二价铁转运体 IRT1 的研究历程及最新进展

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摘要 铁作为生物体内必需的微量元素之一, 在细胞的生理生化过程中发挥着重要作用. 然而铁营养不足已经严重影响到农业生产乃至威胁着人类健康. 铁转运蛋白(IRT1)是植物体吸收二价铁的主要转运体, 几乎存在于所有植物中, 因此IRT1的研究对了解铁吸收机制和维持体内铁稳态意义重大. 近10年对IRT1的研究主要分为3部分: 上游转录因子响应环境铁对IRT1表达的调控, IRT1在细胞内的膜泡运输, IRT1在铁生物强化方面的应用. 以此为依据, 本文首先介绍了IRT1的多跨膜结构及参与金属吸收的位点; 其次, 总结了对IRT1表达的网络调控; 然后分析了细胞水平IRT1细胞内的运输; 最后, 对IRT1仍有待解决的问题进行分析和展望.

关键词 铁, 铁转运体, 铁转运蛋白, 转录调控, 蛋白分选

铁作为功能蛋白的辅助因子, 参与了植物的呼吸作用、光合作用、叶绿素的合成以及生物固氮等生物过程. 植物类食物是人体获取铁的主要来源, 因此植物铁缺乏不仅影响农作物的产量而且直接导致人体缺铁. 缺铁性贫血仍然是困扰人类健康的隐性杀手, 在世界各地缺铁性贫血已影响了多达1/4人口的健康^[1]. 研究铁的吸收机理对改善缺铁环境和解决缺铁性疾病具有重要意义. Römheld和Marschner^[2]根据植物在缺铁环境下对根际土壤中Fe的吸收方式, 把被子植物分为机理 I (还原机制)和机理 II (螯合机制)两类. 机理 I 植物包括双子叶植物和非禾本科单子叶植物, 其吸收二价铁主要分为3步: 位于根部细胞质膜的P型离子泵(H^+ -ATPase)外排 H^+ , 增加根际Fe的溶解性, 高铁还原酶将 Fe^{3+} 还原为 Fe^{2+} , 铁转运蛋白(iron-regulated transporter 1, IRT1)将 Fe^{2+} 转运到植物根内. 机理 II 植物包括禾本科植物. 这类植物将根际合成的铁载体(phytosiderophores, PS)分泌到土壤中, PS螯合土壤中的 Fe^{3+} 并移至根表面, 随之被质膜

上Fe(III)-PS吸收转运系统运输到根内^[3]. IRT属于ZIP (zinc regulated transporter, iron-regulated transporter-like protein)蛋白家族成员. 拟南芥(*Arabidopsis thaliana*) IRT1是最早被发现并克隆得到^[4]. 作为机理 I 植物的代表——拟南芥中AtIRT1对Fe的吸收和稳态至关重要, *irt1*缺失后表型出严重的失绿症, 生长受阻, 甚至表现出致死的表型^[5,6]. 随之, 水稻(*Oryza sativa*)的OsIRT1也得到了克隆, 其序列和功能均与AtIRT1表现出极高的相似性^[7]. 其他物种的IRT1, 包括苹果属小金海棠(*Malus xiaojinensis*)的MxIRT1, 也陆续被克隆得到^[8]. 可见, IRT1在植物中是广泛存在的, 且表现出金属离子吸收的多样性(表1).

1 IRT1的多跨膜结构

结构预测表明, IRT1是由一个信号肽(signal peptide, SP)和8个跨膜结构域(transmembrane domain, TMD)组成(图1)^[4,28], 表达于单细胞或植物体中IRT1均是到达质膜执行吸收金属离子的功能. Eide等人^[4]

