绕过受体结合的代谢需求以增强其功能[17,61]。慢性乙肝患者则表现为外周血NK细胞mTORC1活性降低, EGR2、NR4A2、TOX等转录因子异常表达, 进一步加剧功能耗竭[62]。利巴韦林可通过调控STAT4磷酸化增强NK细胞IFN-γ产生, 在体外亦能提升小鼠脾细胞NK活性, 为慢性病毒感染中NK细胞功能异常的干预提供了潜在药物参考[63]。

进一步研究表明, 抑制性受体的异常表达与NK细胞代谢缺陷存在密切关联。PD-1可通过下调过氧化物酶体增殖物激活受体-γ共激活因子-1α (peroxisome proliferator activated receptor-gamma coactivator-1α, PGC-1α) 表达, 降低NK细胞葡萄糖摄取、糖酵解速率和线粒体活性, 驱动早期功能耗竭[64]。LAG3通过阻碍AKT/STAT5通路, 抑制糖酵解和OXPHOS进程, 减少ATP生成并限制细胞增殖[65]。鉴于慢性病毒感染中LAG3、PD-L1、Siglec-9和Tim-3等多种抑制性受体在NK细胞表面的协同上调, 提示其可能经多重代谢抑制通路形成功能耗竭的"恶性循环"[66,67]。

综上, 慢性病毒感染中NK细胞功能失调的本质是持续炎症驱动的抑制性受体网络与代谢缺陷协同作用的结果, 而靶向代谢重塑或抑制性受体阻断可能成为恢复NK细胞免疫监视功能的潜在策略。

4 其他ILCs代谢特征及其在相关疾病中的改变

4.1 ILC1 尽管已有大量研究阐明了NK细胞的发育、激活及代谢调控机制, 但人们对ILC1在稳态或激活阶段的内在代谢途径仍知之甚少。ILC1源于CHILP, 其分化依赖转录因子T-bet的主导作用, 在IL-12/IL-15信号协同下定向表达IFN-γ基因, 与NK细胞共享T-bet和IFN-γ, 但缺乏NK细胞特有的Eomes表达, 这一转录差异导致二者代谢谱既相似又存在特化[68]。有研究提示糖酵解是支持ILC1活化与功能的关键代谢通路, 调控ILC1的发育、增殖及活化, 而mTORC在其糖酵解重编程中发挥核心作用。对小鼠肠道ILC1的RNA测序显示, 其转录组中与mTOR信号相关的基因高度富集, 提示糖酵解在功能维持中起关键作用[69]。在结核分枝杆菌 (*Mycobacterium tuberculosis*) 感染模型中, 葡萄糖补充可促进肺部IL-18Rα^+的ILC前体细胞向ILC1样细胞分化, 并增强IFN-γ分泌; 使用糖酵解抑制剂2-脱氧葡萄糖 (2-deoxyglucose, 2-DG) 处理后导致ILC1细胞分化受阻及效应功能受损。在肿瘤微环境中的T-bet$^+$NK1.1$^-$ ILC1可通过PD-1信号抑制mTOR通路, 在减弱糖酵解的同时促进脂肪酸摄取。此类代谢重塑导致T-bet$^+$NK1.1$^-$ ILC1的增殖能力下降和功能受损[70]。这些研究表明, 糖酵解是ILC1活化、增殖及效应功能的基础代谢程序, 而mTOR与PD-1通路在其中发挥关键调控作用。Salomé等[71]发现了一类非传统的$CD56^+$ ILC1样细胞, 与传统ILC1相比, 这类细胞具有更强的营养摄取能力和更高效的线粒体活性。这一发现提示, 线

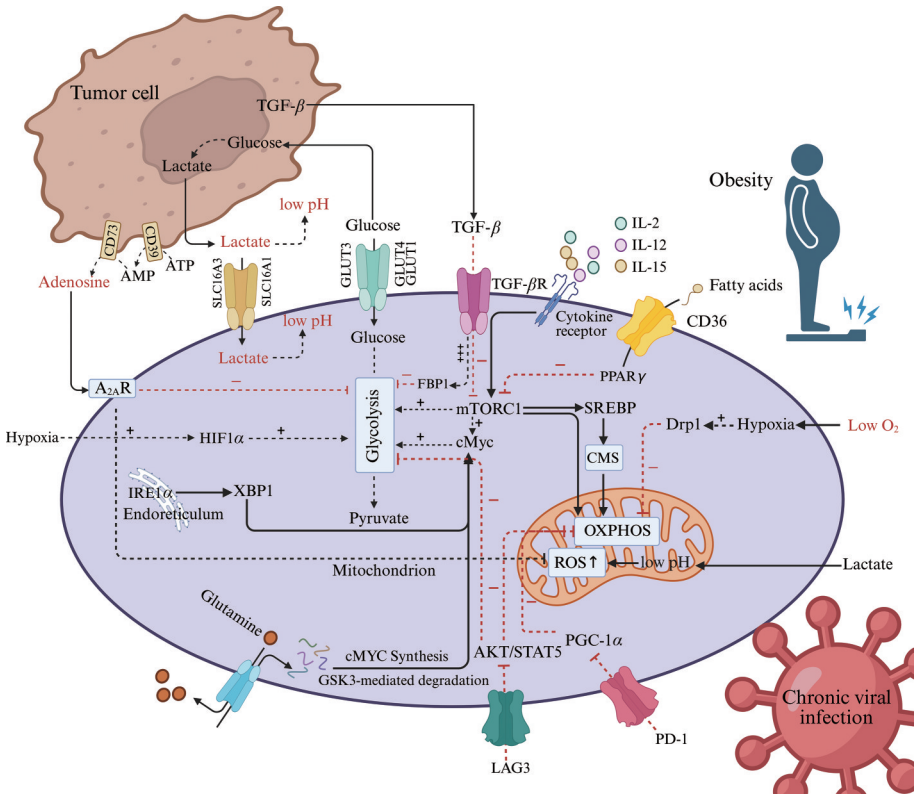


Figure 3 Mechanisms of NK cell metabolic disruption by cancer, obesity, and chronic viral infections, and interactions among NK cell metabolic regulators. The mammalian target of rapamycin complex 1 (mTORC1), which is activated upon cytokine stimulation, plays a crucial role in NK cell metabolism and the production of cytotoxic molecules such as interferon-γ (IFN-γ), granzyme B, and perforin. Its active state is essential for the optimal expression of sterol regulatory element-binding protein [SREBP, a key determinant of the citrate-malate shuttle (CMS)] and cellular myelocytomatosis oncogene (c-MYC, a key determinant of metabolic machinery). The level of c-MYC is maintained by X-box binding protein 1 (XBP1) and glutamine availability, and glutamine deprivation is mediated by the transporter SLC7A5, which transports sufficient amino acids required for c-MYC synthesis. Meanwhile, immunosuppressive molecules in the tumor microenvironment (TME), such as transforming growth factor-β (TGF-β), lactate, adenosine, and fatty acids, can inhibit mitochondrial activity through corresponding mechanisms; in hypoxic environments, hypoxia induces the expression of dynamin-related protein 1 (Drp1), leading to excessive fission of dysfunctional mitochondria. Additionally, chronic viral infections upregulate the expression of inhibitory receptors on the surface of NK cells, and these receptors may impair NK cell function through metabolic pathways. For example, PD-1 can inhibit the expression of PGC-1α, reduce glucose uptake, glycolytic rate, and mitochondrial activity in $CD8^+$ T cells, thereby driving their early exhaustion; LAG3, on the other hand, inhibits the AKT and STAT5 pathways, impairs glycolysis and oxidative phosphorylation (OXPHOS) rates in $CD4^+$ T cells, reduces ATP production, and ultimately restricts their proliferation. GSK3: Glycogen synthase kinase 3; IRE1α: Inositol-requiring enzyme-1α; PPARγ: Peroxisome proliferator-activated receptor gamma; A2AR: Adenosine A2a receptor; ROS: Reactive oxygen species. In the aforementioned processes, solid lines represent the release or uptake of various nutrients, metabolites, and other factors; dashed lines represent the metabolic processing of substrates; and among dotted lines, black dotted lines represent factors that promote or sustain specific pathways, while red dotted lines represent factors that inhibit specific pathways

