金属转运蛋白SLC39A14的代谢性功能研究进展

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2020-03-27 收稿, 2020-04-28 修回, 2020-04-28 接受, 2020-04-29 网络版发表

广东省基础与应用基础研究基金(2020B1515020046)、国家自然科学基金(81900797)和广东省科学院发展专项(2016GDASRC-0202)资助

摘要 微量元素是维持人体生理和代谢功能的重要的营养素之一, 既可参与人体生理生化功能调控, 亦可作为生物大分子的组成或辅助成分, 如激素和维生素有机组成。微量元素对维持机体正常生命活动具有重要意义。其中, 必需微量元素是机体内不能产生或合成但又是维持生物体正常生理机能不可或缺的, 如铁、锰、锌等, 主要通过消化道中不同的金属转运蛋白(metal transporter)转运吸收。近年来, 随着金属转运蛋白不断被鉴定与发现以及金属转运蛋白的功能研究进展, 认为SLC39A14在不同组织中参与铁、锌、锰等必需微量元素转运, 并且参与多种生物学功能。基于目前对金属转运蛋白在代谢性器官以及代谢性疾病中的作用机理的了解和认识, 本文回顾性总结了金属转运蛋白SLC39A14在不同代谢组织器官的代谢性功能和作用机制。

关键词 金属转运蛋白, SLC39A14, 代谢性器官, 肥胖, 2型糖尿病

溶质载体家族39(solute-linked carrier 39, SLC39)又称ZIP家族, 是一类金属转运蛋白。根据基因序列同源分析, 该家族共有14个成员SLC39A1~SLC39A14 (或ZIP1~ZIP14)。蛋白质结构分析结果显示, 该家族蛋白大多含有8个跨膜结构(transmembrane domains, TM)、一段长片段的细胞外N-末端、短片段的C-末端以及富含组氨酸的结构域^[1]。此外, 根据蛋白质结构的特点, ZIP家族可分为I、II、Gufa、LIV-1四个子家族。其中, LIV-1子家族(LIV-1 subfamily of ZIP zinc transporters, LZT)的蛋白成员含有具有保守特征性的“HEX-PHEXGD”片段结构域TM V(transmembrane domain V), 该片段被认为与锌离子的转运功能密切相关^[2]。研究发现, LZT家族中的SLC39A6 (ZIP6)可介导上皮间质

转化(epithelial-mesenchymal transition, EMT), 与肿瘤细胞中锌离子转运以及乳腺癌的发生发展密切相关^[3,4]。SLC39A7 (ZIP7)主要在细胞内质网表达, 与细胞内存储的锌离子门控释放功能相关, 发挥转运锌离子至细胞质的功能^[5,6]。研究还发现, SLC39A5 (ZIP5)可通过沉默信息调节因子2相关酶1(Sirt1)及过氧化物酶体增殖物激活受体- γ 共激活因子-1 α (Pgc-1 α)介导的葡萄糖转运蛋白2(Glut2)的表达, 参与调控胰岛 β 细胞的葡萄糖感应和胰岛素分泌等内分泌代谢功能^[7]。SLC39A14(ZIP14)除参与机体锌离子吸收和利用, 还与多种组织器官的代谢性调控密不可分。本文主要回顾了SLC39A14在不同代谢性器官, 如肝脏、胰腺、脂肪和骨骼肌中的功能和调控机制(图1)。

引用格式: 麦旭东, 韩木兰, 印遇龙, 等. 金属转运蛋白SLC39A14的代谢性功能研究进展. 科学通报, 2020, 65: 2571–2576

Mai X D, Han M L, Yin Y L, et al. The metabolic function of the metal transporter SLC39A14 (in Chinese). Chin Sci Bull, 2020, 65: 2571–2576, doi: 10.1360/TB-2020-0329

图1 金属转运蛋白SLC39A14的代谢性功能机制
Figure 1 Metabolic mechanism of metal transporter SLC39A14