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表 1 植物中IRT1 的功能和在组织中定位

Table 1 The IRTs' function and tissue localization in plants

基因名称	主要表达器官	转运金属	参考文献
花生(<i>Arachis hypogaea</i>)铁转运体-1 (AhIRT1)	根(Root), 茎(Shoot)	Fe	[9,10]
拟南芥铁转运体-1 (AtIRT1)	根表皮(Root epidermis), 花(Flower)	Fe, Mn, Zn, Cd, Ni	[4~6,11]
AtIRT2	根表皮	Fe, Zn	[12]
AtIRT3	所有组织(Each organ)	Fe, Zn	[13]
黄瓜(<i>Cucumis sativus</i>)铁转运体-1 (CsIRT1)	根	Fe	[14]
大麦(<i>Hordeum vulgare</i>)铁转运体-1 (HvIRT1)	根	Mn, Zn, Cd	[15]
番茄(<i>Lycopersicon esculentum</i>)铁转运体-1 (LeIRT1)	根, 茎	Fe, Zn, Cd, Mn, Ni, Co	[16,17]
LeIRT2	根	Fe, Zn, Cd, Mn, Ni, Co	[17]
小金海棠铁转运体-1 (MxIRT1)	根	Fe, Zn, Mn, Cd	[18,19]
烟草(<i>Nicotiana tabacum</i>)铁转运体-1 (NuIRT1)	根	Fe	[20]
水稻铁转运体-1 (OsIRT1)	根, 柄(Stems)和叶(Leaves)	Fe, Cd, Cu, Zn	[7, 21~23]
OsIRT2	根	Fe, Cd	[7, 21]
豌豆(<i>Pisum sativum</i>)铁转运体-1 (PsIRT1)	根	Fe, Zn, Cd	[24]
天蓝遏蓝菜(<i>Thlaspi caerulescens</i>)铁转运体-1 (TcIRT1)	根	Fe, Zn, Cd	[25, 26]
TcIRT2	根	Fe	[26]
玉米(<i>Zea mays</i>)铁转运体-1 (ZmIRT1)	根, 茎	Fe, Zn	[27]

图 1 IRT1 的结构模式图

Figure 1 The structure of AtIRT1

发现AtIRT1是由1017 bp的可读框编码出的339个氨基酸残基的多肽。随后, Vert等人^[6]发现此序列并非全长, 其基因上游24 bp处仍存在另一个起始位点, 所以IRT1应该是由1041 bp的开放阅读框编码出的347个氨基酸残基的多肽。MxIRT1是长度为364个氨基酸的多肽, N端序列比对的结果与Vert的一致^[18,28],

说明AtIRT1是包含信号肽且全长为347个氨基酸的铁转运体(图1)。

1.1 参与离子吸收的重要位点

当MxIRT1的信号肽缺失后, DsIRT1 (deleted SP of MxIRT1)丧失了恢复拟南芥突变体*irt1*和酵母突变

体*fet3fet4*生长的功能. 蛋白的信号肽序列在细胞质中合成后, 先被信号识别颗粒(singal recognition particle, SRP)所识别. 在SRP的指引下, 由SRP、肽段、核糖体形成的复合体与内质网膜上的SRP受体相结合, 蛋白质多肽继续合成并随之进入内质网. 由于DsIRT1缺失了信号肽, 不能被SRP所识别, 因此只能停留在细胞质中并以弥散的形式分布^[28]. 根据信号肽假说, 多数蛋白多肽通过易位子进入内质网腔或到内质网膜上后, 信号肽会在信号肽酶的作用下被切除. 而完整的MxIRT1到达质膜后, 研究者发现这个信号肽仍未被切掉^[28]. 就目前研究所知, IRT1转运功能的缺失可能有两个原因: 由于IRT1不能到达质膜发挥功能, 如DsIRT1; 可能质膜上IRT1与金属吸收相关功能位点发生改变, 丧失转运能力. 为了找到IRT1跨膜结构域和非跨膜结构域上影响转运离子特异性和能力的关键位点, Rogers等人^[29]对AtIRT1中预测与金属吸收相关的位点进行了点突变分析(图1, 表2), 并且找到了8个影响离子吸收的位点(96-His, 100-Asp, 103-Glu, 136-Asp, 197-His, 198-Ser, 224-His, 228-Glu). 将其中96-His, 197-His, 198-Ser, 224-His, 228-Glu等位点分别替换成丙氨酸(Ala)后, IRT1均完全丧失了吸收离子的能力, 说明这几个位点是

发挥转运功能所必需的位点. 将100-Asp和136-Asp替换成Ala后, IRT1均丧失了吸收Fe和Mn的能力, 且136-Asp替换成Ala后, Cd的吸收能力也减弱了, 说明100-Asp和136-Asp均参与Fe和Mn的转运, 且136-Asp还参与了Cd的转运. 将103-Glu替换成Ala后, IRT1丧失了吸收Zn的能力, 说明103-Glu是吸收Zn的关键位点. 而将100-Asp和103-Glu同时替换成Ala, 对IRT1 Zn的吸收能力没有影响, 有可能是100-Asp突变能恢复103-Glu突变造成的Zn吸收的影响. 146-Lys和171-Lys参与了IRT1泛素化, 替换掉后会因为铁过量造成氧化毒性^[30]. 在146-Lys和171-Lys之间有个富含组氨酸的区域(154-His, 156-His, 158-His, 160-His)推测其参与铁的结合^[29]. 而点突变的结果显示, 转运功能并没有明显的变化^[31], 且His段区域最亲和的是Fe³⁺^[32]. 在铁高效转运体MxIRT1中, 这段区域是转运铁所必需的^[33]. 组氨酸富集区域功能的差异可能由于IRT1存在物种之间的多样性, 如MxIRT1有5个His位点, 而AtIRT1仅有4个His位点. 因此对IRT1与铁的结合和吸收机理还有待于进一步研究.