粒体呼吸作用可能在特定ILC1亚群的细胞毒功能中发挥独特支持作用。但关于OXPHOS和脂肪酸代谢在ILC1命运决定及功能调控中的潜在作用仍亟待深入研究。

ILC1与NK细胞共享关键转录因子T-bet和效应分子IFN-γ, 且具有相似的转录组特征和效应器功能, 因此推测二者代谢谱可能相似[72]。有研究表明在肥胖相关非酒精性脂肪性肝病 (NAFLD) 模型中, 肝脏NK细胞会向ILC1样细胞转化。在此转化过程中, 表现出葡萄糖摄取能力及糖酵解关键通路活性下降, 且可能受TGF-β诱导的糖异生酶调控[73]; 转化后的ILC1样细胞与ILC1、静息态NK细胞类似, 均维持低水平OXPHOS以满足基础功能需求[20]。而在机制上, NK细胞和ILC1可能共享mTORC1这一核心代谢调控分子, mTORC1活性对二者的糖酵解与OXPHOS协同激活以及IFN-γ分泌功能均有影响[22]。此外, 在肿瘤微环

境中, NK细胞可在TGF-β介导下转分化为ILC1样细胞 ($CD49a^+CD49b^-$), 此过程伴随Eomes表达下调; 而TGF-β会通过抑制mTOR信号通路, 降低细胞葡萄糖摄取、氨基酸转运体表达及糖酵解和OXPHOS水平, 限制IL-15对NK细胞活化及代谢活性调控[74-76]。环境因素对ILC1代谢影响显著, 如肥胖时脂肪细胞表面NCR1和NKG2D的配体表达上调, 局部及全身IL-12水平升高, 驱动ILC1在脂肪组织增殖与积累[39,77,78]。脂肪组织巨噬细胞分泌的IL-15可能通过增强代谢活性促进ILC1功能与增殖[40,79-81]。此外, ILC1代谢还与微生物群存在相互作用, 先天免疫系统中T-bet缺失会改变微生物群组成, 而肠道微生物群在生命早期发育阶段中为NK细胞与ILC1的分化提供启动信号。不过这一启动过程并非独立发生, 需与局部微环境中的细胞因子协同作用, 其具体分子机制仍有待进一步深入研究验证[1]。饮食相关因素 (如特定益生菌与膳食纤维组合、维生素、黄酮类等) 也能影响其增殖和功能, 而脂质代谢增强则可能损害其抗肿瘤活性[82-85]。

ILC1在维持代谢稳态和参与相关疾病中发挥关键作用, 且具有组织特异性。在脂肪组织中, 组织驻留ILC1亚群表型和功能有别于脂肪NK细胞。稳态下, 组织驻留ILC1可通过细胞毒性作用, 清除表达NKG2D配体RAE-1的活化M2巨噬细胞, 以维持稳态[86]。而在饮食诱导的肥胖中, 组织驻留ILC1数量增加并分泌IFN-γ, 诱导巨噬细胞向促炎表型极化, 加剧胰岛素抵抗和脂肪组织炎症, 甚至可能促进肥胖向2型糖尿病 (T2D) 转变。T2D患者脂肪组织中ILC1数量与胰岛素抵抗呈正相关, 并通过IFN-γ依赖机制诱导脂肪纤维化[87]。ILC1参与NAFLD发展, 然而肥胖小鼠NK细胞向ILC1的表型和功能转变可能对NAFLD具有保护作用[73]。

目前, ILC1代谢研究仍存在诸多待解问题: 其代谢与细胞可塑性的关联如IL-12和IL-15驱动RORγt$^+$ ILC3分化为ex-RORγt$^+$ ILC1样细胞的代谢重编程机制、组织特异性代谢差异、在肿瘤或感染中整合信号调节代谢和效应功能的具体方式, 以及代谢途径如何支持其持续分泌细胞因子等核心功能, 均需进一步探索。

4.2 ILC2 ILC2代谢具有显著的适应性和环境依赖性, 主要通过糖酵解、FAO及氨基酸代谢满足不同生理需求。ILC2由CHILP分化而来, 其特化过程依赖转录因子GATA3和RORα的双重调控: GATA3直接结合IL-5、IL-13基因启动子, 确立2型细胞因子分泌程序, 同时调控精氨酸代谢相关基因 (如Arg1) 的表达; RORα则通过增强IL-33受体 (ST2) 的表达, 提升ILC2对微环境信号的响应能力, 进而影响其代谢重编程方向[88]。人ILC2展现出双重代谢特征, 静息状态下的ILC2依赖支链氨基酸和精氨酸, 通过OXPHOS供能; 激活后则增强糖酵解和OXPHOS, 以支持细胞因子产生。

在糖酵解方面, ILC2前体和成熟细胞均高表达精氨酸酶1 (arginase 1, Arg1), 可将*L*-精氨酸代谢为尿素和鸟氨酸, 鸟氨酸为多胺合成提供底物, 进而调控其增殖和细胞因子产生, 但这种调节具有疾病背景特异性。在过敏原诱导的气道炎症中, Arg1缺失导致ILC2扩增和细胞因子产生功能受损进而减轻气道炎症。但在蠕虫感染中, Arg1缺失却不影响肺脏组织ILC2细胞数量、细胞因子产生及机体蠕虫清除的能力[89]。Helou等[90]研究发现, PD-1信号通路可抑制肺脏ILC2的糖酵解活性, 从而促进细胞凋亡并减少IL-5、IL-9和IL-13等2型细胞因子的产生。而PD-1阻断则可恢复葡萄糖代谢, 促使细胞代谢转向有氧糖酵解, 而使用2-DG抑制葡萄糖利用则会消除上述效应, 这充分证实了葡萄糖代谢对ILC2存活与活化的不可或缺性。类似地, Surace等[11]发现, 在IL-33刺激下, 糖酵解及mTOR信号通路对ILC2 IL-5和IL-13的产生必不可少。近期有研究发现过度的糖酵解可能对ILC2产生负面影响。事实上, "适度"与"过度"糖酵解在ILC2中的界定核心是"代谢平衡与功能适配": 功能层面上, "适度糖酵解"是ILC2响应IL-33/IL-25等刺激后实现活化、增殖及IL-5、IL-13等2型细胞因子分泌的必要支撑, 能保障其抗蠕虫感染、参与气道炎症应答等核心功能, 且维持细胞存活与稳态[91]; 而"过度糖酵解"则会导致ILC2细胞因子产生显著减少、增殖能力下降、存活率降低, 还常伴随线粒体功能障碍, 无法与OXPHOS协同维持代谢平衡, 甚至诱发氧化应激损伤[90,92]。分子层面上,"适度糖酵解"表现为GLUT1、HK等糖酵解关键酶适度上调, mTOR通路适度激活以支持代谢重编程与细胞因子合成, 线粒体与糖酵解协同且ROS水平可控, STAT3、ATG5等调控分子正常表达以维持代谢–功能平衡[93];"过度糖酵解"则呈现GLUT1、HK等异常高表达, HIF-1α异常积累、mTOR过度激活引发代谢失衡, 线粒体活性受抑且ROS过量产生, PD-1上调、LKB1缺陷等导致线粒体自噬或功能衰竭。这一临界状态由细胞内在因素与微环境外在因素共同决定[94-98]。内在因素方面, E3泛素连接酶VHL的核心作用是抑制HIF-1α积累, 从而避免糖酵解过度[99]; 自噬关键基因Atg5可维持糖酵解平衡[100]; 转录因子STAT3能通过调节线粒体呼吸与蛋氨酸代谢, 保障代谢协同效应[101]; 抑癌基因LKB1可维持线粒体完整性, 防止ROS-NFAT2通路激活诱发糖酵解过度[94]; Arg1则通过介导精氨酸