SLC39A14是SLC39家族的成员,具有8个TM和富含组氨酸的结构域,并且还含有保守的特征性“HEX-PHEXGD”片段。人体组织的cDNA探针芯片研究显示,SLC39A14主要在肝脏、胰腺、心脏、小肠中表达^[1]。在无饮食及药物干预的小鼠研究中发现,*Slc39a14* mRNA在空肠、肝脏、心脏、肾脏、白色脂肪组织、骨骼肌、胰腺中均有表达^[1,8]。细胞分子生物学研究发现,SLC39A14蛋白主要在细胞膜上表达,可在十二指肠上皮细胞膜上发挥锌离子(Zn^{2+})吸收的功能^[9,10]。在不同代谢性组织或器官中,SLC39A14还具有转运铁(Fe)^[8,11]、锰(Mn)^[12]等金属离子的功能。

1 SLC39A14在不同代谢性组织器官中的研究

1.1 SLC39A14参与脂肪组织发育及分化

对减重前后的肥胖人群皮下脂肪组织中SLC39A14基因表达水平的临床研究结果显示,减重后皮下脂肪组织中的SLC39A14表达上调,且与体重指数(body mass index, BMI)、甘油三酯、胰岛素抵抗呈负相关^[13]。在无外界环境干预的条件下,小鼠成熟白色脂肪中*Slc39a14*低表达^[14]。然而,Tominaga等人^[15]发现,在脂肪前体细胞系3T3-L1中,*Slc39a14*在诱导分化早期(3 h)表达水平上调,直至诱导24 h后才逐渐下降。此外,从白色脂肪组织(white adipose tissue, WAT)分离的血管基质(stroma vascular fraction, SVF)和成熟脂肪两个不同组分中,*Slc39a14*主要在SVF中表达。⁶⁵Zn同位素标记法也证实,在脂肪分化早期,SLC39A14主要发挥锌离子转运的功能,提示SLC39A14主要在脂肪细胞形成早期

及分化过程中发挥作用。

Troche等人^[16]研究证明,SLC39A14参与脂肪组织中脂肪因子的合成,也参与脂肪细胞的发育及脂肪沉积过程中锌离子的转运。对全身性*Slc39a14*敲除的小鼠(*Slc39a14*-KO)研究发现,小鼠白色脂肪组织出现锌离子蓄积的同时,还表现出脂肪分化能力减弱和胰岛素敏感性降低的表型。其中,*Slc39a14*-KO小鼠脂肪前体细胞表现出较低的分化能力和更少的脂滴集聚,该表型可被脂多糖(LPS)诱导急性炎症所抑制,并促进*Slc39a14*-KO小鼠脂肪前体细胞分化,提示在低度炎症下,SLC39A14介导的锌离子转运是肥胖疾病中脂肪沉积的重要因素。既往针对SLC39A14转运蛋白在脂肪组织中的功能性研究主要是基于全身性*Slc39a14*敲除小鼠的脂肪分化能力及胰岛素敏感性等表型而开展的,目前尚无基于脂肪组织特异性敲除*Slc39a14*的小鼠模型的相关研究,SLC39A14金属转运蛋白是否参与调控棕色脂肪、米色脂肪产热功能以及微量元素在脂肪组织发育过程中的稳态平衡仍需进一步研究和探讨。

1.2 SLC39A14参与肝脏组织中多种微量元素转运

肝脏是机体调节锌、铁、锰微量元素代谢以及糖脂代谢的重要器官。糖异生是机体将多种非糖物质转变成葡萄糖或糖原的重要生物过程,其主要由肝脏中多种催化酶参与完成,而糖异生中的限速酶、果糖1,6-二磷酸酶(F-1,6-bPase)、葡萄糖-6-磷酸酶(G6Pase)和磷酸烯醇丙酮酸羧激酶(Pepck)等酶活性具有锌剂量的依赖性。Aydemir等人^[17]利用*Slc39a14*-KO小鼠研究发现,*Slc39a14*敲除可以改善高脂饮食(HFD)诱导的胰岛素抵抗,其肝脏表现出更强的葡萄糖摄取能力。但在进

一步糖稳态实验,如糖耐量实验、丙酮酸耐受性实验中研究人员发现,*Slc39a14-KO*小鼠肝细胞中出现锌缺乏并诱发糖异生受损,通过补充高锌饲料或注射锌剂可部分缓解该表型,分子生物学研究证实糖异生合成的受损主要与Pepck和G6Pase的酶活性有关.SLC39A14转运蛋白以及 Zn^{2+} 调节糖异生的限速酶活性的机制仍需进一步研究。

