糖酵解–脂肪酸代谢失衡调控的铁死亡在代谢性疾病中的研究进展

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摘要: 在代谢性疾病中, 活性氧累积及氧化应激与铁死亡密切相关。糖酵解–脂肪酸代谢失衡作为代谢性疾病关键调控方式, 能够直接或间接参与铁死亡, 影响其发生发展。而铁死亡是一种新型调节性细胞死亡方式, 由铁依赖性脂肪酸过氧化物过度累积引发。其与糖酵解–脂肪酸代谢密切相关, 在代谢性疾病中发挥重要作用。该调节性细胞死亡方式显著区别于其他程序性死亡方式, 在细胞形态、标志性特征及机制等方面均有独特变化。本文首先阐明糖酵解及脂肪酸代谢失衡参与铁死亡发生的主要机制, 并进一步综述铁死亡在肿瘤、2型糖尿病及类风湿关节炎等代谢性疾病中的研究进展, 揭示糖酵解–脂肪酸代谢失衡与铁死亡异常的内在联系及其对代谢性疾病的影响, 以期为代谢性疾病防治提供新策略。

关键词: 铁死亡; 糖酵解; 脂肪酸代谢; 代谢性疾病; 脂质过氧化

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Research progress on ferroptosis regulated by glycolysis-fatty acid metabolism in metabolic diseases

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Abstract: In metabolic diseases, the accumulation of reactive oxygen species and oxidative stress are closely associated with ferroptosis. As a key regulatory factor, the imbalance between glycolysis and fatty acid metabolism can participate in ferroptosis directly or indirectly, thereby regulating the occurrence and development of various metabolic diseases. The essence of ferroptosis is a new regulatory cell death mode, which is caused by the excessive accumulation of iron-dependent lipid peroxide. It is closely related to glycolysis and fatty acid metabolism, which plays an important role in metabolic diseases. This regulatory cell death mode is significantly distinguished from other programmed cell death modes and has unique changes in cell morphology, symbolic characteristics and mechanisms. This paper first illustrates the main mechanism of glycolysis and fatty acid metabolism imbalance in the occurrence of ferroptosis, then reviews the research progress of ferroptosis in tumor, diabetes, rheumatoid arthritis and other metabolic diseases, and finally reveals the internal connection between glycolysis-fatty acid metabolism imbalance and ferroptosis, as well as its impacts on metabolic diseases, which provide new strategies for the prevention and treatment of metabolic diseases.

Key words: ferroptosis; glycolysis; fatty acid metabolism; metabolic disease; lipid peroxidation

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铁死亡最早由Dixon等[1]提出, 是一种由脂肪酸过氧化驱动, 依赖于铁的独特细胞死亡方式。铁死亡的触发主要有氧化还原失衡和游离铁增加两种形式。其与多种细胞代谢途径存在内在联系, 包括能量、脂肪酸和氨基酸代谢, 这些代谢途径直接影响铁死亡易感性[2]。磷脂氢过氧化物 (phospholipid hydroperoxides, PLOOHs) 作为一种脂肪酸活性氧 (reactive oxygen species, ROS), 是铁死亡重要执行者[3]。PLOOHs的合成机制, 特别是PLOOHs的前体—多不饱和脂肪酸 (polyunsaturated fatty acids, PUFA) 的合成和激活, 已得到广泛研究。重要的是, 这些研究都集中于细胞代谢, 揭示铁死亡和代谢途径间密切关系。

