王璐, 中国医学科学院血液学研究所研究员。主要从事造血干细胞发育及血液疾病模型方面的研究, 从表观修饰(RNA甲基化及DNA甲基化)、炎性信号、神经递质以及微环境等崭新的视角阐释血细胞发育过程, 取得一系列原创性成果; 目前研究从体内发育、疾病模型和作用机制三个层次深入探讨关键调控因子在血液系统发育和血液疾病发生中的作用机理, 构建相关疾病模型, 为相关疾病治疗和药物开发提供理论依据。研究成果在*Nature Commun*、*EMBO J*、*Nature*、*Blood*以及*J Exp Med*等杂志上发表。主持多项基金项目, 包括国家重点研发计划青年科学家项目、国家自然科学基金以及天津市杰出青年项目等。

脂质代谢调控与造血干细胞发育及功能维持

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摘要 造血干细胞(hematopoietic stem cells, HSCs)是一类具有自我更新及多向分化潜能的多能干细胞, 成体期主要存在于骨髓微环境中, 其功能受到诸多内外在因素的精细调控。脂质是机体重要营养素之一, 可用于能量存储和代谢, 参与调控多项重要生物学过程。然而, 脂质代谢在造血调控中所发挥的作用尚处于探索阶段。该文就近期有关脂质代谢调控HSC命运决定以及功能维持的研究进展进行综述和展望, 重点阐述了脂肪酸合成、氧化代谢和胆固醇转运等在其中的作用及其内在调控机制。

关键词 脂质代谢; 脂肪酸氧化; 造血干细胞; 干性维持; 细胞命运决定

Lipid Metabolism in Hematopoietic Stem Cell Development and Function

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Abstract HSCs (hematopoietic stem cells) are a population of multipotent stem cells with abilities to self-renew and differentiate into multiple blood cell lineages. Adult HSCs reside in the bone marrow microenvironment and are tightly regulated by complex cell-intrinsic and extrinsic factors. Lipids, one of the essential nutrients for the organism, are used in energy storage and metabolism and have important roles in many pivotal biological processes. However, the role of lipid metabolism in hematopoiesis has not been fully explored. Here,

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this review summarizes and discusses recent progress on lipid metabolism in the regulation of HSCs fate and function, focusing on the underlying mechanisms related with fatty acid synthesis, fatty acid oxidation and cholesterol transportation.

Keywords lipid metabolism; fatty acid oxidation; hematopoietic stem cells; stemness maintenance; cell fate determination

造血干细胞(hematopoietic stem cells, HSCs)具有自我更新以及多向分化潜能, 能够分化产生所有成熟血细胞, 从而维持机体造血稳态和生理活动[1]。HSCs在不同的发育阶段具有不同的代谢特征和调控网络。胚胎期HSCs增殖活跃, 对能量需求较大, 与成体期HSCs相比, 胚胎期HSCs中含有更多线粒体[2]。提高葡萄糖水平可显著增加胚胎期造血发育过程中HSCs数目[3]。成体期HSCs主要存在于低氧骨髓造血微环境中, 且保持静息状态[4]。在低氧条件下, 糖酵解途径是HSCs获取能量的主要方式, 而不是线粒体氧化磷酸化(oxidative phosphorylation, OXPHOS)途径, 研究表明糖酵解所提供的低代谢状态和相对较低的活性氧(reactive oxygen species, ROS)水平有利于维持HSC自我更新能力[5-7]。当HSCs从静息态退出并开始向下游的造血祖细胞或成熟血细胞分化时, 其能量代谢方式转换为线粒体OXPHOS[8-9], 提示HSC分化依赖于OXPHOS过程所提供的大量能量。

脂质种类丰富, 包括脂肪酸、甘油三脂、胆固醇、磷脂等[10], 其中脂肪酸分为饱和脂肪酸和不饱和脂肪酸, 其可在线粒体内进行氧化分解并释放能量以供正常生命活动所需[11]。脂肪酸氧化(fatty-acid oxidation, FAO)可通过影响不对称分裂维持HSC自我更新及造血稳态[12]。另外, 血液中胆固醇的稳态平衡受到精密调控, 以避免胆固醇含量过高引起动脉粥样硬化等[13]。胆固醇水平升高可对HSCs产生多种影响, 包括促进骨髓中HSCs动员并进入外周血、促进HSCs增殖以及诱导HSCs分化为单核细胞和中性粒细胞以参与动脉粥样硬化过程等[14-15]。脂质代谢在HSC功能维持方面发挥重要调控作用, 本文将对相关脂质代谢调控造血发育的研究进展进行系统总结, 并重点探讨脂质代谢对HSC命运决定及功能维持的作用及调控机制。