1.2 IRT1在生物强化方面的应用

作为铁的直接转运体, IRT1也广泛用于植物铁

表2 影响IRT1金属吸收的位点^{a)}
Table 2 The sites affect metal uptake^{a)}

突变位点	Fe转运	Mn转运	Zn转运	Cd转运
无(野生型)	+	+	+	+
H96A	-	-	-	-
D100A	-	-	+	+
E103A	+	+	-	+
D100A, E103A	-	-	+	+
C109A	+	+	+	+
D136A	-	-	+	-
H197A	-	-	-	-
H197E	-	-	-	-
S198A	-	-	-	-
H224A	-	-	-	-
E228A	-	-	-	-
Y295A	+	+	+	+
D300A	+	+	+	+
K146A, K171A	++	++	++	++

a) +表示能正常转运金属离子, ++表示过量积累金属离子, -表示不能正常转运金属离子^[29,30]

生物强化. 过表达AtIRT1的拟南芥小苗中镉和锌的含量均有明显增加, 而铁的含量却降低^[5]. 将146 Lys和171-Lys替换后, 过表达拟南芥小苗的铁和锰含量得到了明显增加^[31]. 将AtIRT1与AtNAS1 (Nicotianamine synthase 1)和Pvferitin组合后导入水稻中能明显提高水稻籽粒中铁的含量^[34]. 另外, 过表达OsIRT1能提高水稻根、茎、种子中铁和锌的含量^[22], 同时过表达AhIRT1能增加烟草和水稻的缺铁耐受性和提高植物中铁的含量^[10]. 过表达MxIRT1也能明显提高水稻籽粒中铁和锌的含量, 值得注意的是MxIRT1相比AtIRT1和OsIRT1, 转运镉的能力更弱一些, 而且环境中的铁能减少MxIRT1对镉的吸收^[8]. 镉(Cd)作为人类健康的威胁之一, 造成体内镉积累的直接来源是植物食物中镉的富集^[35]. 而IRT1转运选择性很低, 各种IRT1转基因水稻中镉的含量均有明显提高. 所以想通过IRT1来提高籽粒中铁含量而避免镉的富集将会是IRT1用于生物铁强化需要面对的主要问题之一.

2 IRT1表达的调控网络

过量的铁会产生过氧化毒性, 而且IRT1的选择

性极低, 能转运Cd等其他有毒重金属, 因此IRT1在转录水平和转录后水平均受到严格的调控^[5]. 例如, IRT1的mRNA在缺铁24 h后出现上调, 蛋白在缺铁72 h后出现最高值, 当将小苗移至正常培养基中IRT1的mRNA和蛋白水平均在12 h内消失^[5]. 可见IRT1表达的转录水平调控是第一关.

2.1 以bHLH类蛋白为核心的转录水平调控

转录水平调控在缺铁响应中扮演着重要角色, 其中拟南芥的碱性/螺旋-环-螺旋家族(basic helix-loop-helix, bHLH)蛋白FIT1 (fer-like iron deficiency-induced transcription factor 1)作为调控中心元件, 缺铁环境下启动IRT1的表达^[36]. FIT执行功能需要与bHLHs (bHLH038, bHLH039, bHLH100, bHLH101)中的一个结合, 且这些基因在缺铁情况下均上调表达(图2). 但与FIT不一样, bHLHs在叶中也有高表达, 可能参与了叶片的缺铁响应和叶片的发育^[37].

另一种bHLH蛋白PYE (POPYEYE)通过调节NAS的表达影响铁在植物体组织内的再分布(图2(5))^[38]. bHLH104能够与ILR3 (IAA-Leu resistant 3)结合, 可以直接作用于PYE的启动子上, 通过PYE影

图2 IRT1表达的网状调控模式图

Figure 2 The network-like regulation of IRT1 expression

响铁的分布,也可以调节bHLHs的表达,进一步调节IRT1的表达.具有RING (really interesting new gene)结构的E3连接酶BTS (TRUTUS)对PYE网络起到的是负调控的作用.考虑到BTS能与bHLH104结合,且bHLH104的突变体能减弱BTS的缺铁耐受性^[39],推测BTS可能影响bHLH蛋白的降解.BTS蛋白由于含有血红蛋白区域,具有铁和锌结合能力,有可能扮演着铁响应的功能^[40].