糖酵解 (glycolysis) 与脂肪酸代谢 (fatty acid metabolism) 异常被认为是代谢重编程的关键部分, 在铁死亡调控中至关重要。越来越多研究将糖酵解–脂肪酸代谢失衡与铁死亡相联系, 旨在干预相关靶点调控异常的铁死亡。脂肪酸过氧化在铁死亡过程中发挥核心作用, 细胞中脂肪酸代谢参与铁死亡易感性调节。铁死亡由PUFA过氧化作用所驱动, 而单不饱和脂肪酸 (monounsaturated fatty acids, MUFA) 通过取代脂膜中PUFA, 减少脂肪酸ROS积累, 从而产生铁死亡抗性[4]。铁死亡细胞呈现出独特氧化磷脂 (phospholipid, PL) 谱, 这种特点不同于经历其他程序性死亡方式的细胞。近来发现有氧糖酵解与脂肪酸代谢联系逐渐增多, 通过有氧糖酵解调节脂肪酸代谢, 成为研究铁死亡的潜在策略。铁死亡在代谢性疾病中起重要作用, 在某些代谢性疾病动物模型中, 发挥铁死亡抑制作用的几种抗氧化剂已显示出治疗作用。该综述从糖酵解–脂肪酸代谢紊乱方面系统阐述了铁死亡的关键调控因子, 重点介绍了铁死亡在代谢性疾病中的作用及调控机制。

1 脂肪酸代谢产生铁死亡的底物和天然抑制剂

代谢正常时, 细胞一方面产生使脂肪酸过氧化的底物和氧化剂; 另一方面产生阻止脂肪酸过氧化的抑制剂。特定的脂肪酸过氧化及其天然防御机制受损, 是铁死亡触发条件。脂肪酸过氧化物的消除受损或过度产生都会导致它们在铁死亡期间积累至致死水平。

1.1 ACSL4和LPCAT3生产铁死亡的脂肪酸底物 (PUFA) 铁死亡执行关键是铁催化的底物变化。多不饱和脂肪酸磷脂 (phospholipids of polyunsaturated fatty acids, PUFA-PLs) 过氧化, 导致脂肪酸过氧化物在胞膜上致命积累及随后细胞膜崩坏破裂, 触发铁死亡[4]。Acyl-CoA合成酶长链家族成员4 (acyl-CoA synthetase long-chain family member 4, ACSL4) 和卵磷脂酰基转移酶3 (lecithin-cholesterolacyltransferase 3, LPCAT3) 是PUFA-PLs合成的两个关键调控因子[5]。ACSL4将游离的PUFA与辅酶A (coenzyme A, CoA) 连接到细胞膜, 丰富PUFAs, 从而生成脂肪酰基辅酶A酯 (PUFA-CoAs), 最终通过LPCAT3酯化并入PUFA-PLs[6]。因此, 增加ACSL4表达或活性在各种病理生理环境下促进铁死亡发生[7]。

由于ACSL4对铁死亡的促进作用和优先表达, 会放大细胞对铁死亡易感性, 可作为不同细胞环境下铁死亡易感性的预测标记。抑制ACSL4表达是一种有力的药理干预手段[8]。基因缺失或药物抑制ACSL4可降低膜脂不饱和度, 使磷脂中长链PUFA尾部向MUFA尾部急剧转变[9]。此将恢复铁死亡易感性并抑制炎症, 保护组织或器官。已证实*ACSL4*缺陷细胞在谷胱甘肽过氧化物酶4 (glutathione peroxidase 4, *GPX4*) 敲除后仍保持异常增殖能力, *ACSL4-GPX4*双敲除细胞对铁死亡表现明显抗性[10]。罗格列酮和右美托碇等药物显著抑制ACSL4活性, 但不良反应严重[11]。缺氧诱导因子-1α (hypoxia inducible factor-1α, HIF-1α) 作为一种具有转录活性核蛋白, 具有广泛靶基因谱。HIF-1α可与ACSL4启动子结合抑制铁死亡, 但具体机制仍不清晰[12]。因此, 抑制ACSL4表达可能是细胞铁死亡抗性的重要机制。

