**特约综述**

微量元素稳态代谢平衡分子机制是我们实验室的主要研究方向。必需微量元素如铁、锌、铜等对维持生物体代谢和健康至关重要，其过多或过少都会造成代谢异常甚至死亡，因此生物体存在复杂机制维持这些微量元素的稳态代谢平衡(Homeostasis)。我们实验室建立了特色的基因敲除小鼠平台及基因突变斑马鱼平台用于筛选微量元素代谢新基因并阐明其分子机制; 近年还开展了以中国和欧美澳居民为调研对象的分子营养流行病学人群项目, 用于开拓“人群离子组学”的研究。
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# 哺乳动物铁稳态分子机制研究进展

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**摘要** 铁是机体必需微量元素, 参与机体合成血红蛋白、肌红蛋白及多种酶的组成和功能发挥, 对维持生命和健康至关重要。近四分之一的世界人口遭受铁缺乏或缺铁性贫血的威胁。此外, 部分人群还存在铁过载问题, 以脏器铁离子蓄积为主要病理改变的遗传性血色病, 其在欧美发病率高达1/200, 在中国也有报道。血色病后期多诱发肝脏、胰腺及心脏的功能衰退。铁过少或过多对健康都会造成严重危害, 机体需要复杂而精密的调控体系维持铁稳态平衡。铁代谢主要包括小肠吸收、肝脏储存、血液转运、巨噬细胞再循环以及周身细胞利用。过去十多年是铁代谢研究的“黄金时期”, 先后发现众多铁稳态代谢相关基因。该文综述了近年来哺乳动物铁代谢领域的研究进展, 并对铁稳态代谢中存在的问题进行了初步讨论, 为理解和进一步深入研究铁代谢分子机制提供参考。

**关键词** 铁; 铁稳态; 贫血; 血色病

必需微量元素铁是多种酶的重要组成部分, 在机体内广泛参与氧气运输、电子转运、DNA合成、细胞增殖、分化、基因表达调控等生命过程[1-2]。在世界范围内, 尤其是在发展中国家, 缺铁性贫血(iron-deficiency anemia, IDA)是最常见的营养不良疾病之一, 妊娠妇女和儿童的症状尤为严重[3]。婴儿期铁缺乏会严重影响认知和情感的发育[4], 这些影响可能是短暂的, 补铁可以康复, 但也可能持续到青春期和成人期[5]。铁过量也有很多危害, 过量的游离铁在细胞内, 催化自由基生成, 进而损伤细胞膜结构、蛋白质及DNA, 最终导致细胞凋亡、组织损伤。越来越多的研究表明, 铁蓄积与老年退行性病变相关, 包括阿尔茨海默症(Alzheimer’s disease)、帕金森病(Parkinson’s disease)和动脉粥样硬化(atherosclerosis)等[6]。此外, 很多疾病都伴随铁代谢紊乱症状, 如肝硬化(liver cirrhosis)、性腺机能减退(hypogonadism)、糖尿病(diabetes)、心肌病(cardiomyopathy)、关节炎(arthritis)等[7-9]。研究发现, 人体有5个基因的突变

国家重点基础研究发展计划(No.2009CB941400, No.2011CB966200)、国家自然科学基金项目(No.1097907, No.30970665, No.10JC1416800, No.81000358)、中国科学院百人计划(No.KSCX2-YW-R-141)、上海市科委项目(No.10JC1416800)和中国博士后科学基金(No.20100480637)资助项目

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均可引发以铁元素脏器蓄积为主要病理特征的遗传病——血色病(hereditary hemochromatosis, HH)。这5个基因分别为*Hfe*、*Tfr2*、*Hamp*、*Hfe2*和*Fpn*。正常生理状态下, 机体通过非常复杂的体系来调控和维持自身的铁稳态(iron homeostasis)。

## 1 细胞铁代谢

机体每天需要大量的铁来维持正常的生理功能。铁的主要来源有两部分: 一是巨噬细胞吞噬受损或衰老的红细胞, 分解释放血红蛋白中的铁(约占90%~95%); 二是来源于食物(约占5%~10%)[10]。机体铁主要储存在肝脏和网状内皮系统, 而肠上皮黏膜细胞和皮肤细胞脱落以及流血才会丢失铁, 但目前并不认为铁丢失过程与体内铁的调控相关, 铁排出调控机制的研究尚未清楚, 体内铁稳态的维持主要通过调控铁的摄取和储存来完成[10-11]。几乎所有的真核细胞都存在特定机制摄取和利用铁, 但某些特殊细胞在铁代谢中行使特殊功能, 如肠上皮细胞对食物铁的吸收、肝细胞的铁储存功能和巨噬细胞的铁再循环功能, 从而确保机体内铁稳态。