1 脂肪酸合成及氧化代谢与HSC功能维持

作为机体重要能量来源之一, 脂肪酸代谢在早期胚胎发育及维持干细胞多能性方面发挥关键调控作用[16-19]。脂肪酸主要有两个来源, 包括食物中的脂肪经乳化水解形成脂肪酸以及内源性合成脂肪酸, 即脂肪酸从头合成。脂肪酸从头合成主要以乙酰辅酶A(acetyl-coenzyme A, acetyl-CoA)为主要底物, 它由三羧酸循环(tricarboxylic acid cycle, TCA)的中间产物柠檬酸经ATP-柠檬酸裂解酶(ATP-citrate lyase, ACLY)催化生成, 随后被乙酰辅酶A羧化酶(acetyl-CoA carboxylase, ACC)催化生成丙二酰辅酶A(malonyl-coenzyme A, malonyl-CoA)[20-21]。脂肪酸合酶(fatty acid synthetase, FASN)催化1分子乙酰辅酶A和7分子丙二酰辅酶A连续缩合生成棕榈酸(palmitate)[22]。棕榈酸是含16个碳原子的饱和脂肪酸, 可继续进行延长及去饱和反应, 产生不同长度的不饱和脂肪酸分子[20](图1)。近期的研究报道了多不饱和脂肪酸在调控HSCs功能方面的作用。亚油酸(linoleic acid)、花生四烯酸(arachidonic acid)、α-亚麻酸(α-linolenic acid)和二十二碳六烯酸(dcosahexaenoic acid, DHA)属于不饱和脂肪酸, 与对照组小鼠相比, 口服上述任意一种不饱和脂肪酸的小鼠表现出更强的造血能力, 骨髓微环境中的Wnt、CXCR4和Notch通路被激活, HSCs集落形成和增殖能力明显提高[23-24]。此外, 在HSCs激活过程中分子伴侣HSC70介导的细胞自噬可通过调节细胞内代谢酶活性促进脂质代谢, 特别是亚油酸和α-亚麻酸的合成, 维持HSCs功能, 并且能够促进衰老HSCs功能恢复[25]。前列腺素E_2(prostaglandin E_2, PGE_2)是由花生四烯酸经酶促代谢产生的一类有活性的不饱和脂肪酸, 其可提高HSCs的移植后骨髓重建能力, 加速辐射损伤后小鼠或斑马鱼的造血稳态重建[26-27]。其内在机制是PGE_2诱导趋化因子受体CXCR4和抗凋亡因子survivin表达上调, 从而促进HSCs增殖并抑制其凋亡[28]。

脂肪酸主要以甘油三酯的形式储存在脂肪组织中, 在长期饥饿或应激状态下, 机体可通过FAO紧急供能[29]。其中, 线粒体是FAO发生的主要场所。短、

中链脂肪酸可直接进入线粒体基质进行氧化代谢，而长链脂肪酸需先经脂酰辅酶A合成酶活化生成脂酰辅酶A(acyl-coenzyme A, acyl-CoA)，再依次通过线粒体外膜上的肉碱棕榈酰转移酶-1(camitine palmitoyl transterase-1, CPT-1)和内膜上的CPT-2转运进入线粒体基质。随后，脂酰辅酶A在脂肪酸β氧化酶系催化下进行脱氢、加水、再脱氢、硫解4步连续反应，产生乙酰辅酶A、还原型烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, NADH)和还原型黄素腺嘌呤二核苷酸(flavine adenine dinucleotide, FADH2)，这些产物可进一步用于三羧酸循环和电子传递链，以产生大量ATP[30](图1)。单细胞数据显示，HSCs中高表达与FAO代谢调控通路相关的基因，包括*Cpt1a*、*Pml*以及*Ppard*等，这提示FAO可能参与HSC功能调控[31]。

CPT-1是FAO过程的关键限速酶，其活性可被脂肪酸合成的中间产物丙二酰辅酶A抑制[32]。果蝇中的研究结果显示，敲除*CPT-1*可提高造血祖细胞增殖能力但降低其分化能力。其机制是CPT-1缺失导致FAO受阻，乙酰辅酶A合成量减少，从而抑制造血祖细胞中分化相关因子的组蛋白乙酰化，导致细胞分化能力降低[33]。同样的结果也在人HSCs中得到了证实，与丙二酰辅酶A共培养的HSCs表现出FAO受阻，增殖能力提高[34]。