1.2 SCD1、ACSL3和AMPK参与合成铁死亡的天然抑制剂 (MUFA) MUFA如油酸和棕榈油酸, 由于缺乏双烯丙基部分而不易过氧化。与PUFA相比, MUFA通过从质膜磷脂中置换PUFA, 来抑制脂肪酸过氧化和铁死亡。硬脂酰辅酶A去饱和酶-1 (stearoyl-CoA desaturase 1, SCD1) 和长链酰基辅酶A合成酶3 (acyl-CoA synthetase long chain family member 3, ACSL3) 参与MUFA-PLs合成。它们使饱和脂肪酸去饱和至MUFA, 通过减少细胞质膜中毒性脂肪酸、ROS的积累, 降低可氧化PUFA-PLs, 以增强铁死亡抗性[13]。代谢调节剂腺苷酸活化蛋白激酶 [adenosine 5′-monophosphate (AMP)-activated protein kinase, AMPK] 参与乙酰辅酶A羧化酶 (acetyl-CoA carboxylase, ACC) 和PUFA的生物合成调控。在能量胁迫下AMPK抑制铁死亡并对MUFA介导细胞保护作用提供基础, 但其保护机制尚不清楚[14]。因此, SCD1、ACSL4和AMPK的激活或抑制可有效靶向铁死亡。合成MUFA有助于抑制饱和脂肪酸引发的肌肉萎缩及胰岛素抵抗, 并与心血管疾病的预后改善相联系, 抑制MUFA促铁死亡可防止多种肿瘤细胞扩散[15]。

MUFA可直接外源性添加, 也可通过糖酵解途径从乙酰辅酶A中生物合成[16]。抑制MUFA合成促进细胞铁死亡方式多通过药物抑制或基因敲除方式实现。MUFA是固醇调节元件结合蛋白1 (sterol regulatory

element binding protein-1, SREBP-1) 转录靶点, 其与SCD1发生异位表达恢复细胞铁死亡易感性[17]。甲硫氨酸腺苷转移酶2A为铁死亡抗性驱动因子, 与上调ACSL3使MUFA合成增多有关。基因敲除甲硫氨酸腺苷转移酶2A可能是恢复癌细胞铁死亡易感性的有效途径[18]。更多的促铁死亡途径是采用小分子SCD1抑制剂发挥作用。SCD1抑制剂MF-438不仅改善肿瘤细胞辐射敏感性, 还可联合预后指标SCD1使铁死亡致敏[19]。索拉菲尼作为一种多激酶抑制剂, 显著影响SCD1表达, 扰乱MUFA合成[20]。

2 糖酵解途径提供铁死亡的产物与限速酶

异常代谢时, 细胞将葡萄糖重新连接至有氧糖酵解, 满足过度增殖导致ROS应激的细胞代谢需求, 产生铁死亡抗性以维持氧化还原稳态[21]。这一过程涉及众多限速酶的催化与产物的调控, 常见有己糖激酶(hexokinase, HK)、磷酸果糖激酶 (phosphofructokinase, PFK)、丙酮酸激酶 (pyruvate kinase, PK)、乳酸脱氢酶(lactate dehydrogenase, LDH)、葡萄糖转运体 (glucose transporter, GLUT)、M2-型丙酮酸激酶 (pyruvate kinase isozyme type M2, PKM2) 等酶及丙酮酸、乳酸(lactate) 等产物。该过程的抑制是铁死亡致敏潜在机制, 铁死亡致敏又是阻止细胞代谢异常的天然屏障。

丙酮酸与乳酸作为糖酵解产物, 在铁死亡调控中作用更为直接。谷胱甘肽耗尽不仅导致铁死亡, 且反作用于丙酮酸脱氢酶激酶 (pyruvate dehydrogenase kinase, PDK) 促进丙酮酸代谢, 通过脂肪酸合成途径更有利于铁死亡[22]。此外, 抑制线粒体丙酮酸载体1 (mitochondrial pyruvate carrier 1, MPC1) 进入线粒体也可降低丙酮酸含量[23]。同样, 通过羟羧酸受体1 (hydroxycarboxylic acid receptor 1, HCAR1) 和单羧酸转运蛋白1 (monocarborxylat transporter 1, MCT1) 阻断细胞对乳酸摄取, 可激活AMPK下调SCD1表达, 从而促进铁死亡[8]。