### 1.1 小肠细胞铁代谢

机体对外源铁的摄入, 主要是通过十二指肠和空肠上端黏膜完成[11]。食物中的铁包括无机铁(即非血红素铁, non heme)和血红素铁(heme)两种类型。无机铁经肠道吸收并转入体内需穿过2个屏障: 面向肠腔的小肠细胞微绒毛顶膜[12]和另一侧的基底膜[13]。食物中溶解度低的三价铁离子($Fe^{3+}$)首先被定位于十二指肠刷状缘的还原酶还原为溶解度较高的亚铁离子($Fe^{2+}$), 在胃和十二指肠肠腔酸环境中稳定存在, 随后被刷状缘上二价金属离子转运体(divalent metal transporter 1, DMT1)转运至肠黏膜内[12,14]。Mckie等[15]研究发现, 十二指肠细胞色素b (duodenal cytochrome b, Dcytb)是细胞色素b561家族的同系物, 定位于肠上皮细胞刷状缘, 具有高价铁还原能力, 低铁日粮喂养小鼠能显著增加*Dcytb* mRNA和蛋白的表达。但是正常喂养*Dcytb* (*Cybrd1*)基因敲除小鼠并没有任何明显的铁代谢异常, 表明Dcytb不是小鼠必需的高价铁还原酶[16]。肠黏膜细胞内大部分$Fe^{2+}$直接经由基底膜上的铁转运蛋白1 (ferroportin 1, FPN1)转运进入血液, 进而被机体利用[13], 此转运过程中, 定位在黏膜细胞绒毛上的多铜氧化酶家族的铁转运辅助蛋白(hephaestin, Hp)发挥重要协同作用, *Heph*基因敲除小鼠, 表现为肠道铁转运障碍和较严重的小细胞低色素性贫血(microcytic hypochromic anaemia)[17]。此外, 肠黏膜中一部分$Fe^{2+}$, 可能在亚铁氧化酶的作用下, 被氧化为$Fe^{3+}$, 与铁蛋白(Ferritin, Fn)结合, 每分子Fn可以结合4 500个$Fe^{3+}$。此外, 当肠道一次性铁吸收过多时, 黏膜可能将$Fe^{2+}$储存在一个临时"活性铁池(labile iron pool, LIP)"内, 以减少向血液中转运过量游离铁, 而当机体需要铁时再释放(图1)。

无机铁在肠腔的吸收率受到pH值、磷酸根和其它拮抗因子的影响, 而动物组织来源的血红素——Heme, 是铁与原卟啉的复合物, 吸收利用率较高。位于十二指肠上皮细胞的Heme转运蛋白HCP1 (heme carrier protein 1)可以吸收Heme[18], 但HCP1 (PCFT)是肠黏膜细胞叶酸吸收的特异转运蛋白, *HCP1*$^{-/-}$小鼠表现为全身性叶酸缺乏症[19]。在HepG2细胞系内, 叶酸的吸收受到Heme的抑制[20], 显示了HCP1只能转运少量的Heme, 不是肠道Heme吸收的主要转运蛋白。Heme可能是通过其他途径或者细胞表面受体介导的内吞方式被肠黏膜细胞大量吸收, 但有待进一步研究。进入胞内的Heme一部分会被附着在内质网上的Heme加氧酶1 (heme oxygenase 1, HO-1)降解; 或者被胞质内囊泡内吞, 由Heme加氧酶2 (HO-2)降解, 释放出$Fe^{2+}$, 之后参与到肠上皮细胞内铁的储存和转运过程[21]。此外, 细胞内的Heme有一部分能够直接经由细胞基底膜上的(feline leukemia virus receptor C, FLVRC)转运进入血液, 参与红细胞成熟过程[22](图1)。

### 1.2 体细胞铁代谢

食物中的铁经肠道吸收进入血液后, $Fe^{2+}$在亚铁氧化酶如血浆铜蓝蛋白(ceruloplasmin, CP)的作用下被氧化成为$Fe^{3+}$, 与血浆中的转铁蛋白(transferring, Tf)结合, 运输到各个器官组织, 与细胞膜上转铁蛋白受体(transferrin receptor, TfR)结合, 转运入细胞, 被吸收利用[23]。

机体细胞如红细胞前体细胞(erythroid precursors), 主要通过Tf-TfR介导的细胞内吞作用方式摄入足够量的铁, 保证血红蛋白正常合成[24]。现已发现, TfR具有两个同源蛋白(TfR1和TfR2), TfR1广泛表达, 在介导细胞铁吸收过程中发挥重要作用, *TfR1*基因敲除小鼠因严重的缺铁性贫血导致其在妊娠中期便死亡[25]。TfR2主要在肝脏表达[26], 与Tf的结合能力比TfR1低, 但也能介导铁转运[27]。