最初研究表明，早幼粒细胞白血病基因(promyelocytic leukemi, PML)可以与RARα融合表达，导致急性早幼粒细胞白血病[35]。后续研究发现，PML参与调节包括HSCs在内的多种干细胞代谢过程[36-38]。过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptor-delta, PPARδ)属于核激素受体家族中的配体激活受体，可影响FAO过程催化酶的转录水平[39]。ITO等[12]研究指出，PML可通过激活PPARδ促进FAO过程，从而诱导HSCs进行不对称分裂。HSCs通过不对称分裂产生具有自我更新能力的HSCs以及具有分化潜能的造血祖细胞，维持自我更新与分化之间的平衡[40]。当PML缺失或FAO受阻时，HSCs倾向于进行对称分裂，产生分化的造血祖细胞，从而引起HSC自我更新能力受损、干细胞库耗竭[12]。HSCs也可通过对称分裂产生具有干细胞特性的HSCs，实现扩增。该过程依赖于线粒体自噬以清除子代细胞中损伤或衰老的线粒体，从而维持子代HSC功能及造血稳态[40]。PPARδ介导的FAO可通过募集Parkin来激活线粒体自噬，从而维持HSC干性，促进HSC扩增[31]。在炎症等应激情况下，*PPARδ*和FAO相关基因表达上调则可导致HSC自我更新及多向分化能力受损，最终使干细胞库耗竭[41-42]。

脂肪酸合成及氧化代谢均可参与HSC功能维持，但其内在调控机制有待进一步探究。靶向脂肪酸代谢过程的关键调控因子(如CPT-1、PPARδ等)对于提高骨髓移植后HSC重建能力以及促进放化疗损伤后HSCs恢复具有临床应用潜力。