糖酵解限速酶众多, 抑制糖酵解途径多样, 尽管目前特异性限速酶抑制剂研究较少, 针对糖酵解整体的代谢重编程是铁死亡研究热点。RSL3小分子化合物不但使GPX4失活诱导铁死亡, 还会引起糖酵解功能障碍[24]。进一步研究发现RSL3降低了HK2、PFKP和PKM2表达, ATP和丙酮酸含量都有所下降[25]。p53介导的肿瘤代谢在糖酵解各个过程都体现对铁死亡的促进作用。p53可阻止糖酵解碳导入磷酸戊糖途径(pentose phosphate pathway, PPP), 阻碍乳酸排出[26]。此外, HIF-1α是一种广谱基因, 其积累在糖酵解异常中发挥关键作用。TEPP-46为PKM2二聚体抑制剂, 可特异性抑制HIF-1α累积, 靶向HK、GLUT、LDHA和PKM等糖酵解限速酶活性, 加速铁死亡[27,28]。在糖酵解代谢重编程中各种转录因子也发挥重要作用, 串扰BACH1和Zeb1等转录因子, 可增加癌细胞对铁死亡易感性[29,30]。有关糖酵解途径诱发铁死亡方式, 目前还停留在转录因子、限速酶和肿瘤抑制因子等调控机制的探索阶段, 需要更进一步的机制和药物干预研究。

3 糖酵解−脂肪酸代谢失衡在铁死亡中的作用

脂肪酸代谢与糖酵解在代谢中相辅相成。铁死亡发生与抑制糖酵解及促进脂肪酸代谢密不可分。糖酵解可通过代谢重编程一方面促进脂肪酸代谢使铁死亡致敏, 一方面触发Warburg效应诱导铁死亡发生。其中AMPK和HIF-α是重编程关键调节剂。

3.1 AMPK AMPK是糖酵解与脂肪酸代谢平衡的桥梁。代谢应激细胞缺乏葡萄糖会增加ROS产生, 诱导铁死亡抗性, 这种保护作用依赖于能量感应激酶AMPK活性[31]。AMPK由能量胁迫激活, 这可能因葡萄糖缺乏或糖噬缺陷产生, 并通过葡萄糖可用性传感器醛度酶与AMPK建立连接[32]。AMPK与HIF-1α形成蛋白质复合物抑制糖酵解, 而糖酵解过低会降低AMPK表达, 两者相互拮抗[33]。代谢异常肿瘤细胞存在Warburg效应, 大量丙酮酸转化为乳酸无法进入三羧酸循环完成氧化磷酸化, 从而抑制铁死亡[34]。

AMPK干扰正常脂肪酸代谢, 使PUFA生物合成受损, 这对脂肪酸过氧化驱动铁死亡至关重要。首先, AMPK激活抑制ACC磷酸化, 或联合肿瘤抑制因子肝激酶B1阻碍PUFA合成, 负调控铁死亡[35]。其次, AMPK也会抑制SCD1表达, 使铁死亡天然抑制剂MUFA耗竭[36]。因此, AMPK在糖酵解−脂肪酸代谢失衡的复杂调控中扮演重要角色, 探讨HIF-1α与AMPK交叉对话可能有新发现。