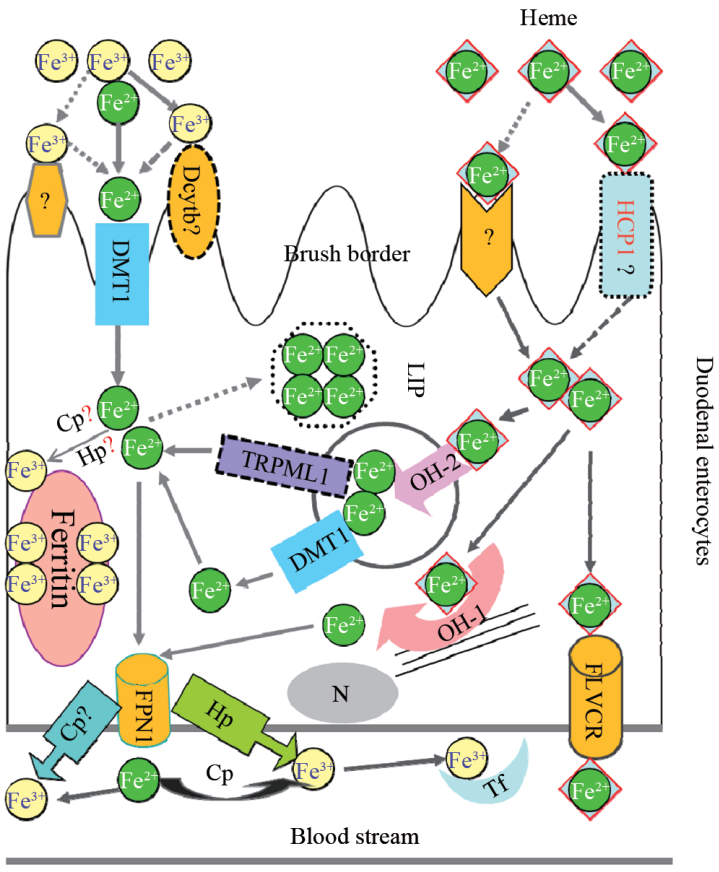


**图 1　小肠上皮细胞铁离子吸收模式图**

**Fig.1　Scheme of iron absorption pathways in the intestinal enterocytes**

血浆中含有大量的Tf, TfR1则特异性高表达于大量需铁或快速增殖的细胞中, 如红系前体细胞、激活的淋巴细胞、肿瘤细胞等[10]。在胞外微碱性环境中, Tf对$Fe^{3+}$具有高度亲和性, 每分子Tf能够结合两分子$Fe^{3+}$, 细胞表面的TfR1特异识别并结合两分子载铁的Tf (Tf-$(Fe^{3+})_2$) (图2)。Tf和TfR1相互作用引发细胞膜内陷形成内涵体(endosome), 其内pH值在离子泵作用下逐渐降低, Tf-TfR1结合紧密但构象改变, 同时释放出$Fe^{3+}$, 内涵体内Tf-TfR1回到细胞表面, 在微碱性pH时Tf与TfR1分离, 重复运铁过程[10,23]。Steap3 (six-transmembrane epithelial antigen of the prostate-3)在造血组织细胞内高表达且定位于Tf-TfR1介导的铁转运的内涵体膜上, 具有高价铁还原活性, 将Tf-TfR1介导内吞的$Fe^{3+}$还原为$Fe^{2+}$, 由DMT1输出至胞质内。Steap3蛋白错义突变的小鼠表现为低血色素性小红细胞贫血[28]。Steap3蛋白的发现, 完善了红系细胞发育过程中Tf-TfR1转铁过程。Steap家族其他成员Steap1、Steap2、Steap4的组织表达及亚细胞定位的研究发现: Steap2、Steap4同样具有高价铁还原功能, 与Steap3一起, 在介导造血组织细胞的铁转运过程中发挥关键作用[29]。此外, TRPML1也可能是介导晚期内涵体和溶酶体$Fe^{2+}$释放的另一条渠道[30]。

### 1.3　巨噬细胞介导的“铁再循环”

网织内皮巨噬细胞在维持机体铁稳态过程中发挥关键作用[31], 正常成年人, 体内接近80%的铁存在于红细胞血红蛋白内, 而红细胞以200万个/秒的速度代谢更新, 人体每天需要大约20~25 mg铁来满足红细胞血红蛋白合成。其中约0.5~2.0 mg铁来源于食物经由小肠吸收, 其余大部分铁来源于巨噬细胞对衰老红细胞中铁的再循环利用[10,32]。巨噬细胞还可以通过膜上TfR1介导内吞作用, 吸收转铁蛋白结合的铁(transferrin bound iron, TBI); 在一些促炎症因子刺激下, DMT1表达上调, 促进巨噬细胞对非转铁蛋白结合的铁(non-transferrin bound iron, NTBI)的吸收[33](图3)。