代谢为多胺, 调控糖酵解强度以适配细胞增殖需求等[90]; 外在因素方面, IL-33与IL-25的刺激强度具有显著影响: 适度激活可支持ILC2正常功能, 而持续高强度刺激则易突破糖酵解的临界平衡状态; 铁缺乏会在增强糖酵解通量的同时抑制OXPHOS, 直接诱发糖酵解过度[102]; PD-1信号对糖酵解具有稳态调控作用, PD-1可抑制糖酵解以维持代谢平衡, 其缺失会导致糖酵解失控, 而PD-1激动剂则能下调糖酵解水平, 避免过度; 短链脂肪酸 (如丁酸盐) 可通过代谢重编程抑制糖酵解过度[103]; 多巴胺能通过抑制OXPHOS, 间接调控糖酵解与线粒体代谢的平衡[104]; 葡萄糖浓度过高则会直接驱动糖酵解通量超标, 突破代谢临界状态[90,91]。Li等[105]证实, E3泛素连接酶VHL蛋白缺失虽然增强了糖酵解, 但却降低了2型细胞因子的产生及细胞存活率。铁缺乏在增强糖酵解通量的同时抑制了OXPHOS, 导致ILC2功能受损[95]。这些发现揭示糖酵解在ILC2中的环境依赖性调控作用, 为通过精确调节糖酵解通路治疗ILC2相关疾病提供了潜在靶点。

脂肪酸代谢是ILC2生物学功能的核心支柱, 既能供能又可产生信号分子。ILC2相较于其他ILC亚群具有更强的脂肪酸摄取能力, 其在蠕虫感染期间依赖脂质代谢维持增殖和细胞因子分泌[11,106]。转录组分析发现, ILC2高表达脂代谢相关基因, 这从分子层面印证了脂肪酸代谢在ILC2中的核心地位[107]。蠕虫感染或营养不良背景下, 肠道ILC2显著依赖脂肪酸代谢[106]。而在过敏原驱动的气道炎症中, ILC2显著增加外源性脂肪酸摄取转化为磷脂, 进而促进ILC2扩增及其介导的气道炎症损伤。而葡萄糖代谢介导的mTOR、PPARγ活化是上调FAO的关键上游信号, 且葡萄糖与外源性脂肪酸协同上调FAO; 葡萄糖限制的生酮饮食可下调ILC2 FAO, 从而降低气道炎症[108]。此外, 人类ILC2展现出双重代谢特征。静息状态下, ILC2依赖支链氨基酸和精氨酸, 通过OXPHOS供能; 激活后则增强糖酵解和OXPHOS, 以支持细胞因子产生[11]。

ILC2代谢受到细胞内源性和外在环境信号的多重精细调控。在细胞内源性调控中, 自噬通过代谢重编程将能量依赖从FAO转向糖酵解, 在ILC2稳态和效应功能维持中具有关键作用。自噬关键基因Atg5的缺失可导致ILC2中细胞死亡增加和细胞因子产生受损[109]。转录因子STAT3则通过调节线粒体呼吸和蛋氨酸代谢, 促进ILC2效应细胞因子产生[101]。PD-1作为代谢检查点, 其缺失会使ILC2代谢偏向糖酵解、谷氨酰胺分解等, 加剧气道炎症[90]。抑癌基因肝脏激酶B1 (LKB1) 在维持脂肪组织ILC2的线粒体完整性及2型细胞因子产生中起关键作用。肥胖诱导的LKB1缺陷可通过ROS活化T细胞核因子2 (nuclear factor of activated T-cells 2, NFAT2) 信号触发线粒体功能障碍, 导致ILC2中PD-1上调及线粒体自噬, 进而抑制OXPHOS, 损害ILC2的2型细胞因子分泌, 并最终加剧胰岛素抵抗[94]。钙释放通过激活钙通道 (Ca^{2+} release-activated Ca^{2+} channels, CRAC) Orai1和Orai2维持肺脏ILC2中的OXPHOS和脂肪酸摄取。抑制Orai通道会损害线粒体功能并增加ROS产生, 且无糖酵解代偿性增强[110]。此外, 氨基酸转运蛋白SLC7A5和SLC7A8介导的氨基酸吸收受mTOR信号调控, 影响ILC2对肠道蠕虫的免疫反应[111]。外在环境信号方面, 维生素A可抑制ILC2功能, 维生素A缺乏导致产生IL13的ILC2细胞剧烈扩增, 从而增强其对抗蠕虫感染[112]。AHR是配体依赖的细胞外环境传感器, 在ILC2中尤其高表达。宿主细胞、食物及微生物等来源的AHR配体可通过AHR通路抑制ILC2的功能, AHR缺失可增强ILC2对抗蠕虫感染的能力[113]。短链脂肪酸 (如丁酸盐) 则可通过诱导代谢重编程而抑制肺ILC2的激活和细胞因子产生; 而通过全身或气道局部补充丁酸盐可抑制ILC2增殖及其介导的气道炎症[114,115]。多巴胺通过ILC2细胞表面多巴胺受体抑制肺脏ILC2的OXPHOS, 从而抑制ILC2增殖及细胞因子分泌, 缓解屋尘螨 (house dust mite, HDM) 诱导的气道炎症[92]。这些调控机制共同塑造了ILC2在不同组织微环境中的代谢表型和功能。

4.3 ILC3 ILC3源于CHILP, 其分化和功能维持依赖转录因子RORγt和AHR。ILC3则在转录因子RORγt和IL-7、TGF-β等细胞因子的作用下分化形成, 通过分泌IL-17/IL-22参与黏膜免疫和组织修复。ILC3的代谢调控与其功能紧密关联, 依赖多种信号通路的协同作用, 且在稳态维持与感染等不同情境下, 有氧糖酵解、线粒体OXPHOS及脂肪酸代谢可通过核心调控分子实现动态协调或相互制约, 以精准适配ILC3功能需求。RORγt不仅激活IL-17、IL-22等效应分子基因, 还可通过调控mTORC1信号, 上调糖酵解和脂肪酸合成相关基因 (如己糖激酶2、ACC1) 的表达[1]。AHR作为环境信号传感器, 结合微生物代谢产物 (如吲哚-3-醛) 后, 可进一步增强RORγt的转录活性, 协同调控ILC3的代谢适应[116]。此外, c-Maf可通过抑制T-bet表达, 阻止ILC3向ILC1表型转换, 同时维持胆固醇代谢稳态, 为RORγt提供配体支持, 间接保障ILC3的代谢特征[117]。除上述通路外, 胆固醇代谢亦参与其中, 并通过mTORC1、HIF-1α、c-Maf等核心分子构建起“内在通路交叉互作与外部信号调控相协同”的完整