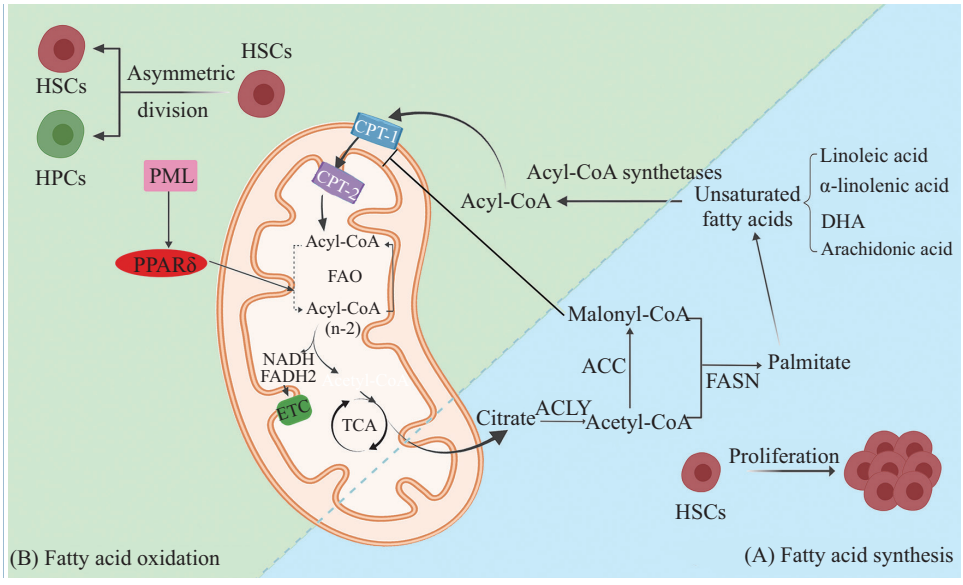

图1　脂肪酸代谢参与HSC功能维持

Fig.1　Fatty acid metabolism is essential for HSC function

2 胆固醇转运与HSC增殖、分化及动员

FAO过程产生的乙酰辅酶A不仅能进入三羧酸循环氧化供能, 也是包括胆固醇在内的多种脂质分子的合成原料[43]。在肝脏中, 内源性合成和外源性摄取的胆固醇以低密度脂蛋白(low density lipoprotein, LDL)的形式进入血液以供细胞摄取利用[44]。同时, 外周组织中多余的胆固醇通过ATP结合盒转运子A1(ATP-binding cassette transporter A1, ABCA1)和载脂蛋白A1(apolipoprotein A1, ApoA-1)以高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)的形式逆转运到肝脏中进行再循环或以胆汁酸的形式被排出[45]。血脂水平异常是动脉粥样硬化病的高危因素。血液中大量的胆固醇沉积于动脉内皮下基质, 被平滑肌、巨噬细胞等吞噬并形成泡沫细胞, 引起炎症反应, 最终导致粥样斑块形成[46-47]。有研究发现, 高胆固醇血症小鼠模型中的HSCs及单核细胞数目明显增多[48]。高胆固醇喂养可诱导小鼠HSCs从骨髓迁移到胸腺并进行髓外造血, 产生中性粒细胞、巨噬细胞和淋巴细胞等, 参与粥样硬化形成过程[49-50]。由LDL受体缺陷引起的胆固醇摄取异常或ABCA1缺陷引起的胆固醇外排受阻也可诱导HSCs动员至外周血, 促进HSCs增殖并向单核细胞分化[51-53]。上述研究提示了高胆固醇水平引起的外周血中HSC增殖及分化能力增强与动脉粥样硬化形成之间存在紧密联系, 但胆固醇诱导HSCs动员以及HSCs影响斑块形成的内在机制尚不清楚。

3 骨髓微环境中脂质与HSC功能

目前认为, HSCs所在的骨髓微环境具有独特的结构和组成成分, 存在不同类型的支持细胞, 如内皮细胞、间充质干细胞、成骨细胞、脂肪细胞、交感神经细胞和巨噬细胞等[54-55]。这些细胞可产生不同的细胞因子或细胞外基质蛋白以维持HSC自我更新及多向分化能力, 避免干细胞库耗竭[56]。正常情况下, 骨髓中瘦素受体阳性(leptin receptor$^+$, LepR$^+$)的基质细胞和内皮细胞是干细胞因子(stem cell factor, SCF)的主要来源[57]。而经过辐射损伤, 小鼠骨髓中的HSCs、内皮细胞及LepR$^+$基质细胞数目显著减少, 脂肪细胞数目则明显增多, 这些增多的脂肪细胞成为SCF的主要来源, 可促进骨髓中HSCs功能的恢复[58]。这说明, 骨髓微环境中的脂肪细胞对于HSCs损伤后的造血功能恢复有重要作用。然而, 衰老或高脂饮食引起的骨髓中脂肪细胞累积则会影响HSC干性, 导致其数目下降[59-60]。因此, 在衰老和肥胖个体中, 骨髓中大量累积的脂肪细胞对造血起负向调控作用, 但不能排除骨髓结构以及其他支持细胞改变的影响[61-62]。

骨髓微环境中的可溶性因子可通过HSCs质膜上存在的脂筏(lipid rafts, LRs)发挥信号传递作用[63]。LRs是由胆固醇、鞘磷脂、神经节苷脂及蛋白质组成的高度可变的细胞膜微结构, 可通过蛋白质–蛋白质或蛋白质–脂质相互作用参与细胞信号转导[64-65]。HSCs质膜脂筏相关蛋白VLA-4以及CXCR4可分别与骨髓微环境中的VCAM-1和SDF-1相互作用, 促进HSCs归巢[66]。造血特异性磷脂酶C-β2(phospholipase C-β2, PLC-β2)则可破坏HSCs质膜脂筏结构, 从而抑制上述的受体配体相互作用, 使HSCs动员到外周血中[67]。此外, SCF、IL-3、IL-6以及VEGF可通过HSCs质膜脂筏将信号传递给下游PI3K-AKT-FOXO通路, 促使HSCs进入细胞分裂周期并进行增殖[68]。由此可见, 由多种脂质分子构成的质膜脂筏介导了HSCs与其所处的骨髓微环境之间的信号传递, 可影响HSC功能维持, 包括归巢、动员、静息和增殖等(图2)。