吞噬细胞吞噬衰老的红细胞之后, HO-1表达随

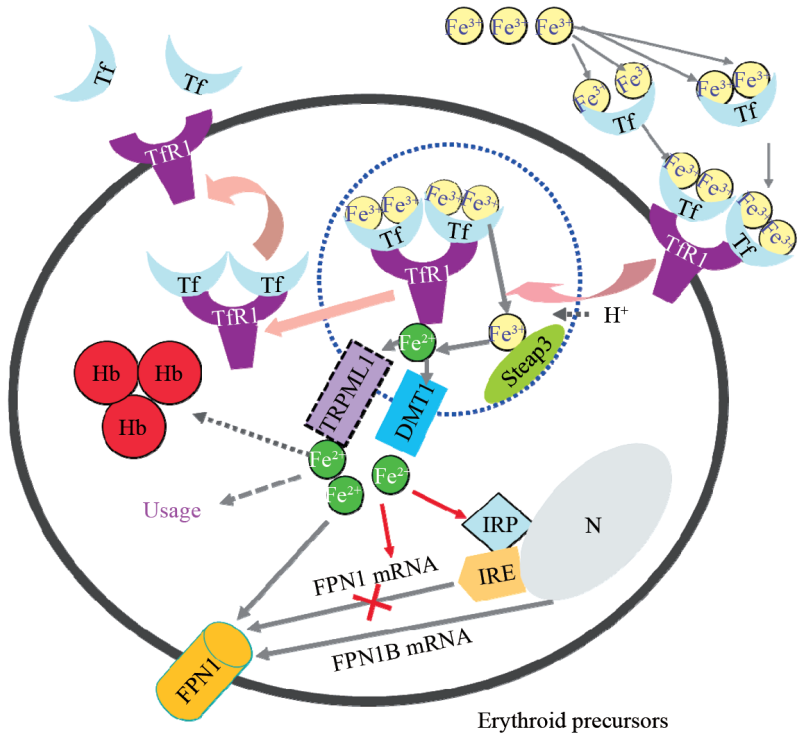


**图 2　造血细胞Tf和TfR1铁离子摄取模式图**

**Fig.2　Scheme of erythroid precursors iron uptake mediated by Tf and TfR1**

之增加, 有效地将Heme降解, 释放出$Fe^{2+}$, 经由内涵体膜上的转运体介导囊泡中的$Fe^{2+}$转运到到胞质中。再由细胞膜上FPN1将铁转运到血浆[34]。*HO-1*基因敲除小鼠巨噬细胞Heme代谢障碍, 表现为溶血性贫

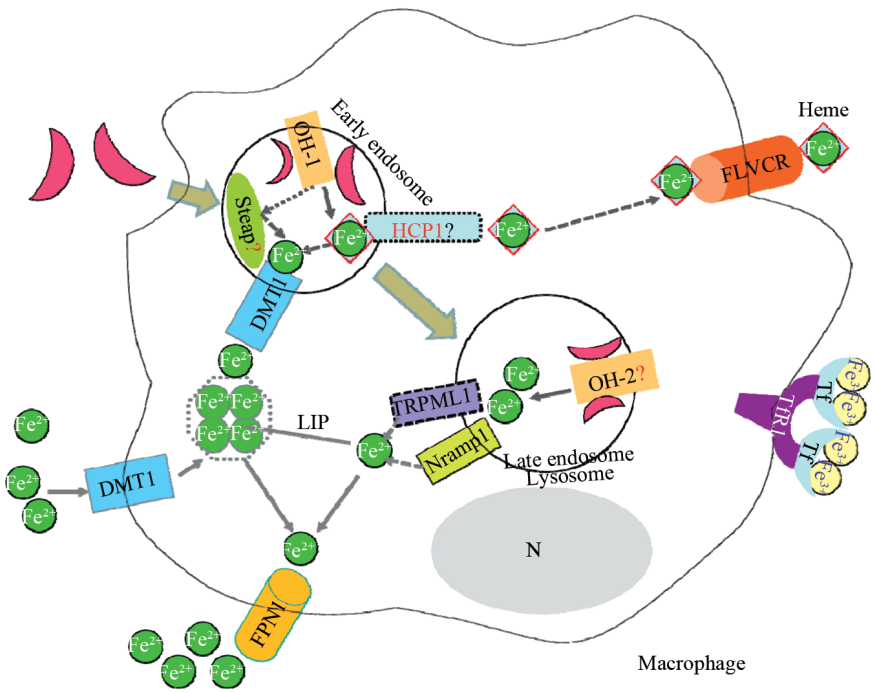


**图 3　巨噬细胞铁代谢模式图**

**Fig.3 Scheme of iron metabolism in macrophages**

血、内脏器官损伤[35]。HCP1在人体巨噬细胞内表达, 且在早期内涵体上与内吞的血红蛋白共定位, 为Heme的转运提供了新的证据[36](图3)。内涵体膜上$Fe^{2+}$的转运体主要有DMT1 (Nramp2)及其同源蛋白Nramp1, 前者几乎在所有细胞中表达, 定位于早期的内涵体(early endosome)膜上[37], 后者则特异表达于吞噬功能的巨噬细胞和中性粒细胞, 且定位于晚期内涵体(late endosome)膜上[38-39]。巨噬细胞缺失功能性DMT1或者Nramp1时, 会在一定程度上降低铁循环效率, 而同时缺失功能性DMT1和Nramp1, 会严重损害巨噬细胞铁循环功能[40]。

FPN1是目前发现的细胞膜上唯一的铁输出膜蛋白[41], 主要在十二指肠上皮细胞和网状内皮组织的巨噬细胞中高表达, 前者主要将食源铁通过肠细胞基底膜转运到血液, 而巨噬细胞囊泡内FPN1可以转移到巨噬细胞膜上, 将被吞噬的衰老红细胞释放的铁转运出来[13,42]。小鼠*Fpn1*靶向敲除, 由于母鼠无法向*Fpn1*$^{-/-}$小鼠转铁, 导致*Fpn1*$^{-/-}$小鼠胚胎死亡, 而十二指肠*Fpn1*条件性敲除, 则表现为严重贫血[41]。最近, 我们分别用LysM-cre与F4/80-cre小鼠与Fpn1-floxed小鼠杂交, 制备了两种巨噬细胞*Fpn1*条件性敲除小鼠模型。在正常饲料饲养时, 巨噬细胞*Fpn1*敲除小鼠表现出轻度贫血与肝脏、脾脏及骨髓巨噬细胞轻度铁累积的复杂表型; 在注射葡聚糖铁或苯肼诱导溶血性贫血的实验中, *Fpn1*敲除小鼠巨噬细胞中累积了更多的铁离子; 在低铁日粮饲养时, *Fpn1*敲除小鼠表现为更严重的贫血表型, 脾脏和肝脏铁水平与对照小鼠差异加大, 提示*Fpn1*敲除后巨噬细胞铁动员受阻, 同时还提示在正常日粮饲养的*Fpn1*敲除小鼠, 肠道铁吸收起到了一定的代偿作用。进一步实验还发现巨噬细胞*Fpn1*缺失可导致小鼠炎症刺激细胞因子分泌异常, 并最终证实是Fpn1外排细胞铁异常而影响了巨噬细胞免疫功能[43]。