调控网络[94]。有氧糖酵解是ILC3能量与生物合成中间体的重要来源, 其核心调控分子是mTOR信号与HIF-1α。IL-1β和IL-23激活的ILC3通过mTORC1增强糖酵解, 进而维持RORγt表达并促进IL-17A和IL-22分泌, 最终驱动ILC3增殖, 以对抗肠道病原体 (如鼠柠檬酸杆菌) 感染[12]。此过程中, 糖酵解与OXPHOS并非独立激活, 而是协同增强——mTORC1激活后不仅诱导糖酵解关键酶HK2表达, 还通过提升线粒体氧耗速率, 快速供给能量以支持IL-17A/IL-22大量分泌及细胞增殖[8,117]; 同时, 脂肪酸代谢同步转向“合成优先”, ACC1介导的从头脂质合成显著增强, 为免疫突触形成、细胞毒性分子组装提供磷脂前体, 而FAO则被抑制以避免能量代谢冲突[116]。缺氧诱导因子HIF-1α作为糖酵解的关键协调因子, 可诱导肠道ILC3中Tox2及其下游靶点糖酵解关键酶HK2的表达, 使ILC3能在组织损伤或细菌感染常见的缺氧环境中实现代谢适应[118]。缺氧环境下, HIF-1α除调控糖酵解外, 可通过调节Tbx21转录控制肠道NKp46$^+$ ILC的可塑性, 促进ILC3向ILC1转化, 此时代谢模式同步切换为ILC1依赖的糖酵解主导型, 实现抗感染功能的精准适配[119]。

值得关注的是, 近年针对肿瘤微环境的研究进一步揭示了ILC3的代谢亚群异质性, 同时为其与NK细胞的功能关联提供了代谢层面的支持: 在转移性肿瘤相关淋巴结中, ILC3可分化为一类特殊的CD56$^+$亚群, 该亚群既保留ILC3的标志性特征, 表达RORγt且具备IL-22分泌能力, 又能上调NK细胞特有的细胞毒性基因, 包括颗粒酶B与穿孔素, 其代谢表型也呈现“ILC3核心程序与NK细胞毒性代谢特征”的交叉特性。如该亚群在糖代谢中依赖CMS将线粒体柠檬酸转运至胞质, 为效应分子合成提供乙酰辅酶A, 这与NK细胞通过CMS支持细胞毒性功能的代谢模式高度一致[94]; 在氨基酸代谢中, 其调控谷氨酰胺摄取的*L*型氨基酸转运体, 如SLC7A5表达水平显著升高, 谷氨酰胺分解速率加快, 这一特征也与NK细胞活化时“谷氨酰胺维持c-MYC活性、支撑代谢重编程”的机制存在一致性, 提示ILC3与NK细胞在细胞毒性相关代谢通路中可能存在重叠[118]。

线粒体OXPHOS对ILC3稳态与功能不可或缺。线粒体转录因子A (mitochondrial transcription factor A, TFAM) 通过调控线粒体DNA和OXPHOS维持ILC3存活[120]。稳态下, ILC3以OXPHOS为主要能量来源, 糖酵解仅维持基础水平——TFAM通过调控线粒体DNA复制与OXPHOS效率, 保障细胞存活与低水平IL-22分泌[118,121]; 脂肪酸代谢则以FAO为核心, 为OXPHOS提供底物, 同时通过ACC1介导基础脂肪酸合成, 维持细胞膜完整性与细胞稳态[116]; 胆固醇代谢则通过转录因子c-Maf调控, 其代谢产物作为RORγt的配体, 稳定ILC3表型, 阻止其向ILC1异常转化, 维系黏膜免疫稳态[117,118]。CCR6$^+$淋巴组织诱导性细胞 (lymphoid tissue inducer, LTi) 样ILC3的IL-22分泌依赖OXPHOS, 但若缺乏抗凋亡蛋白Bcl-2, 过度线粒体呼吸产生ROS反而会损害细胞存活[122]。

脂肪酸代谢 (尤其是从头脂质合成) 深刻影响ILC3功能。脂肪酸代谢与胆固醇代谢并非独立通路, 而是存在交叉调控: mTORC1激活时, 会通过抑制FAO关键酶CPT1A、上调ACC1, 推动脂肪酸代谢流从“氧化供能”向“合成支撑”转移[118]; 胆固醇合成的前体乙酰辅酶A, 可通过脂肪酸代谢通路逆向生成, 形成“脂肪酸–胆固醇代谢循环”, 确保脂代谢网络的稳定性, 避免单一通路紊乱导致的功能失衡[116]; 同时, c-Maf在调控胆固醇合成的同时, 通过代谢产物激活RORγt、抑制T-bet, 进一步阻断ILC3向ILC1转化的分子通路[117]。ACC1介导的脂肪酸合成是ILC3在啮齿柠檬酸杆菌感染或IL-1β/IL-23刺激下产生IL-22的关键[123]。此外, 调控胆固醇合成的转录因子c-Maf不仅能维持ILC3特征性表型、阻止其向ILC1转化, 其代谢产物还可作为RORγt配体, 直接将脂代谢与ILC3可塑性相偶联[123]。与之相对, FAO被证实可抑制LTi细胞活化。DSS结肠炎中, 上调的PD-1信号通过抑制LTi细胞FAO驱动代谢向糖酵解转换, 进而促进IL-22分泌。PD-1缺陷反而因减少IL-22加剧结肠炎[124]。这种代谢转换若过度则会导致功能异常——如炎症性肠病中, PD-1信号过度上调会持续抑制FAO, 驱动代谢向糖酵解异常倾斜, 最终导致IL-22分泌失衡[125,126]; 而阻断PD-1可恢复FAO与糖酵解的平衡, 改善ILC3功能[127]。

营养物质和微生物代谢物通过多种机制调控ILC3功能, 并影响代谢稳态。维生素与微生物代谢物作为关键外部信号, 进一步靶向ILC3核心代谢通路优化功能: 维生素A缺乏会减少ILC3数量及IL-22的产生, 增加肠道感染易感性, 而视黄酸 (RA) 可促进ILC3的IL-22生成以增强防御[128]; 维生素D的活性形式 (1, 25-二羟维生素D3) 通过上调HIF-1α表达增强糖酵解效率, 同时促进胆固醇代谢产物与RORγt结合, 提升ILC3对肠道病原体 (如鼠柠檬酸杆菌) 的防御能力[129]; 短链脂肪酸 (SCFA, 如丁酸盐、乙酸盐) 通过GPR受体激活mTORC1信号, 协同增强糖酵解与脂肪酸合成, 促进ILC3增殖及IL-22分泌[130,131]; AHR配体 (如吲哚-3-醛) 则直接结合IL-22启动子, 增强ILC3的抗感染功能[132-135] (图4)。