3.2 HIF-α 细胞通过稳定HIF-α适应缺氧环境。HIF-α激活下游多种靶基因, 包含代谢、增殖及侵袭中发挥作用的酶。其擅于将脂肪酸利用转向糖酵解和脂肪酸积累, 产生铁死亡抗性以适应细胞缺氧环境[37]。靶向HIF-α本身似乎不能逆转糖酵解代谢重编程, 研究者倾向于抑制HIF-1α介导的转激活, 而不是转录因子本身[38]。已有研究表明, 丙酮酸脱氢酶激酶同工酶4作为重要的共激活因子, 刺激肿瘤细胞并被HIF-1α转激活, 通过抑制LDH阻断三羧酸循环[39]。在脂肪酸代谢中, 过多脂肪酸会促进HIF-1α富集更多PUFA, 促进其积累与细胞增殖。这种作用可配合脂肪酸结合蛋白5以促进HIF-1α合成, 或配合肉碱棕榈酰转移酶1A抑制脂肪酸转运至线粒体, 迫使脂滴储存, 形成HIF-1α与PUFA互促循环[40,41]。研究发现, 三阴性乳腺癌细胞中HIF-α表达对介导脂肪酸储存和转移至关重

要[42]。然而，脂肪酸在调节HIF-1α活性和细胞存活中的具体作用机制研究尚少。糖酵解–脂肪酸代谢失衡调节铁死亡相关信号通路见图1。

4 代谢性疾病与铁死亡

多种多样的代谢途径在代谢性疾病中发挥重要作用，其中糖酵解–脂肪酸代谢重编程与铁死亡关系密切。本文列举了肿瘤、类风湿关节炎与2型糖尿病3种代谢性疾病相关研究进展，以期找寻铁死亡规律。

4.1 肿瘤 肿瘤细胞以代谢重编程为突出特征，为维持不受控制的增殖并避免细胞死亡，常引起一些代谢性疾病。为克服化学耐药性，卵巢癌研究常以AMPK活化方式增强GPX4依赖性铁死亡，并通过上调p53表达实现多靶点治疗[43]。肺腺癌研究证明铁死亡抵抗与SCD1表达显著升高相关，是研究靶向药物开发候选者[44]。透明细胞肾细胞癌研究发现，外源性脂肪酸特异性依赖于ACSL3，促进脂滴形成，调节细胞铁死亡敏感性[45]。肿瘤细胞通过调节脂肪酸代谢产生铁死亡抗性，促进癌症转移。已证实淋巴环境有助于癌细胞铁死亡抗性，由于淋巴液中富含油酸（一种MUFA），油酸以ACSL3依赖性方式在血液中转移，保护肿瘤细胞免于铁死亡[46]。T细胞衍生的干扰素γ联合花生四烯酸（一种PUFA）诱导免疫原性肿瘤铁死亡。干扰素γ激活ACSL4并改变肿瘤细胞脂肪酸代谢模式，从而使花生四烯酸并入PUFA-PLs，诱导ACSL4依赖性铁死亡，因此靶向ACSL4途径是一种潜在的抗癌方法[47]。

4.2 类风湿关节炎 代谢失调是类风湿关节炎（rheumatoid arthritis, RA）所有阶段基本致病方式，其代谢特征为葡萄糖分流至磷酸戊糖及生物合成途径[48]。RA模型显示铁过载、脂肪酸过氧化、氧化应激和线粒体功能障碍，与铁死亡减少有关[49]。RA患者脾脏及滑膜中糖酵解关键酶PKM2高表达，在巨噬细胞与破骨细胞显著积累[50]。此外，糖原积累阻断AMPK活化并使HIF-1α高表达，加重滑膜炎症[51]。研究证实，RA滑膜和成纤维样滑膜细胞中显示ACSL4减少与铁死亡下降有关，通过甘氨酸介导的GPX4甲基化和铁蛋白减少可增强铁死亡[52]。有关铁死亡在RA关节骨破坏中的作用知之甚少。Zhou等[53]证实瞬时性受体电位通道M7抑制可减轻关节软骨损伤和软骨细胞铁死亡，是预防和治疗RA的一个可靠靶点。综上，进一步探讨RA患者的铁死亡治疗策略意义重大。