### 1.4 细胞铁稳态的自我调节

哺乳动物细胞铁代谢相关基因的表达, 受到精确的转录后调控, 由IRP (iron-response proteins, IRP1/IRP2)和基因mRNA非转录区域(untranslated regions, UTRs)的IREs (iron-response elements, IREs)来完成, IREs是受铁调控基因mRNA 5’-UTR一段茎环结构, 序列保守, 如Ferritin和FPN1 5’-UTR含有IREs[44-46], 而TfR1和DMT1 3’-UTR含有IREs[47]。IRPs与5’-UTR端IREs结合时, 抑制基因表达; 而与3’-UTR端IREs结合则促进其表达。当细胞内铁含量下降时, IRPs-IREs系统调控相关基因表达, 通过抑制铁的向外转运、增加铁的吸收来维持细胞内的铁处于一定水平。有研究发现了FPN1另一个转录本FPN1B, 其启动子区域不具有IREs, 不受IRPs的调控, 且其只在十二指肠上皮细胞和红细胞前体细胞内特异表达, 在细胞内铁不足时, 肠上皮细胞FPN1B能逃避IRP/IRE系统抑制, 以便继续向胞外转运一定的铁, 满足机体的需要; 而红细胞前体细胞FPN1B的表达, 能增强其对机体铁水平变化的实时敏感性, 决定红细胞前体细胞的增殖、分化或者启动造血功能, 以便最大限度维持机体铁稳态[48]。此外, Wang等[49]利用小鼠基因定位技术筛选出新基因*Mon1a*。研究证实, *Mon1a*是将FPN1转运至细胞膜上的决定性分子。Mon1a对于分子运输至细胞表面以及分泌都非常重要, 但并未发现其与铁稳态的直接关系, 但这预示了它可能是维持哺乳动物蛋白分泌、转运的基础分子。

## 2 机体调节铁稳态的分子机制

### 2.1 机体对铁稳态调节的关键基因*Hamp*

研究者已发现, 四个编码铁稳态相关蛋白的基因, *Hfe* (编码HFE蛋白)、*Tfr2* (编码TfR2蛋白)、*Hamp* (编码Hepcidin)、*Hfe2* (编码HJV蛋白)突变都能导致遗传性血色沉积症(hereditary hemochromatosis, HH), *Fpn* (编码FPN1蛋白)基因突变, 则表现为严重的病理性铁代谢紊乱, 这些都与体内Hepcidin表达紊乱相关[50]。

Hepcidin是一种富含半胱氨酸的抗菌肽, 主要在肝脏表达[51], 是机体铁吸收和代谢调控的关键分子[52], Hepcidin的表达, 受到机体铁贮存、贫血、低氧、炎症或是细胞因子等多重信号直接或者间接的调节[53-54]。机体铁过量诱导肝脏分泌Hepcidin, 与细胞表面的FPN1结合, 从而诱导FPN1发生内吞并在溶酶体内降解, 减少十二指肠上皮细胞和巨噬细胞铁的释放, 维持机体血液循环中铁稳态[55]。有研究发现, Hepcidin与FPN1结合后, 激活Jak2蛋白(janus kinase 2), 使FPN1发生磷酸化, 进而降解[56], 血液中的2-巨球蛋白(2-macroglobulin, 2-M)是Hepcidin特异结合分子, 在J774细胞系内, 2-M-hepcidin的结合物较之单独的Hepcidin更能有效减少FPN1在膜上的含量[57]。*Hamp*$^{-/-}$小鼠表现为严重铁过量的血色沉积症[50,58], 而小鼠体内过表达Hepcidin能够导致与慢性感染型

贫血类似的铁缺乏的表型, 但巨噬细胞会出现铁蓄积[54]。以珠蛋白生成障碍性贫血老鼠为模型, 构建*Hamp*转基因小鼠, 通过增加*Hamp*表达水平或者给予外源Hepcidin, 减少其对铁的异常吸收[59], 以期预防在治疗严重贫血时频繁输血导致的铁的过多蓄积。