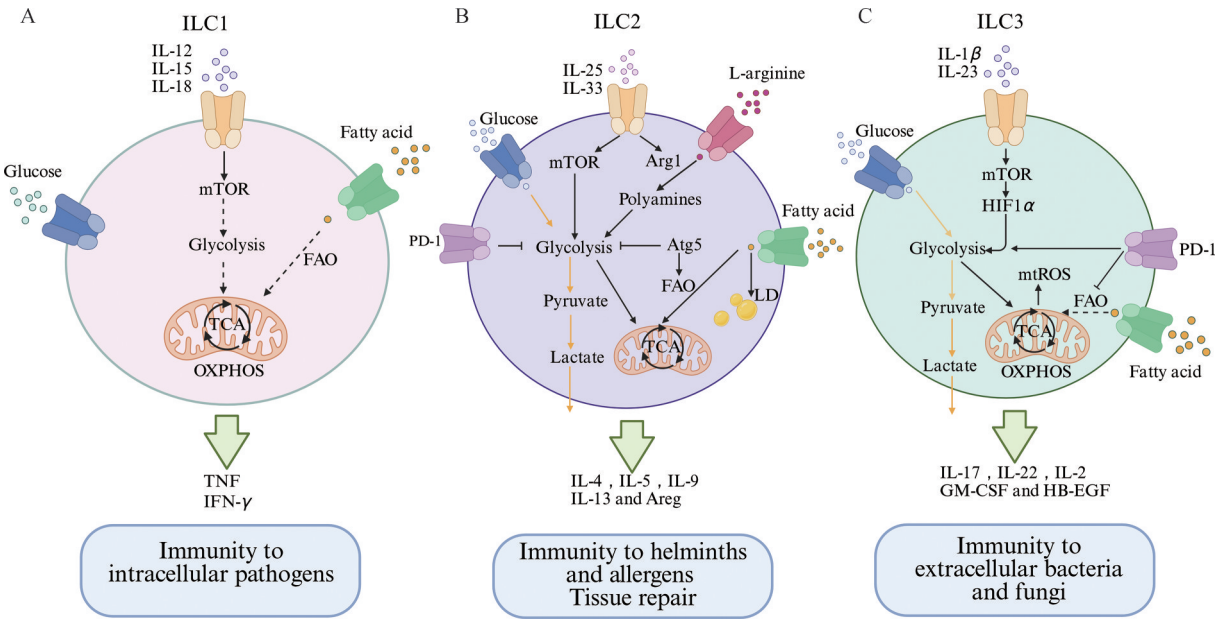


Figure 4 Intrinsic metabolic pathways of the ILC family cells. A: IL-12, IL-15, or IL-18 signaling induces ILC1 activation and function through mTOR-dependent glycolysis; B: ILC2 activated following stimulation with IL-25 or IL-33 metabolize extracellular *L*-arginine into polyamines *via* Arg1 to promote glycolysis. In addition, autophagy mediated by Atg5 or PD-1 signaling negatively regulates glycolysis in ILC2. ILC2 can also take up extracellular fatty acids and utilize mitochondrial FAO to promote proliferation and effector functions during worm infection, or transiently form lipid droplets (LDs) and convert them into phospholipids to promote cell proliferation and drive pathogenic responses in chronic airway inflammation induced by allergens; C: In response to IL-1β and IL-23, ILC3 increase glucose metabolism and show increased mitochondrial oxygen consumption through the mTORC1-HIF1α signaling axis. ILC3 respond to enhanced glycolysis through PD-1 signaling and inhibit FAO during activation and effector cytokine production. mtROS: Mitochondrial reactive oxygen species; TCA: Tricarboxylic acid

综上, ILC3 整合外部维生素与微生物信号, 通过糖酵解、OXPHOS 和脂肪酸代谢的协同互作, 及胆固醇代谢的参与, 支撑其在稳态维持和免疫应答中的多功能性。mTORC1-HIF-1α 轴调控糖酵解, TFAM 等因子维持 OXPHOS, 而脂代谢途径则决定 ILC3 的身份特征与可塑性。这种代谢适应性使 ILC3 能精准响应组织微环境变化, 在保障细胞因子高效分泌的同时, 也为相关疾病的靶向治疗提供新窗口。

5 基于 ILC 功能调控的免疫治疗策略对 ILC 代谢特征的影响

5.1 免疫抑制性检查点抑制剂对 NK 细胞代谢特征的影响 在肿瘤微环境中, 缺氧、营养物质缺乏、抑制性因子等多种抑制因素, 导致肿瘤微环境中 NK 细胞功能严重受损。多种基于恢复体内内源性 NK 细胞功能耗竭的调控策略也展现出较好的预期。

在靶向抗体药物治疗领域, NK 细胞凭借其独特的免疫特性, 成为提升治疗效果的关键因素。NK 细胞表面表达的 FcγR 受体, 尤其是 FcγRIIIA (CD16a), 为与抗体药物建立联系搭建了桥梁。当抗体药物与肿瘤细胞表面抗原特异性结合后, 其 Fc 段能够与 NK 细胞表面的 CD16a 受体紧密结合, 引发一系列激活信号传导。从分子机制层面深入探究, CD16a 受体被激活后, 会促使 NK 细胞内的磷脂酶 Cγ (PLCγ) 活化, 进而生成三磷酸肌醇 (IP3) 和二酰基甘油 (DAG)。IP3 诱导内质网释放钙离子, 使细胞内钙离子浓度迅速升高, 激活下游的信号通路, 如激活 NFAT, 促使其向细胞核内移位, 诱导相关靶基因的转录, 增强 NK 细胞的细胞毒性。DAG 则激活蛋白激酶 C (PKC) 家族, 这对触发 NK 细胞脱颗粒, 释放穿孔素、颗粒酶等细胞毒性分子起到关键作用, 这些分子能够直接破坏肿瘤细胞膜结构, 诱导肿瘤细胞凋亡。此外, CD16a 还参与激活 ERK2 丝裂原活化蛋白激酶 (MAPK) 途径等, 进一步增强 NK 细胞的活性和杀伤功能。以多发性骨髓瘤治疗药物埃罗妥珠单抗 (elotuzumab) 为例, 它是一种靶向信号淋巴细胞激活分子家族成员 7 (SLAMF7) 的人源化 IgG1 单克隆抗体, 而 SLAMF7 在骨髓瘤细胞表面高度表达[136]。Elotuzumab 一方面可通过与 NK 细胞表面的 FcγRIIIa (CD16) 结合, 引发经典的 ADCC; 另一方面, SLAMF7 在细胞毒性 NK 细胞上也有表达, 埃罗妥珠单抗与 NK 细胞表面的 SLAMF7 结合后, 能够直

接诱导NK细胞内的信号转导, 协同其他表面受体 (如NKp46和NKG2D) 触发的钙信号, 增强NK细胞的激活, 促进NK细胞对骨髓瘤细胞的杀伤作用[137-139]。

已有证据表明, 抗PD-1或抗PD-L1抗体能增强多种肿瘤模型中NK细胞的抗肿瘤功效, 其机制可能与T细胞中已证实的代谢修复作用类似, 通过恢复糖酵解和线粒体代谢活性, 逆转功能障碍。深入研究揭示, 免疫检查点分子对代谢的调控是关键。PD-1可通过激活AMPK抑制糖酵解, 并上调$CD4^+$ T细胞中CPT1A的表达以促进FAO, 从而抑制效应T细胞发育[64,140]。PD-1或CTLA-4过表达还会阻碍T细胞受体刺激引发的葡萄糖和谷氨酰胺代谢上调, 且PD-1与PD-L1/PD-L2的相互作用可抑制PI3K-Akt-mTORC1通路, 破坏T细胞代谢重编程[141,142]。而当使用抗体阻断PD-1/PD-L1结合时, 能通过PGC-1α途径提升$CD8^+$ T细胞的糖酵解水平和线粒体活性[64]。研究发现, TLR激动剂可通过激活下游NF-κB、mTORC1通路, 上调NK细胞GLUT1与糖酵解关键酶 (HK2、LDHA) 的表达, 增强糖酵解与OXPHOS的协同活性, 进而促进IFN-γ分泌与细胞毒性颗粒释放。通过将TLR激动剂与PD-L1靶向分子 (如非阻断型纳米抗体) 偶联, 可实现激动剂向肿瘤微环境的精准递送, 在避免全身免疫毒性的同时, 高效激活NK细胞的代谢与效应功能[143]。这些发现提示, 改善代谢或许是免疫检查点阻断逆转NK细胞功能障碍的重要机制, 进而为通过靶向免疫检查点分子恢复NK细胞代谢活性、增强其抗肿瘤及抗病毒功能提供了理论依据。最新的临床研究结果显示: 回输NK免疫细胞后, 胆囊癌转移淋巴结的数量减少了82.3%, 这直接证实了NK细胞作为免疫系统核心力量在抵御癌细胞中的关键作用。而异体NK细胞与PD-1药物的联合使用, 已成为晚期癌症患者的重要治疗选择, 甚至有望成为这类患者的首选方案[144,145]。