Slc39a14除参与转运锌离子外,Liuzzi等人^[8]发现,肝脏Slc39a14可以将非转铁蛋白结合的铁离子(non-transferrin-bound iron, NTBI)转运至细胞.Jenkitkasemwong等人^[18]利用遗传血色素沉着病(*Hfe1*^(-/-), *Hfe2*^(-/-))和*Slc39a14-KO*小鼠模型研究发现,在以肝脏病理性铁蓄积为主要特征的遗传性血色素沉着病发病机制中,敲低*Slc39a14*表达可显著降低肝脏铁负荷,减轻肝脏中铁沉积.此外,研究还发现,高脂饮食可能通过抑制转铁蛋白受体-2(TfR2)和SLC39A14减少肝脏NTBI存储,提示SLC39A14是肝脏中重要的铁转运蛋白^[19].但SLC39A14与肝细胞中铁离子摄取相关的其他金属转运蛋白之间的关系及其在维持肝脏铁稳态中所发挥的作用,仍需要进一步研究和挖掘。

SLC39A14还参与肝脏中锰离子的转运.Xin等人^[12]利用*Slc39a14-KO*和肝脏特异性*Slc39a14*敲除的小鼠(*Slc39a14*^{fl/fl}; *Alb-Cre*⁺)及高锰饲料证实,在正常饮食条件下,锰离子可通过SLC39A14被肝细胞吸收,也可通过肝细胞SLC30A10转运蛋白外排.此外,高锰饮食并不能缓解*Slc39a14*^{fl/fl}; *Alb-Cre*⁺小鼠中肝脏低锰水平,还会进一步诱导机体出现全身性Mn离子蓄积.Thompson等人^[20]研究还发现,高锰刺激可抑制人肝癌细胞(HepaRG Cell) *SLC39A14*表达,从而限制高锰环境下肝胆系统对锰离子的转运功能.因此,分子遗传学检测确诊的SLC39A14缺乏症患者,临床指南建议避免摄入高锰食物,以降低机体锰离子的蓄积^[21]。

1.3 Slc39a14参与调控胰腺组织内分泌功能

糖尿病是一类以胰岛素分泌缺陷或胰岛素生物作用受损为特征的代谢性疾病。

在2型糖尿病发病过程中,持续高血糖的刺激作用是损害胰岛β细胞功能的重要因素之一.而胰岛β细胞分泌的胰岛素主要依赖于锌离子作为胰岛素晶体的基本成分.研究发现,人类和小鼠胰岛组织中,SLC39A1、SLC39A4、SLC39A6、SLC39A7和SLC39A14是调节胰岛β细胞锌稳态的重要转运蛋白^[22-25].Lawson等人^[23]

发现,持续高糖刺激可抑制SLC39A6、SLC39A7、SLC39A14等锌转运蛋白的表达,大幅度耗竭胰岛β细胞系Min6细胞中锌含量并抑制Pdx1、MafA等成熟胰岛β细胞标志物的表达,进而促进β细胞去分化,损害胰岛素合成及分泌的功能.但SLC39A14在胰岛素β细胞发育、分化以及胰岛素合成与分泌中所参与的精准调控仍需大量细胞及动物实验进一步研究。

有学者认为,胰岛β细胞中铁超载也是损害β细胞合成及胰岛素分泌功能的因素之一^[26,27],但胰岛β细胞中铁离子的代谢调控尚未明确.Coffey等人^[26]发现,过表达SLC39A14和SLC39A8均可促进人胰岛β细胞系βlox5摄取NTBI,与此相反,siRNA介导的SLC39A14敲低可降低βlox5细胞50% NTBI摄取率.值得注意的是,在*Slc39a14*与*Hfe1*或*Hfe2*双敲除的遗传性血色素沉着病动物模型中,依然有大量铁在肝脏和胰腺中积累^[18].此外,Lunova等人^[28]利用铁调素基因缺陷的小鼠(*Hepcidin-KO*)发现,机体在铁调素信号缺失的情况下可促进铁转运蛋白*Dmt1*和*Slc39a14*的表达,进而加重胰腺组织铁负荷并诱发胰腺炎性损伤.胰岛β细胞中是否真正存在铁超载以及是否具有影响胰岛素分泌及合成功能还有待探讨。