### 2.2 机体对Hepcidin的转录调控

机体Hepcidin表达与铁水平呈负反馈关系, 机体铁过量, Hepcidin表达上调: 机体铁不足, Hepcidin表达下调。在对机体铁稳态调节的分子机制的研究中发现, HFE或者TfR2功能缺失, Hepcidin表达都会下降, *Hfe*和*Tfr2*同时敲除小鼠较任一单敲小鼠出现更严重的铁过量和更低水平的Hepcidin[60]。HFE、TfR2和Hepcidin都主要在肝细胞表达, TfR1与TFR2竞争结合HFE, 将小鼠体内*TfR1*基因突变, 增加其与HFE的结合能力, 表现为*Hepcidin*的表达降低, 机体铁过量, 反之亦然; 这提示一种假设, 生理状态下TfR1与HFE结合, 从而抑制HFE参与Hepcidin上调通路[61]。当机体铁过量时, 铁结合转运蛋白(holotransferrin, Holo-Tf)较多, Holo-Tf与HFE竞争TfR1结合位点, 促使HFE与TFR1解离, 进而与TFR2结合, 形成HFE/TfR2/Tf复合物, 从而上调Hepcidin表达[62-63]。研究发现, 十二指肠上皮细胞*Hfe*基因敲除并不引起Hepcidin表达紊乱, 也不会导致HH, 说明十二指肠HFE不是机体铁稳态所必需的分子[64]。而在红细胞中, HFE通过抑制Hepcidin表达, 降低Holo-Tf吸收, 影响正常的红细胞生成, 而红细胞*Hfe*$^{-/-}$小鼠体内铁循环加快, 红细胞合成增强, 以克服因静脉放血导致的贫血[65]。在炎症因子脂多糖(lipopolysaccharide, LPS)刺激下, 野生型和*Hfe*$^{-/-}$小鼠血清铁显著减少; 而*Tfr2*$^{-/-}$和*Tfr2*$^{-/-}$*Hfe*$^{-/-}$小鼠血清铁只轻微减少, 尽管基因双敲, Hepcidin仍能对炎症刺激有反应, 但其表达水平并不能有效降低血浆铁水平[66]。

虽然HFE和TfR2结合能够调节Hepcidin的表达, 但其机制尚未完全清楚。且HFE和Holo-Tf以及TfR1、TfR2之间如何达到一定的结合比例关系, 从而精确调控Hepcidin的表达, 仍有待进一步的研究。

#### 2.2.1 Hemojuvelin通过BMP信号通路调控Hepcidin的表达

有关机体调控Hepcidin的表达, 目前研究较为清楚的主要有两条信号通路, 一是通过转化生长因子(transforming growth factor)超家族的BMP-SMAD信号通路调控[67]。另一条是炎症状态下, 炎症因子通过STAT信号通路(signal transducer and activator of transcription 3)调节Hepcidin表达[68]。

Hemojuvelin (HJV, 又称RGMc)是反义导向分子(repulsive guidance molecule, RGM)家族的一个成员, 此外还包括RGMa和RGMb[69], 它们都能增强细胞内骨形态发生蛋白(bone morphogenetic protein, BMP)的信号[70]。而BMPs是转化生长因子(transforming growth factor)家族成员, 在调节细胞增殖、分化、凋亡及组织发育过程中发挥关键作用[71]。

BMPs与丝氨酸/苏氨酸激酶受体I型(ALK3、ALK6、ALK2)和II型(BMPPII、ActRIIA、ActRIIB)的复合体结合, 激活的II型受体使I型受体磷酸化, 进而促进特异受体调节Smads (receptor-regulated Smads, R-Smads: Smad1/5/8)的磷酸化, 与共受体Smad4形成复合物后进入细胞核, 靶向调节基因转录[72](图4)。肝脏*Smad4*条件性敲除小鼠, 肝脏Hepcidin表达减少, 机体总铁过量[73]。体内、外研究发现, HJV作为BMPs的共受体, 介导BMPs信号促进Hepcidin的表达[67,70]。伴有HJV突变的青少年血色病病人以及*Hjv*$^{-/-}$小鼠体内Hepcidin严重缺乏[58,74]。

HJV定位于细胞膜, 主要在骨骼肌、心肌、肝脏细胞中高表达[75], 人类肝脏细胞BMPs mRNA都有内源性表达, 如BMP-2、BMP-4、BMP-5、BMP-6、BMP-9[76], 而HJV并不与BMP-7或者BMP-9结合[67]。HJV介导BMP信号通路的II型受体为ActRIIA、BMPRII而不是ActRIIB, 且ActRIIA可能是肝细胞系BMP-2、BMP-4主要的II型受体, ALK3是主要I型受体[76]; 其他细胞系则主要是BMPRII[77]。体内实验发现, BMP-2、BMP-4配基并不能显著调控Hepcidin表达, 饲喂铁含量不同的日粮, 只有*BMP-6* mRNA与Hepcidin的mRNA变化趋势一致[78], 且*BMP-6*$^{-/-}$小鼠, 磷酸化Smad1/5/8水平很低, 进入细胞核内的减少[79], 机体铁过量, 但并未发现肝脏*BMP-2*和*BMP-4* mRNA水平改变, 可见, BMP-6可能是调节体内Hepcidin表达维持铁稳态的主要内源BMPs因子[80]。BMPs信号刺激Hepcidin表达必须依赖*Hamp*启动子区域的BMP反应元件(BMP responsive elements, BMP-RE1和BMP-RE2), 两基因双敲后, 基础水平的Hepcidin表达完全缺失, 且不随BMP信号的刺激而增加[81]。

*Hjv*基因能编码不同剪切形式的mRNA, 最长亚型的mRNA能编码426个氨基酸的蛋白, C末端含有“糖基膜锚链接”跨膜域的膜蛋白(membrane HJV, m-