除PD-1/PD-L1通路外, 靶向TIGIT通路及联合方案也是解除内源性NK细胞抑制、增强其活性的重要策略。从单一通路阻断来看, TIGIT作为NK细胞表面关键的抑制性受体, 其与肿瘤细胞高表达的CD155/CD112配体结合后, 会通过胞内ITIM结构域传递抑制信号, 导致内源性NK细胞毒性分子分泌减少及IFN-γ产生降低, 削弱其抗肿瘤能力[146]。利用TIGIT特异性抗体, 可通过两种机制恢复NK细胞功能。一是直接与NK细胞表面TIGIT结合, 竞争性阻断其与CD155/CD112的相互作用, 切断抑制信号传导, 逆转NK细胞功能耗竭; 二是借助抗体Fc段与NK细胞表面CD16a受体结合, 触发ADCC效应, 清除肿瘤微环境中表达TIGIT的耗竭型免疫细胞, 减少抑制性细胞群体对NK细胞的干扰, 间接增强内源性NK细胞对肿瘤细胞的识别与杀伤效率[147]。从联合治疗策略来看, 考虑到肿瘤微环境中NK细胞功能受多重抑制因素协同调控, 单一阻断TIGIT通路难以完全克服免疫抑制, 有必要通过联合方案进一步强化疗效。一方面, 可将TIGIT抗体与PD-1/PD-L1等其他免疫检查点抑制剂联用, TIGIT与PD-1/PD-L1分别通过不同信号通路抑制NK细胞, 双重阻断可协同解除多通路抑制, 更全面地恢复NK细胞的糖酵解、线粒体代谢活性及细胞毒性功能, 避免单一通路阻断时肿瘤细胞通过其他抑制通路逃逸的问题[148-150]。另一方面, 可将TIGIT抗体与IL-15、IL-21等细胞因子联用。TIGIT抗体主要负责解除抑制信号, 而IL-15可激活NK细胞mTORC1信号通路, 促进糖酵解和OXPHOS协同上调, 增强细胞增殖与存活[151,152]; IL-21则能进一步诱导NK细胞效应分子表达, 提升其杀伤活性。理论上二者联合可"去抑制+促激活", 小鼠模型中也观察到NK细胞抗肿瘤能力提升, 但该策略仍处于基础研究阶段, 临床有效性和安全性亟待进一步验证[153,154]。

TGF-β抑制剂可恢复NK细胞激活受体表达及细胞毒性分子合成分泌, 提升肿瘤杀伤效率。如卵巢癌临床前模型中, TGF-β抑制剂 (如bintrafusp alfa) 处理后肿瘤内NK细胞CD107a表达升高, 不仅能阻断NK细胞向ILC1的耗竭型转化, 提升肿瘤杀伤效率, 还可解除对mTOR通路的抑制, 恢复NK细胞代谢适应性。当其与IL-15联用时, 更能协同激活mTORC1信号, 促进ATP生成与线粒体功能维持, 减少凋亡[76,155]。在临床进展方面, bintrafusp alfa、SAR439459等TGF-β抑制剂在非小细胞肺癌、晚期实体瘤患者中显示出增加外周血NK细胞活化标志物CD69和Ki67表达, 但目前仍面临因靶点复杂性导致的系统性毒副作用、肿瘤通过上调腺苷等其他免疫抑制因子产生的耐药性, 以及由于NK细胞异质性而对联合方案提出的优化需求等挑战[156,157]。尽管如此, TGF-β抑制剂与CAR-NK、NK细胞衔接器等NK细胞疗法的联合, 已成为改善实体瘤免疫治疗效果的重要方向。

5.2 基于NK细胞输注的免疫细胞治疗策略进展 随着免疫学、基因编辑、合成生物学、干细胞与再生医学等理论与前沿颠覆性技术的发展, 基于免疫细胞功能重建的干预策略在肿瘤、自身免疫病等人类重大慢病治疗应用中迅速发展。近期研究表明, NK细胞及人ILC1、ILC2等ILCs均具有直接细胞毒作用, 这使其作为免疫细胞治疗的种子细胞展现出巨大潜力。临床实践表明, 以NK细胞为代表的ILC免疫细胞治疗在肿瘤、自身免疫病中表现出高安全性和较好的疗效。由

于其“自我非我”识别机制, 其异体输注治疗无明显的移植排斥反应, 被认为是未来“现货型”免疫细胞药物的重要种子细胞[158]。

多项通过调控NK细胞代谢相关的CAR-NK已进入临床试验 (表1)。通过逆转录病毒载体使脐带血NK细胞共表达抗CD19-CAR与IL-15, 强化IL-15信号轴以支持细胞体内扩增与持久性, 该CAR-NK细胞在复发/难治性CD19阳性肿瘤 (慢性淋巴细胞白血病或非霍奇金淋巴瘤) 的临床试验中表现出优异的疗效和极高的安全性[159,160]。敲除CISH等代谢负调控基因, 可以解除其对IL-15信号的抑制, 增强糖代谢与线粒体功能[161]。I期临床试验表明, 敲除CISH可以增强靶向患者体内$CD19^+$ B肿瘤细胞的诱导性多能干细胞来源的CD19-CAR-NK细胞在复发/难治性B细胞淋巴瘤与急性髓系白血病 (AML) 患者中的治疗作用, 并表现出良好的安全性和有效性[162]。通过CD73靶向CAR修饰或A2AR阻断可阻断肿瘤微环境 (tumor microenvironment, TME) 腺苷代谢抑制, 恢复NK细胞代谢活性。如CD73-CAR-NK细胞可使TME腺苷浓度降低60%, 在肺癌异种移植模型中肿瘤生长抑制率达70%[163]。最新研究显示, CAR-NK细胞在肿瘤微环境中CREM表达显著升高, 既伴随GZMB等效应基因上调, 也引发如TIGIT等抑制基因升高, 部分癌症中其高表达还关联不良预后; 而通过CRISPR-Cas9敲除CREM后, CAR-NK细胞体外杀伤能力增强, 体内在淋巴瘤、乳腺癌PDX、胰腺癌模型中显著控瘤且无明显毒性。CREM敲除后可激活NK细胞MYC靶基因等代谢相关通路, 促进细胞能量代谢与增殖, 同时经表观遗传重编程使细胞形成“记忆样”表型以维持长期杀伤活性[164]。另外, TIPE2作为NK细胞中的内在检查点分子, 可通过抑制IL-15触发的mTOR活性来影响NK细胞的成熟、效应功能及对IL-15的应答, 而NK细胞特异性TIPE2缺失则能增强这些功能, 提示IL-15信号与代谢调控通路存在关联[165]。

Table 1 Summary of NK cell therapy in clinical trials. Allogeneic NK cell therapies currently under clinical development are presented, arranged by sponsor of the clinical study. CLL: Chronic lymphocytic leukemia; AML: Acute myeloid leukemia; MM: Multiple myeloma; MDS: Myelodysplastic syndrome; NSCLC: Non-small cell lung cancer