4 脂质代谢影响胚胎期造血发育

在胚胎发育过程中, HSCs是由主动脉–性腺–中肾(aorta-gonad-mesonephros, AGM)区域特化的动脉内皮细胞–生血内皮(hemogenic endothelium, HE)通过内皮–造血转化(endothelial-to-hematopoietic transition, EHT)产生而来[69]。由不饱和脂肪酸氧化生成的脂肪酸环氧化物 —— 环氧二十碳三烯酸(epoxyeicosatrienoic acids, EET), 可通过PI3K信号通路激活AP-1/Runx1转录因子, 从而促进AGM区域HSC产生[70]。类似地, PGE_2可通过Wnt/β-catenin信号通路促进HSC产生, 抑制合成PGE_2所需的环氧化酶可使HSCs数目明显减少[27,71]。此外, 一项以斑马鱼为实验模型的研究表明, apoA-I结合蛋白(apoA-I binding protein, AIBP)介导的胆固醇外排可激活内皮细胞中的转录因子Srebp2及其下游的Notch信号通路, 诱导EHT过程[52]。新生的HSCs会向小鼠胎肝或斑马鱼尾部造血组织迁移并进行扩增。有研究指出, 抑制脂蛋白脂肪酶介导的DHA合成可使HSCs的扩增能力显著降低, 而其内

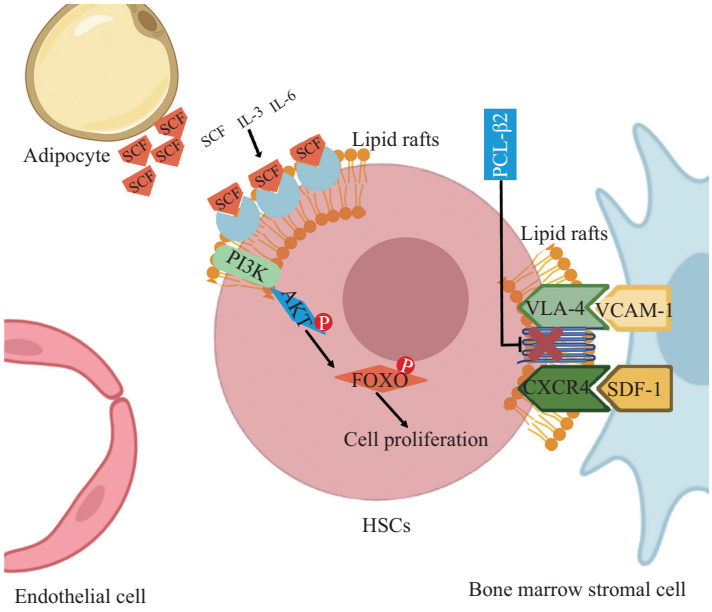

图2　脂筏介导HSCs与骨髓微环境细胞之间的信号传递

Fig.2　Lipid rafts mediate signal transduction between HSCs and bone marrow niche cells

在调控机制有待进一步阐明[72]。

5　总结与展望

综上所述, 作为细胞能量储存和产生的途径之一, 脂质代谢在HSC命运决定及功能维持中发挥重要调控作用。其中FAO过程可诱导HSC不对称分裂, 从而维持HSC自我更新及分化之间的平衡; 机体合成的多种脂肪酸分子可作为信号转导因子, 通过激活下游信号通路来调控HSC命运和功能; 此外, 血液中的胆固醇以及骨髓微环境中的脂质均对HSCs发挥多种调控作用, 包括诱导HSC增殖分化、促进骨髓中HSCs动员并进入外周血等。然而关于脂质代谢调控的内在机制尚不明确。近期多项研究指出, 细胞代谢可通过影响表观遗传修饰调控干细胞功能[73]。细胞中的代谢产物可充当修饰供体参与表观遗传修饰过程, 葡萄糖代谢和FAO产生的乙酰辅酶A可作为组蛋白乙酰转移酶的底物用于组蛋白残基的乙酰化修饰, 维持干细胞的多能性和造血祖细胞的分化能力[33,74]。也有一些代谢物可作为修饰因子的辅因子影响DNA、RNA或组蛋白修饰水平, 发挥调控干细胞功能的作用, 如TCA循环的中间产物α-酮戊二酸可作为JmjC家族组蛋白去甲基化酶和TET家族DNA羟化酶的辅因子, 促进组蛋白和DNA去甲基化, 从而维持小鼠干细胞的自我更新能力[75]。另外, 线粒体OXPHOS过程产生的NAD^+可提高组蛋白去乙酰化酶SIRT1活性并促进小鼠肌肉干细胞的分化[76]。

由于脂质代谢途径的多样性和复杂性, 因此, 关于脂质代谢对HSC功能的调控作用有待进一步阐明, 同时对其内在调控机制的深入及充分的研究对于解决临床上HSCs来源不足、骨髓移植效率低下等问题具有重要意义。

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