1.4 Slc39a14参与调控肌肉组织锌稳态

骨骼肌占人体体重的30%~40%,是机体重要的蛋白库.在长期饥饿、应激等特殊状态下,骨骼肌又是机体的能量代谢库.肿瘤患者,尤其是伴有恶病质(cachexia)的肿瘤晚期患者会出现全身骨骼肌不断分解消耗,进而出现肌肉萎缩的症状.具体而言,恶病质是指由癌症和其他严重慢性消耗性疾病引起的,以食欲不振、极度消瘦、全身代谢紊乱、脏器不同程度受损坏等为主要表现的综合征,危害患者生命活动及生命质量.Wang等人^[29]研究发现,在结肠癌、乳腺癌转移癌小鼠模型及晚期肿瘤恶病质患者的多种肌肉(胫骨前肌、腓肠肌、股四头肌、比目鱼肌等)中,锌转运蛋白SLC39A14显著上调,并可由肿瘤坏死因子α(TNF-α)和转化生长因子-β(TGF-β)所诱导.体外细胞生物学研究证实,SLC39A14所介导的锌过载可抑制C2C12成肌细胞系的肌纤维分化以及抑制转移癌动物模型肌肉生成,并且可诱导肌球蛋白重链(myosin heavy chain, MyHC)降解^[29].肿瘤恶病质条件下,肌肉组织中过表达的SLC39A14所诱导的肌肉细胞结构与功能紊乱,可能是由泛素-蛋白酶的萎缩相关基因和自噬溶酶体降解途

径所介导,进而促进肌肉萎缩的发生发展^[29]。Shakri等人^[30]也在胰腺导管腺癌(PDAC)的转移癌动物模型中有类似的发现,提示肌肉的锌转运蛋白SLC39A14所介导锌稳态与肿瘤恶病质密切相关。值得注意的是,目前SLC39A14转运蛋白在肌肉组织中的研究主要集中在探索晚期肿瘤恶病质发病中的作用,尚未有文献报道SLC39A14在单根肌纤维以及肌卫星细胞上的功能、SLC39A14转运蛋白如何参与肌管分化、是否参与肌纤维的能量代谢以及是否参与肌肉修复与再生。最近的研究发现,SLC39A14是LPS诱导的炎症反应中小鼠骨骼肌的锌转运蛋白,*Slc39a14-KO*小鼠可表现出肌肉萎缩和代谢性内毒素血症等表型^[31]。因此,仍需大量的实验数据以揭示和探讨SLC39A14在肌肉组织中的功能。

1.5 SLC39A14分子调控机制

作为铁、锌、锰离子的重要转运蛋白,SLC39A14受到细胞组织、血液循环中微量元素浓度以及膳食中微量元素摄入水平等条件所调节。在膳食缺铁和肠道铁吸收障碍的动物模型中,肠道上皮的*Slc39a14* mRNA转录水平上调^[32,33]。血色素沉着症等铁超载病理情况下,血浆中NTBI可被肝脏SLC39A14转运入肝脏等组织^[8,11]。敲低*Slc39a14*的表达可显著降低血色素沉着症中肝脏铁负荷,减少肝脏中铁沉积^[18]。此外,炎症因子也参与调控SLC39A14。在LPS诱导的内毒素血症的研究中,肝脏、肌肉、白色脂肪中的*Slc39a14*表达水平升高^[16,31,34]。作为LPS诱导内毒素炎症通路中的下

游因子,白介素6(IL-6)可调节肝细胞膜上的SLC39A14的表达水平,促进细胞摄入锌,诱发低锌血症^[35]。其他炎症因子如IL1 β ,亦诱导肝SLC39A14表达上调,促进锌离子吸收^[36]。不同代谢性器官或组织中,更深入及精细的SLC39A14调控分子机制仍有待进一步研究。