Modification	Mechanism	Malignancy	Combination treatment	Phase	Active clinical trial
CD19 CAR+158V non-cleavable CD16+ constitutively active IL-15/IL-15R fusion	Expresses CD19 CAR, non-cleavable CD16, and IL-15/IL-15R fusion to enhance targeting, persistence, and activation	B cell lymphoma, CLL	Monotherapy or CD20 mAbs	I	NCT04245722
CD19 CAR/IL-15 production	Produces IL-15 *via* CD19 CAR-engineered NK cells to boost proliferation and anti-tumour activity	B cell malignancies	Chemotherapy	I /II	NCT03056339, NCT05020678, NCT05934097, NCT05336409
NKG2DL CAR	Targets NKG2D ligands on tumour cells *via* CAR to mediate cytotoxicity	R/R AML, R/R MDS	Monotherapy	I	NCT04623944, NCT03415100, NCT05213195
HER2 CAR	Targets HER2 on glioblastoma cells *via* CAR for specific killing	Glioblastoma	Monotherapy	I	NCT03383978, NCT05678205
158V non-cleavable CD16 (hnCD16)	Enhances ADCC *via* non-cleavable CD16, combined with mAbs, chemotherapy, or IL-2	B cell lymphoma, AML, solid tumours	CD20/PD-L1 mAbs, chemotherapy, IL-2	I	NCT04023071, NCT04551885
158V non-cleavable CD16 + CD38 KO + constitutively active IL-15/IL-15R fusion	Non-cleavable CD16 for ADCC, CD38 KO to avoid fratricide, and IL-15 fusion for sustained activation	MM, AML, monocytic leukaemia	Daratumumab/ elotuzumab, chemotherapy	I	NCT04614636, NCT04714372
BCMA CAR	Targets BCMA on multiple myeloma cells *via* CAR for specific elimination	MM	Monotherapy	I /II	NCT03940833, NCT05182073, NCT05008536
ROBO1 CAR	Targets ROBO1 on solid tumours *via* CAR for targeted cytotoxicity	ROBO1-positive tumours, pancreatic cancer	Monotherapy	I /II	NCT03940820, NCT03931720, NCT03941457
PDL1 CAR + 158V $CD16^+$ + IL-2 production	Targets PD-L1, uses non-cleavable CD16 for ADCC, and produces IL-2 to enhance anti-tumour activity	Various, pancreatic cancer	Chemotherapy, aldoxorubicin HCl, IL-15 superagonist	II	NCT04390399, NCT03228667, NCT04847466
CD5 CAR + IL-15 production	Targets CD5 on haematological malignancies and produces IL-15 to boost NK cell function	R/R haematological malignancies	Chemotherapy	I/II	NCT05110742

Continued

Modification	Mechanism	Malignancy	Combination treatment	Phase	Active clinical trial
CD33 CAR + gene editing (fratricide avoidance)	Targets CD33 on AML with gene editing to prevent NK cell self-killing	R/R AML	Monotherapy	I	NCT05008575, NCT02944162, NCT05601466
PD-L1 CAR + IL-2/CD16 modification	Targets PD-L1, modifies CD16 for ADCC, and incorporates IL-2 to overcome immunosuppression	NSCLC, pancreatic cancer, glioblastoma, solid tumours	Chemotherapy (varies)	I /II	NCT04050709, NCT03656705
MUC1 CAR + CD28/4-1BB costimulation	Targets MUC1 on solid tumours with costimulatory domains to enhance NK cell activation	NSCLC, pancreatic cancer, colorectal cancer, ovarian cancer	Monotherapy	I/II	NCT02839954
HER2 CAR + CD28 costimulation	Targets HER2 on breast/gastric cancer with CD28 costimulation for enhanced signaling	Breast cancer, gastric cancer	Monotherapy	I/II	NCT05678205
CD19 CAR (autoimmune diseases)	Targets CD16+ B cells in autoimmune diseases to deplete pathogenic cells	SLE, lupus nephritis, ITP	Monotherapy	Early I	NCT06010472, NCT06208280, NCT06337474
NKG2DL/spike bispecific CAR	Dual targets NKG2D ligands and SARS-CoV-2 spike protein to eliminate virus-infected cells	COVID-19	Monotherapy	I/II	NCT04324996
CRISPR-Cas9 knockout of CISH	Knocks out CISH to enhance NK cell cytokine signaling and anti-AML activity	AML	Monotherapy	I	NCT04262467
IL-15 superagonist complex (NKTR-255) + allogeneic NK cells	Combines IL-15 superagonist with allogeneic NK cells to boost proliferation and anti-tumour activity	Myeloid malignancies, solid tumours	Monotherapy	I /II	NCT04256421, NCT03975907
Allogeneic NK cells + lenalidomide	Combines allogeneic NK cells with lenalidomide to enhance anti-MM activity	MM	Lenalidomide	I /II	NCT02619853
Allogeneic NK cells + checkpoint inhibitors (nivolumab)	Combines allogeneic NK cells with nivolumab to block PD-1/PD-L1 axis and enhance anti-tumour immunity	NSCLC, gastric cancer	Nivolumab	I/II	NCT03056369, NCT04155799

上述基于优化NK细胞代谢的基因编辑策略为CAR-NK细胞治疗从实验室走向临床提供了具体的实践路径与数据支撑。需要注意的是, 上述增强CAR-NK细胞代谢适应性的基因编辑策略, 其长期安全性风险目前仍处于理论推测与临床前探索阶段, 尚无明确临床证据证实自身免疫或代谢副产物积累相关毒性。但从自身免疫风险来看, 基因编辑通过强化代谢提升CAR-NK细胞活性的同时, 可能打破免疫稳态, 如CISH敲除解除IL-15信号负调控会导致细胞过度活化, 可能突破“自我–非我”识别边界攻击低表达CAR靶点的正常组织; 共表达IL-15引发的过量细胞因子分泌则可能导致慢性细胞因子血症, 长期或增加自身免疫病风险。如几项临床试验中, 个别患者出现I-II度急性细胞因子释放综合征 (CRS), 部分长期随访提示自身抗体阳性等免疫耐受失衡迹象[160,164,166]; 从代谢副产物毒性来看, 糖酵解过度会导致乳酸堆积, NK细胞ROS生成增加、脂质堆积等影响CAR-NK细胞[160]。当前这些风险因临床研究随访时间短 (< 2年)、样本量有限尚未充分显现, 需要更为长期的随访观察。但鉴于NK细胞在体内存活时间一般为6个月以内, 安全性总体仍属于可控、可接受范畴[167]。

但当前外源性NK细胞输注仍存在待突破的局限, 如部分疗法中暴露–疗效关系尚不明确, 剂量与疗效的关联需更大样本量研究验证; 长期安全性数据不足, 部分远期风险仍需更长时间随访排除; 肿瘤微环境适配性有待优化, 在“免疫冷”肿瘤中疗效可能受限, 需联合免疫检查点阻断剂或代谢调节剂改善肿瘤微环境代谢抑制; 机制研究深度也需加强, 缺乏治疗过程中的肿瘤组织活检样本, 难以系统分析NK细胞对肿瘤微环境的动态影响及关键分子机制, 后续须结合单细胞测序、代谢组学等技术开展更深入的转化研究。

5.3 其他ILCs代谢调控的可能干预策略 ILC1的代谢调控主要涉及“LysoPS-GPR34-cAMP-PKA-CREB”信号轴。在TME中, 溶血磷脂酰丝氨酸 (LysoPS) 通过结合GPR34受体, 激活下游cAMP-PKA-CREB通路, 进而抑制ILC1的功能, 具体干预方式包括4类[168]。① 靶向GPR34受体阻断抑制信号, 通过构建ILC1特异性Gpr34基因敲除模型或使用GPR34拮抗剂, 直接阻断LysoPS与ILC1表面GPR34的结合以切断抑制信号传递, 显著提升TME中ILC1的数量、增强其增殖能力并促进细胞毒性分子表达, 且调控效果严格依赖GPR34靶点特异性; ② 抑制LysoPS合成减少上游抑制源, 通过敲除肿瘤细胞中调控LysoPS合成的Abhd16A基因, 降低TME中LysoPS水平, 从上游减少抑制信号来源, 恢复GPR34通路正常信号平衡以逆转ILC1功能耗竭; ③ 阻断下游信号通路逆转功能抑制,