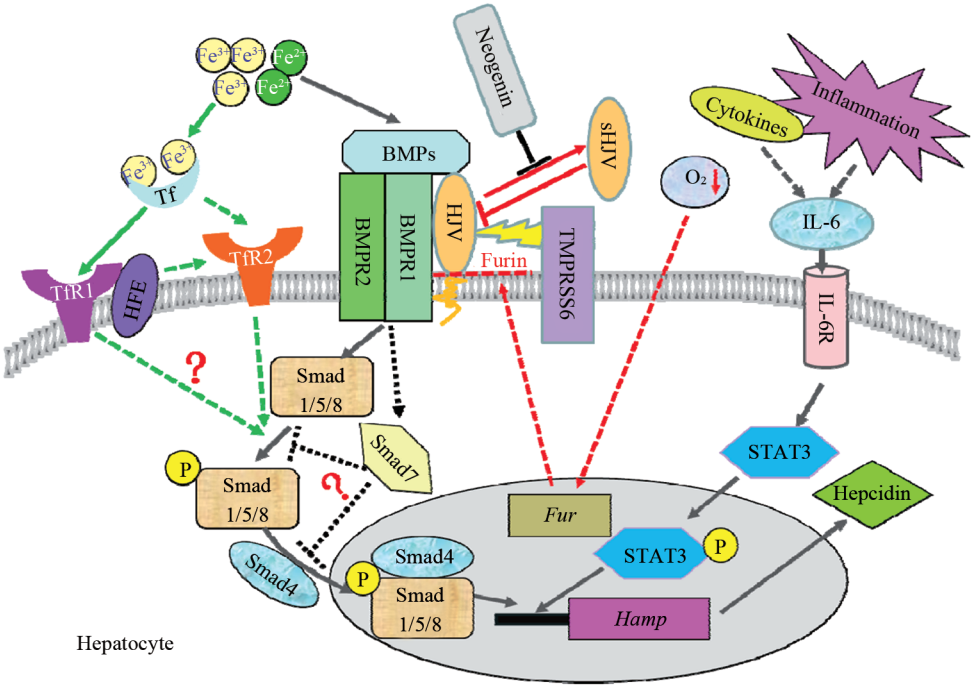


**图 4　哺乳动物Hepcidin表达调控模式图**

**Fig.4　Regulation of Hepcidin expression in hepatocytes**

HJV)[82], 当GPI-anchor被剪切酶解就会产生可溶性HJV(soluble HJV, s-HJV)。机体血液中存在着大量的s-HJV, 其与m-HJV竞争BMPs配体, 功能性负调控Hepcidin表达, 参与铁稳态的调节[83], 体内注射外源s-HJV能抑制Hepcidin的表达, 增加FPN1的表达, 血清铁升高[67]。

Silvestri等[84]研究发现蛋白前体转化酶Furin在332-335位置剪切m-HJV产生s-HJV, 铁缺乏时, s-HJV和Furin表达增加。Furin启动子区包含有低氧反应元件(hypoxia-responsive elements, HREs)结合位点, 当组织处于低氧状态时, 低氧诱导因子(hypoxia-inducible factor-1, HIF-1)转录复合物, 能够与HREs其结合, 显著增加*Fur* mRNA表达[85], 促进s-HJV的生成, 从而抑制*Hamp*的表达。此外, Furin的功能研究发现, Hepcidin前体蛋白缺乏生物功能, 只有在Furin介导成熟后, 才能产生含有25个氨基酸的生物活性肽[86]。

HJV与Neogenin有直接的相互作用, 但是Xia等[76]研究发现, Neogenin表达的改变并不会影响HJV介导的Hepcidin表达。进一步研究发现, Neogenin主要是通过抑制s-HJV的分泌来增强HJV-BMP信号促进Hepcidin表达, 调节机体铁稳态[87]。

*TMPREE6*作为负调控因子降低Hepcidin表达, 维持机体铁平衡, 当机体铁缺乏时, *TMPRSS6*编码的膜结合丝氨酸蛋白酶Matriptase-2能够降解m-HJV[84], 进而减弱BMPs-SMAD信号通路, 下调Hepcidin表达[88], *TMPRSS6*突变使机体Hepcidin表达异常增加, 导致小红细胞贫血, 口服乃至静脉注射补铁剂均难以治疗[89]。另有研究表明, *BMP6*$^{-/-}$与*TMPRSS6*$^{-/-}$双敲小鼠大大减缓了因*BMP-6*$^{-/-}$而造成的肝脏铁沉积[90], 可见, 机体可能存在其他信号通路调节铁稳态。

此外, Smad7也是BMP信号通路的抑制因子, Smad7过表达完全抑制了Hepcidin表达, 可能由于Smad7抑制了Smad1/5/8的磷酸化, 或者抑制了磷酸化的Smad1/5/8与Smad4的结合[91]。BMPs和其他刺激因子都可能促进Smad7表达, 作为调节Hepcidin表达的负反馈因子, 以避免Hepcidin过表达导致的铁缺乏。

2.2.2　炎症因子通过JAK-STAT信号通路调控Hepcidin表达　IL-6信号是肝脏急性期反应主要的调节因子, IL-6与受体结合后激活JAKs, 进而磷酸化STATs蛋白, 主要是STAT3, 进入细胞核, 上调Hepcidin表达。LPS诱导机体产生TNFα和IFNγ, 引起急性期反应显著增加, 血液中IL-6水平显著增加, 而