2 金属转运蛋白SLC39A14的研究展望

金属转运蛋白SLC39A14是转运铁、锌、锰等必需微量元素的重要转运蛋白。目前,虽然对金属转运蛋白SLC39A14的金属离子转运功能有了一定的理解,但是SLC39A14在能量代谢器官中所介导的精准调控机制仍然存在空白,并值得进一步探索。组织特异性基因敲除小鼠模型、转录组学、蛋白质组学和代谢组学等多组学技术将为进一步了解金属转运蛋白SLC39A14功能以及其在代谢性疾病发生和发展过程中的分子机制提供技术保障,研究成果也将为围绕SLC39A14开发的新药研发提供重要的理论基础。例如,棕色脂肪、米色脂肪等产热脂肪组织中特异性*Slc39a14*敲除是否能诱导糖脂代谢紊乱表型的出现,其参与的分子调控机制与组织局部锌、铁元素含量是否存在生物学关系,是进一步探索糖尿病、肥胖症等代谢性疾病发病机制的重要研究方向。此外,骨骼肌是调节机体代谢与运动的重要内分泌器官,*Slc39a14*表达、局部组织锌稳态与肌肉组织胰岛素敏感性的关系以及*Slc39a14*蛋白与肌肉生长、发育及修复的内在关系,都是未来值得深入探索的研究方向。对金属转运蛋白SLC39A14深层次的探索将为代谢性疾病的防治提供新思路、新方法、新策略。

参考文献

- 1 Taylor K M, Morgan H E, Johnson A, et al. Structure-function analysis of a novel member of the LIV-1 subfamily of zinc transporters, ZIP14. *FEBS Lett*, 2005, 579: 427–432
- 2 Taylor K M, Nicholson R I. The LZT proteins; the LIV-1 subfamily of zinc transporters. *Biochim Biophys Acta*, 2003, 1611: 16–30
- 3 Taylor K M, Morgan H E, Johnson A, et al. Structure-function analysis of LIV-1, the breast cancer-associated protein that belongs to a new subfamily of zinc transporters. *Biochem J*, 2003, 375: 51–59
- 4 Hogstrand C, Kille P, Ackland M L, et al. A mechanism for epithelial–mesenchymal transition and anoikis resistance in breast cancer triggered by zinc channel ZIP6 and STAT3 (signal transducer and activator of transcription 3). *Biochem J*, 2013, 455: 229–237
- 5 Taylor K M M H, Johnson A, et al. Structure-function analysis of HKE4, a member of the new LIV-1 subfamily of zinc transporters. *Biochem J*, 2004, 377: 131–1319
- 6 Taylor K M, Hiscox S, Nicholson R I, et al. Protein kinase CK2 triggers cytosolic zinc signaling pathways by phosphorylation of zinc channel ZIP7. *Sci Signal*, 2012, 5: ra11
- 7 Wang X, Gao H, Wu W, et al. The zinc transporter SLC39A5 controls glucose sensing and insulin secretion in pancreatic β -cells via Sirt1- and Pgc-1 α -mediated regulation of Glut2. *Protein Cell*, 2019, 10: 436–449
- 8 Liuzzi J P, Aydemir F, Nam H, et al. Zip14 (SLC39A14) mediates non-transferrin-bound iron uptake into cells. *Proc Natl Acad Sci USA*, 2006, 103: 13612–13617
- 9 Guthrie G J, Aydemir T B, Troche C, et al. Influence of ZIP14 (SLC39A14) on intestinal zinc processing and barrier function. *Am J Physiol*