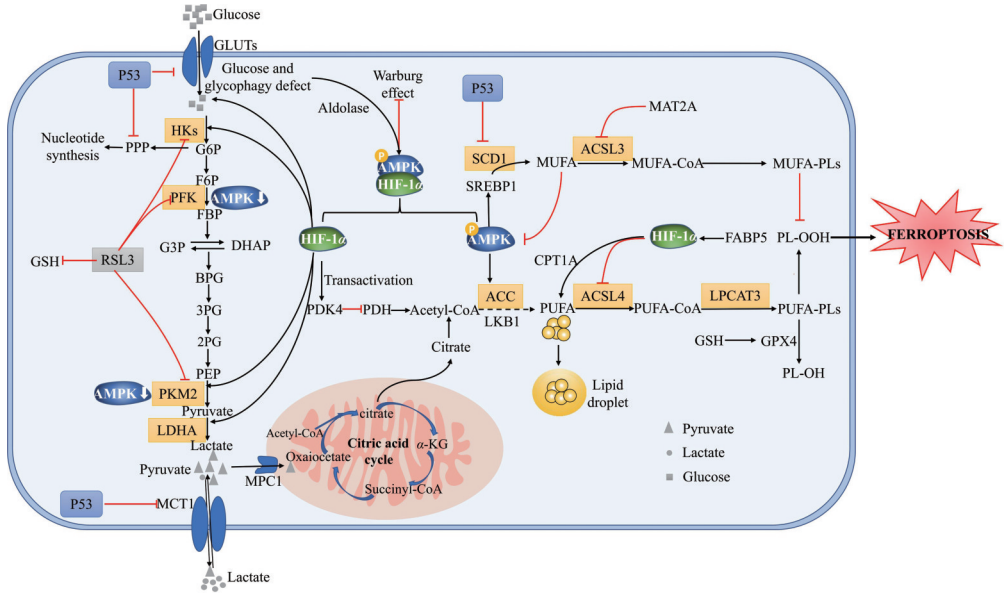

Figure 1 Mechanism of glycolysis-lipid metabolism imbalance regulating iron death. GLUTs: Glucose transporters; G6P: Glucose-6-phosphate; F6P: Fructose-6-phosphate; FBP: Fructose bisphosphate; G3P: Glucose-3-phosphate; BPG: Biphosphate glycerate; 3PG: 3-Phosphoglycerate; 2PG: 2-Phosphoglycerate; PEP: Phosphoenolpyruvate; PPP: Pentose phosphate pathway; HKs: Hexokinases; PFK: Phosphofructokinase; AMPK: Adenosine 5′-monophosphate (AMP)-activated protein kinase; PKM2: Pyruvate kinase M 2; LDHA: Lactate dehydrogenase A; HIF-1α: Hypoxia inducible factor-1α; RSL3: Glutathione peroxidase 4 inhibitor; MCT1: Monocarborxylat transporter 1; MPC1: Mitochondrial pyruvate carrier 1; Acetyl-CoA: Acetyl coenzyme A; PUFA: Polyunsaturated fatty acids; SREBP1: Sterol regulatory element-binding protein 1; MUFA: Monounsaturated fatty acids; ACC: Acetyl-CoA carboxylase; ACSL4: Acyl-CoA synthetase long-chain family member 4; LPCAT3: Lecithin-cholesterolacyltransferase 3; SCD1: Stearoyl-CoA desaturase 1; ACSL3: Acyl-CoA synthetase long chain family member 3; GPX4: Glutathione peroxidase 4; CPT1A: Carnitine palmitoyltransferase 1A; FABP5: Fatty acid binding protein 5; PDK4: Pyruvate dehydrogenase kinase 4; PDH: Pyruvate dehydrogenase; LKB1: Liver kinase B1