Hepcidin作为一种II型急性期反应蛋白, 其释放量增加[92]。研究发现, IL-6调节Hepcidin表达, 主要通过STATs直接与*Hepcidin*基因启动区的位点结合, 且非炎症状态下STAT3自身激活也能促进Hepcidin表达升高[68]。而*STAT3*基因敲除会降低基础Hepcidin表达[93]。

综上所述, 机体主要通过两条不同的调控体系: IRE/IRP和Hepcidin/FPN1来调控细胞内以及全身系统的铁稳态, 它们之间相互协调, 共同维持机体铁稳态代谢[94]。

## 3 小结

随着分子生物学技术的快速发展, 许多铁代谢相关基因被发现, 使人们能够进一步认识到铁稳态调节的奥秘。体内外实验研究发现, Ndfip1 (Nedd4 family-interacting protein 1)能诱导DMT1泛素化降解, *Ndfip*$^{-/-}$小鼠肠上皮细胞DMT1的表达和转录活性显著增高, 血清铁和转铁饱和度及肝脏储铁增加, 类似于铁过量表型, 可见Ndfip1是DMT1表达的关键调控蛋白, 可能与铁转运紊乱疾病相关[95-96], 但铁代谢还存在众多问题没有解答。例如, 体外细胞实验已经证实Dcytb (Cybrd1)具有高价铁的还原功能[97], 在CaCo细胞系转染表达人类的Dcytb后, 促进了$^{59}$Fe(III)的吸收[98]。但仍未有体内实验证明Dcytb就是肠上皮细胞将$Fe^{3+}$还原为$Fe^{2+}$的关键蛋白, 那么体内行使该功能的蛋白到底是否存在? 巨噬细胞*Fpn*基因敲除小鼠显示轻微贫血, 提示可能巨噬细胞中还存在其它铁泵出通路[43], 那么这个通路是什么? 此外, 细胞膜上是否还存在其他能吸收Heme的转运蛋白? 铁离子是如何识别和结合到铁储存蛋白上的? 铁稳态的维持需要多系统、多组织、多细胞间相互协调, 有必要结合多种实验手段和技术深入研究。

铁缺乏可影响生理机能和免疫功能, 还会造成肠道和呼吸相关感染或缺铁性贫血发生, 严重影响机体的正常机能。铁缺乏的高发人群是孕妇、妇女、婴幼儿和老年人, 补充化学形式的铁剂是治疗这些缺铁性贫血常规方法。大规模的人群研究提示孕期服用补充铁剂可能会促进幼儿精神运动发育, 但并不影响幼儿智力发育, 相反, 对非贫血的孕妇和幼儿补铁有增加儿童期行为异常的危险[99]。很多老年性退行性病变常伴随有铁过度蓄积, 服用补充铁剂虽能治疗贫血, 无疑会增加局部器官铁蓄积危险, 因此缺铁性贫血老年人是否补充铁盐治疗贫血还存在争议? 近年来, 有研究试图把Hepcidin及其调控蛋白作为靶点研制安全高效药物治疗铁代谢紊乱及相关疾病, 迄今还没有很好的突破口; 很多中草药被用于治疗缺铁性贫血并显示出良好的效果, 这无疑要比直接服用铁盐安全, 但它们的确切疗效以及分子机制还有待研究证实。总而言之, 铁稳态研究还有很多未知领域亟需我们去开拓。

致谢

感谢河北师范大学铁研究室常颜忠博士、国家纳米科学中心聂广军博士以及王福俤研究组全体人员的审校。

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# Molecular Mechanisms of Mammalian Iron Homeostasis

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**Abstract** Trace element iron is essential for nearly all living organisms. It is the key component of iron-containing enzymes and proteins, which participate in many cellular biological processes. It is estimated that nearly one quarter of population worldwide has been suffered from anemia due to iron deficiency. In contrast, iron overload induces a disease termed as Hemochromatosis, which the incidence is approximately 1/200 in Caucasians. Recently, the disease has also been reported in China. It is fatal if the disease progresses to late stage as the sign of heart, pancreas and liver failures. Therefore, maintenance of iron homeostasis is crucial. It is believed that iron is uptake by small intestine, stored in liver, transported in blood, recycled by macrophages, and finally utilized by cells to fulfill the functions. In last "Golden Decade", many novel iron metabolic genes have been cloned and functionally characterized to further understanding of regulation of iron metabolism and maintenance of iron homeostasis. However, more insights need to be learned considering the complexity of the processes. In this review, we summarize the recent findings in this field and discuss remaining questions, and provide our understanding towards future directions.

**Key words** iron; iron homeostasis; anemia; hemochromatosis

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This work was supported by the National Key Basic Research Program (No.2009CB941400, No.2011CB966200), the National Natural Science Foundation of China (No.1097907, No.30970665, No.10JC1416800, No.81000358), the Chinese Academy of Sciences Hundred Project (No.KSCX2-YW-R-141), Program of Science and Technology Commission Foundation of Shanghai (No.10JC1416800) and China Postdoctoral Science Foundation (No.20100480637)

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