- [Gastrointest Liver Physiol](#), 2015, 308: G171–G178
- 10 Cousins R J. Gastrointestinal factors influencing zinc absorption and homeostasis. [Int J Vit Nutr Res](#), 2010, 80: 243–248
 - 11 Pinilla-Tenas J J, Sparkman B K, Shawki A, et al. Zip14 is a complex broad-scope metal-ion transporter whose functional properties support roles in the cellular uptake of zinc and nontransferrin-bound iron. [Am J Physiol Cell Physiol](#), 2011, 301: C862–C871
 - 12 Xin Y, Gao H, Wang J, et al. Manganese transporter SLC39A14 deficiency revealed its key role in maintaining manganese homeostasis in mice. [Cell Discov](#), 2017, 3: 17025
 - 13 Maxel T, Smidt K, Larsen A, et al. Gene expression of the zinc transporter ZIP14 (SLC39A14) is affected by weight loss and metabolic status and associates with PPAR γ in human adipose tissue and 3T3-L1 pre-adipocytes. [BMC Obes](#), 2015, 2: 46
 - 14 Aydemir T B, Cousins R J. The multiple faces of the metal transporter zip14 (SLC39A14). [J Nutr](#), 2018, 148: 174–184
 - 15 Tominaga K, Kagata T, Johmura Y, et al. SLC39A14, a LZT protein, is induced in adipogenesis and transports zinc. [FEBS J](#), 2005, 272: 1590–1599
 - 16 Troche C, Beker Aydemir T, Cousins R J. Zinc transporter SLC39A14 regulates inflammatory signaling associated with hypertrophic adiposity. [Am J Physiol Endocrinol Metab](#), 2016, 310: E258–E268
 - 17 Aydemir T B, Troche C, Kim M H, et al. Hepatic ZIP14-mediated zinc transport contributes to endosomal insulin receptor trafficking and glucose metabolism. [J Biol Chem](#), 2016, 291: 23939–23951
 - 18 Jenkitkasemwong S, Wang C Y, Coffey R, et al. SLC39A14 is required for the development of hepatocellular iron overload in murine models of hereditary hemochromatosis. [Cell Metab](#), 2015, 22: 138–150
 - 19 Jiang S, Yan K, Sun B, et al. Long-term high-fat diet decreases hepatic iron storage associated with suppressing TFR2 and ZIP14 expression in rats. [J Agric Food Chem](#), 2018, 66: 11612–11621
 - 20 Thompson K J, Wessling-Resnick M. ZIP14 is degraded in response to manganese exposure. [BioMetals](#), 2019, 32: 829–843
 - 21 Tuschl K, Gregory A, Meyer E, et al. SLC39A14 Deficiency. In: Adam M P, Ardinger H H, Pagon R A, et al, eds. Gene Reviews (R). Seattle (WA): University Washington, 1993
 - 22 Liu Y, Batchuluun B, Ho L, et al. Characterization of zinc influx transporters (ZIPs) in pancreatic β Cells. [J Biol Chem](#), 2015, 290: 18757–18769
 - 23 Lawson R, Maret W, Hogstrand C. Prolonged stimulation of insulin release from MIN6 cells causes zinc depletion and loss of β -cell markers. [J Trace Elem Med Biol](#), 2018, 49: 51–59
 - 24 Hardy A B, Prentice K J, Froese S, et al. Zip4 mediated zinc influx stimulates insulin secretion in pancreatic beta cells. [PLoS One](#), 2015, 10: e0119136
 - 25 Lawson R, Maret W, Hogstrand C. Expression of the ZIP/SLC39A transporters in β -cells: A systematic review and integration of multiple datasets. [BMC Genomics](#), 2017, 18: 719
 - 26 Coffey R, Knutson M D. The plasma membrane metal-ion transporter ZIP14 contributes to nontransferrin-bound iron uptake by human β -cells. [Am J Physiol Cell Physiol](#), 2017, 312: C169–C175
 - 27 Kishimoto M, Endo H, Hagiwara S, et al. Immunohistochemical findings in the pancreatic islets of a patient with transfusional iron overload and diabetes: Case report. [J Med Invest](#), 2010, 57: 345–349
 - 28 Lunova M, Schwarz P, Nuraldeen R, et al. Hepsidin knockout mice spontaneously develop chronic pancreatitis owing to cytoplasmic iron overload in acinar cells. [J Pathol](#), 2017, 241: 104–114
 - 29 Wang G, Biswas A K, Ma W, et al. Metastatic cancers promote cachexia through ZIP14 upregulation in skeletal muscle. [Nat Med](#), 2018, 24: 770–781
 - 30 Shakri A R, Zhong T J, Ma W, et al. Upregulation of ZIP14 and altered zinc homeostasis in muscles in pancreatic cancer cachexia. [Cancers](#), 2019, 12: 3
 - 31 Kim J, Aydemir T B, Jimenez-Rondan F R, et al. Deletion of metal transporter Zip14 (SLC39A14) produces skeletal muscle wasting, endotoxemia, Mef2c activation and induction of miR-675 and Hspb7. [Sci Rep](#), 2020, 10: 4050
 - 32 Yeh K, Yeh M, Polk P, et al. Hypoxia-inducible factor-2 α and iron absorptive gene expression in Belgrade rat intestine. [Am J Physiol Gastrointest Liver Physiol](#), 2011, 301: G82–G90
 - 33 Hansen S L, Trakooljul N, Liu H C, et al. Iron transporters are differentially regulated by dietary iron, and modifications are associated with changes in manganese metabolism in young pigs. [J Nutr](#), 2009, 139: 1474–1479
 - 34 Gálvez-Peralta M, Wang Z, Bao S, et al. Tissue-specific induction of mouse ZIP8 and ZIP14 divalent cation/bicarbonate symporters by, and cytokine response to, inflammatory signals. [Int J Toxicol](#), 2014, 33: 246–258
 - 35 Liuzzi J P, Lichten L A, Rivera S, et al. Interleukin-6 regulates the zinc transporter Zip14 in liver and contributes to the hypozincemia of the acute-phase response. [Proc Natl Acad Sci USA](#), 2005, 102: 6843–6848
 - 36 Lichten L A, Liuzzi J P, Cousins R J. Interleukin-1 β contributes via nitric oxide to the upregulation and functional activity of the zinc transporter Zip14 (SLC39A14) in murine hepatocytes. [Am J Physiol Gastrointest Liver Physiol](#), 2009, 296: G860–G867