使用腺苷酸环化酶 (AC) 抑制剂 (如SQ22536)、蛋白激酶 A (PKA) 抑制剂 (如 H-89) 或 CREB 抑制剂 (如 666-15), 直接抑制 cAMP-PKA-CREB 通路活性, 抵消 LysoPS 对 ILC1 的功能抑制, 恢复其细胞毒性及细胞因子分泌能力; ④ 联合免疫检查点阻断强化疗效, 考虑到 TME 中 ILC1 功能受多重抑制因素协同调控, 将 GPR34 拮抗剂与抗 TIGIT 抗体联用, 实现“双重解除抑制”, 既阻断 LysoPS-GPR34 介导的代谢抑制, 又阻断 TIGIT-CD155/CD112 通路的免疫抑制, 不仅增强敏感肿瘤模型抑瘤效果, 还能恢复耐药模型中抗 TIGIT 治疗活性, 协同提升抗肿瘤免疫应答[168]。

ILC2的代谢调控干预聚焦“LKB1-PD-1”与“HIF-1α/糖酵解”双信号轴, 其代谢失衡与功能异常主要受这两大信号轴调控, 针对“LKB1-PD-1”线粒体调控轴, 可通过靶向 PD-1 恢复线粒体活性, 如 PD-1 激动剂 CT-0508 在肥胖小鼠模型中, 可使脂肪组织 ILC2 线粒体膜电位恢复正常, 同时降低胰岛素抵抗指数 (下降 35%); 还可通过调控 Bcl-xL 保护线粒体结构、抑制 ROS-NFAT 通路降低 PD-1 表达、过继转移联合 PD-1 阻断强化组织特异性疗效, 最终改善线粒体功能与胰岛素敏感性。针对“HIF-1α/糖酵解”能量代谢轴调控 ILC2 致病性的研究表明, 靶向该轴可通过两种策略减轻过敏性气道炎症。一是直接抑制糖酵解或 HIF-1α 活性方面, 在 IL-33 或屋尘螨诱导的过敏性气道炎症小鼠模型中, HIF-1α 抑制剂 2-甲氧基雌二醇 (2-ME) 或 2-DG 可显著降低肺 ILC2 的糖酵解水平, 减弱其 IL-5、IL-13 等促炎细胞因子分泌, 进而缓解气道嗜酸性粒细胞浸润与气道高反应性[91]。而 HIF-1α 抑制剂 PX-478 虽未直接在 ILC2 介导的气道炎症中验证, 但已在过敏性鼻炎鼻上皮细胞模型中展现出对“HIF-1α/糖酵解轴”的抑制及抗炎潜力, 为其在 ILC2 相关炎症中的应用提供了机制参考[169]。二是通过基因编辑或细胞预处理降低 ILC2 致病性方面, 已建立高效的 CRISPR-Cas9 编辑人 ILC2 的技术方案 (核转染+RNP 递送), 可在维持细胞活力的同时实现精准基因敲除[170]。结合 ILC2 特异性敲除 HIF-1α 可抑制其致病性的研究结论, 提示该编辑技术靶向 HIF-1α 的潜在价值, 而 ILC2 过继转移策略已在卒中模型中被证实可通过分泌双调蛋白促进炎症修复, 为后续相关过继转移治疗研究提供了技术路径支撑[171]。此外, 近期临床研究显示, 口服谷氨酰胺代谢调节剂 CB-839 可靶向调控 ILC2 氨基酸代谢, 使中重度哮喘患者肺功能指标 FEV1 提升 12%, 症状缓解率达 45%, 为 ILC2 相关炎症疾病治疗提供了临床转化依据[91]。

ILC3 的代谢调控干预从多维度协同维持代谢稳态与功能平衡, 其代谢功能依赖糖酵解、mTOR 信号及外部营养/微生物信号调控, 分泌的 IL-22 对代谢稳态至关重要。昼夜节律调控通路是维持 ILC3 功能稳态的关键靶点, 核心时钟蛋白 (如 REV-ERBα/β、Arntl) 可通过表观遗传调控 RORγt 表达、稳定线粒体代谢, 直接影响 ILC3 的 IL-22 分泌能力及肠道黏膜保护功能, 其功能失调会导致 ILC3 向促炎 ILC1 转化, 加剧肠道炎症损伤[172]。小分子化合物 SR-8278 作为 REV-ERB 受体拮抗剂, 可通过干预这一昼夜节律调控轴, 逆转 ILC3 的功能失衡与可塑性异常, 在肠道炎症模型中促进保护性 IL-22 分泌、减轻黏膜炎症损伤, 为炎症性肠病等 ILC3 相关黏膜疾病的临床干预提供了潜在策略[173,174]。ACC1 抑制剂 (如工具药 TOFA) 可通过靶向纠正 ILC3 的脂肪酸合成异常, 调控其 IL-22 分泌功能与黏膜炎症应答, 在肠道炎症小鼠模型中已证实能显著减轻黏膜炎症损伤、维持肠道屏障稳态, 为 ILC3 相关黏膜疾病 (如炎症性肠病) 的临床干预提供了潜在药物研发方向, 相关作用机制已得到免疫代谢领域核心综述的明确支撑[125]。此外, 有研究者通过干预营养代谢产物与微生物信号可增强 ILC3 IL-22 分泌。如口服丁酸盐制剂联合罗伊氏乳杆菌可通过微生物代谢产物调控 ILC3 糖酵解与脂肪酸代谢, 使溃疡性结肠炎患者肠道 ILC3 的 IL-22 分泌量提升 2 倍, 疾病缓解率达 58%[131,175]; 维生素 D3 补充剂可增强 ILC3 糖酵解适应性, 在肠道感染模型中使病原体清除率提升 47%, 相关联合营养干预方案已作为辅助治疗纳入炎症性肠病临床管理指南, 为 ILC3 相关黏膜疾病治疗提供了安全可行的临床路径[129,176]。通过协同激活 mTORC1-HIF-1α 轴与 AHR 信号, 强化 ILC3 在缺氧或营养匮乏微环境中的代谢适应能力, 为后续靶向药物研发提供了新的分子靶点[3,172]。

总体说来, 基于调控 ILC1、ILC2 和 ILC3 功能的免疫治疗策略尚属于初步探索阶段, 未来仍需要进一步深入研究。

6 结语与展望

代谢调控在 ILCs 发育、活化及功能中具有极其重要的作用, NK 细胞和其他 ILCs 均遵循“静息低代谢−活化重编程”的共性规律, 以糖酵解和 OXPHOS 为核心供能基础, 但各亚群间在不同的组织微环境仍存在明确的差异化路径。随着单细胞多组学、实时活体成像等免疫力解码先进技术的发展, 系统解析肿瘤、肥胖、感染等疾病发生、发展中 ILCs 代谢重编程的时空规律, 突破传统研究在捕捉细胞异质性及时空动态特征上的局限, 深度挖掘驱动 ILC 功能表型改变的代谢调控网络及核心分子, 更为基于代谢调控的免疫治疗

策略开发奠定了理论支撑, 有望为靶向代谢调控ILCs命运的疾病防治提供新的分子靶点。

随着基因编辑与递送、合成免疫学等前沿颠覆性技术的发展, 一方面通过基因编辑等技术在体外或体内优化CAR-NK细胞或其他ILCs的代谢适配性, 增强其向体内输注后在疾病微环境中的抗耗竭能力与存活持久性; 另一方面, 开发新型代谢调节剂, 通过精准靶向递送, 并开展与免疫检查点抑制剂、细胞因子疗法等的联合治疗, 有望进一步优化基于ILCs功能调控的免疫治疗策略, 为突破现有临床应用瓶颈提供更精准的理论依据, 推动该领域向更深入、更广阔的方向发展。

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