Table 1 Summary of targeted glycolysis-lipid metabolism imbalance regulators

Intervention/treatment		Target/mechanism	Indication	Reference
ACSL4 inhibitor	Rosiglitazone Pioglitazone Troglitazone	Decreased GPX4 expression and inhibited the synthesis of MUFA-PLs	Breast cancer	[47]
SCD1 inhibitor	MF-438	Decreased MUFA and inhibited the synthesis of MUFA-PLs	Esophageal squamous cell carcinoma	[19]
	Sorafenib		Liver cancer	[20]
AMPK activator	Metformin	Up-regulated P53 expression and promoted aerobic glycolysis	Ovarian cancer	[43]
	AICAR	Lowered HIF-1α expression and promoted the synthesis of PUFA-PLs	Type 2 diabetic mellitus Rheumatoid arthritis	[16,51]
	SCT-1015	Lowered HIF-1α abundance and inhibited aerobic glycolysis	Liver cancer	[33]
	O304	Increased glucose intake and promoted aerobic glycolysis	Type 2 diabetic mellitus	[60]
HIF-1α inhibitor	Pioglitazone	Lowered HIF-1α expression and inhibited aerobic glycolysis	Diabetic mellitus	[37]
PKM2 inhibitor	TEPP-46	Increased HIF-1α expression and promoted aerobic glycolysis	Diabetes nephropathy	[28]
	DASA-10		Type 2 diabetic mellitus	[57]
PKM2 inhibitor	Shikonin	Decreased pyruvate production and inhibited aerobic glycolysis	Rheumatoid arthritis	[50]

4.3 2型糖尿病 2型糖尿病 (type 2 diabetic mellitus, T2DM) 以代谢紊乱及细胞应激为主要特征, 与肥胖息息相关[54]。近年来, T2DM与抑制铁死亡的研究逐渐兴起。通过平衡细胞代谢如糖酵解–脂肪酸代谢和氧化应激等方式改善胰岛素分泌, 恢复胰岛功能, 实现抗T2DM作用[55]。T2DM患者糖酵解酶表达显著升高, 毒性葡萄糖代谢物减少[56]。尤以PKM2与*L*-半胱氨酸结合失活为主, 使胰岛素分泌受损, 是T2DM潜在治疗靶点[57]。二甲双胍抗T2DM作用常依赖糖酵解–脂肪酸代谢平衡关键靶点AMPK, 抑制ROS产生和炎症[58]。T2DM患者脂肪酸代谢中SCD1变体表达过度, 而SCD1在代谢性疾病中至关重要。其催化单不饱和脂肪酸钠合成, 既提供脂肪储存又有助于细胞防御饱和脂肪酸毒性[59]。因此, 基于胰腺β细胞铁死亡治疗2型糖尿病, 糖酵解–脂肪酸代谢通路研究及相关基因的开发与验证有待探索。靶向糖酵解–脂肪酸代谢失衡相关药物的靶点或机制见表1[16,19,20,28,33,37,43,47,50,51,57,60]。

5 展望

细胞在应激状态下出现的糖酵解–脂肪酸代谢失衡是多种代谢性疾病的必要条件, 对铁死亡的干预作用已被证实是潜在治疗手段。关于脂肪酸代谢的调节可能为缺铁相关疾病提供新治疗选择。虽有大量研究已在癌症模型中被确定和验证, 其是否也与其他各种疾病, 尤其在RA方面铁死亡相关程度研究尚未确定。在某些情况下, 细胞外环境存在刺激PUFA (如其他细胞或病原体释放) 或PUFA-PLs合成的ACSL4等酶表达, 其中一些机制可能参与组织大小的发育和调节、肿瘤抑制或免疫系统清除感染细胞。此外, 由于不同细胞类型对铁死亡易感性不同, 且同时调控多种细胞死亡途径对RA的治疗至关重要, 需要进一步探索不同细胞死亡之间的联系, 以验证其是否被整合到一个复杂监管网络。靶向脂肪酸代谢与糖酵解相关调控因子是研究热点, 不仅可以调节肿瘤细胞铁死亡易感性, 还可以降低过度免疫损伤非靶点细胞的可能性。因此, 铁死亡发生伴随着的代谢性疾病, 通过干预脂肪酸代谢与糖酵解的代谢重编程, 是一个新兴且具有重要意义的领域, 有待进一步探索发现。

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