Summary for “金属转运蛋白SLC39A14的代谢性功能研究进展”

The metabolic function of the metal transporter SLC39A14

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Microelement is one of the nutritional elements of the human body. They participate in a wide range of physiological and biochemical functions of the human body, such as electron transport, oxygen delivery, enzyme activity, and cell growth and differentiation, etc. They also could be used as auxiliary components of biological macromolecules, or as the functional components of hormones and vitamins, which are of great significance to maintain life activities. Among them, essential trace elements, such as iron, zinc, and manganese, are not produced or synthesized in the body, but indispensable to maintain the whole-body physiological function. Essential trace elements are absorbed and transported into the blood circulation by a variety of metal transporters in the upper digest tract. Recently, with the identification and discovery of metal transporters and multifunctional study, we gain an in-depth understanding of metal transporters in metabolic organs and various metabolic diseases. Solute carrier 39 (SLC39), also known as zinc importer protein (ZIP) family, is a metal importer. According to the homology analysis of gene sequence, this family has 14 members, SLC39A1–SLC39A14 (ZIP1–ZIP14).

Based on the protein structure, ZIP family could be divided into four subfamilies: I, II, Gufa, and LIV-1. SLC39A14 belongs to the LIV-1 subfamily of ZIP zinc transporters (LZT) family. It has 8 transmembrane domains (TM), histidine-rich domains and a conserved “HEXHEXGD” fragment. SLC39A14 is mainly expressed on the cellular membrane. Recent studies have demonstrated that it is involved in the absorption of metals like zinc, iron, and manganese in different metabolic tissues or organs. The function of SLC39A14 was investigated by generating global or tissue-specific knockout mice in different metabolic organs such as the liver, pancreas, adipose, and skeletal muscle. Most of these studies indicate that *Slc39a14*-deletion may perturb tissue metabolic functions, such as insulin synthesis and secretion, disrupted insulin sensitivity or tissue metal absorption. More specifically, for the *Slc39a14* global knockout mice (*Slc39a14-KO*), the insulin sensitivity and adipocyte differentiation are impaired in adipose tissue. *Slc39a14-KO* also disrupts gluconeogenesis in hepatic tissue induced by low tissue zinc content. Meanwhile, hepatocyte-specific knockout of *Slc39a14* shows that SLC39A14 may be involved in hepatic manganese transportation and non-transferrin-bound iron (NTBI). In the mouse β cell line (Min6), SLC39A14 is involved in the endocrinal function of the pancreas, especially the insulin synthesis and secretion function in β cell. Furthermore, SLC39A14 function in skeletal muscle and myoblast suggests that SLC39A14 may regulate tissue zinc homeostasis in skeletal muscle of tumor metastasis animal model. In C2C12 myoblasts, SLC39A14 participates in myogenic differentiation and myotube development. In addition, the expression of SLC39A14 is not only regulated by the concentration of trace elements in blood circulation and intake level of elements from diets but also regulated by inflammatory factors such as LPS and IL-6. In this review, the metabolic function of metal transporters SLC39A14 in different tissues and organs is summarized.

metal transporter, SLC39A14, metabolic organs, obesity, type 2 diabetesdoi: [10.1360/TB-2020-0329](https://doi.org/10.1360/TB-2020-0329)