在水稻缺铁早期,转录因子IDEF1 (IDE1-binding factor1)通过结合IRT1基因调控区的顺式元件IDE1 (iron-deficiency-responsive *cis*-acting elements 1)启动IRT1的表达^[41].同时缺铁早期IBP1 (IDEF1-binding protein 1)上调表达抑制了IDEF1蛋白的降解,积累的IDEF1得以上调下游IRT1的表达,进而促进铁的吸收^[42].缺铁早期CSN6 (COP9 signalosome subunit 6)的下调表达抑制了COP9的活性,进一步抑制了原来要进入蛋白酶体的多泛素化修饰后的IDEF1 (图2(4))^[43].在水稻中也找到了与BTS结构和功能相似的蛋白HRZs (haemerythrin motif-containing really interesting new gene (ring)-and zinc-finger proteins)^[40],而且有可能作为F-box参与IDEF1的降解^[43].

2.2 赤霉素、NO和乙烯对IRT1表达的调控

越来越多的研究发现,植物激素参与了铁响应信号通路.最近的报道介绍了各种激素参与了缺铁响应,但是大多数都是在生理水平的工作,然后对可能的调控过程进行推测^[44,45].目前从分子水平研究的比较清楚的是:赤霉素(gibberellin, GA)、NO (nitric oxide)、乙烯.赤霉素作为生长促进因子贯穿于整个植物生长发育过程.植物通过调节GA抑制N端具有高度保守的DELLA结构域的蛋白家族在根中的不均匀分布来调节两个重要的缺铁特征:主根生长的抑制和铁吸收能力的促进. DELLA能够与FIT直接结合,阻止与启动子的结合,进而抑制下游基因的表达(图2(1)).当环境中铁缺乏时,位于根分化区外表皮细胞中DELLA蛋白的减少释放了FIT蛋白,进而促进IRT1的表达,同时GA在分生区的减少抑制了主根的生长^[44].

NO作为信号分子也参与了植物的缺铁响应.缺铁环境下,NO一方面在转录水平上调FIT的表达,激活下游IRT1的表达;一方面在蛋白水平抑制FIT进入蛋白酶体降解途径(图2(2))^[46].一种14-3-3蛋白——GRF11 (growth regulating factor 11)作为NO的下游因

子调节FIT的上调表达^[47].

缺铁同时上调了拟南芥根中一些与乙烯合成相关基因的表达,增加了根中乙烯的含量^[48].随之乙烯信号元件EIN3 (ethylene insensitive 3)和EIL1 (EIN3-Like 1)上调表达,增加的EIN3/EIL1与FIT直接结合,从而阻止FIT进入蛋白酶体途径(图2(3))^[49].缺铁响应中许多基因的上调表达也依赖于乙烯,包括转录因子(FIT, bHLH38和bHLH39)、高铁还原酶(ferric reduction oxidase 2, FRO2)和二价铁转运体(IRT1)、液泡膜铁转运体(a CCC1-like protein, CCCL)、参与组织内铁转移基因(NAS)、参与木质部铁转移基因(ferric chelate reductase defective 3, FRD3).除了影响铁吸收相关基因,乙烯也参与缺铁下近顶端根毛的形成.

3 IRT1的蛋白分选和膜泡运输调控

3.1 IRT1蛋白质分选的调控

IRT1作为多跨膜蛋白在细胞内的运输必然受到严格的调控.位于N端的SP指导MxIRT1进入内质网,进而能够通过膜泡运输到达质膜(图3)^[28].AtIRT1可出现在反面高尔基网/早期核内体(trans-Golgi network/earlyendosome, TGN/EE)上,且在TGN/EE与质膜之间进行循环,此循环受到IRT1的次级底物Zn, Mn, Co的调控,而非Fe^[30].而MxIRT1在缺铁环境中是以小泡的形式靠近质膜,只有当加铁时MxIRT1才与质膜发生融合,说明MxIRT1运输小泡响应环境铁的变化与质膜融合^[18,50].表达于根部的AtIRT1是以极性形式存在于表皮细胞外表面的,而且IRT1的极性分布可能与脂筏相关.内吞后定位于晚期内体的IRT1需要磷脂酰肌醇结合蛋白(a phosphatidylinositol-3-phosphate-binding protein, FYVE)调控才能进入质膜的再循环^[51].同时分选连接蛋白(sorting nexin 1, SNX1)也参与IRT1细胞内的运输和稳定性^[52].

3.2 泛素化介导的IRT1细胞内运输的调控

位于AtIRT1第Ⅲ和第Ⅳ跨膜结构域之间的K146和K171参与了AtIRT1蛋白的泛素化^[30].当这两个点被替换之后,IRT1被限制在质膜上,导致植物体内铁过量进而严重影响植物的生长^[30].进一步证据表明,IRT1在这两个泛素化位点进行的是单泛素化.至此,AtIRT1是植物中第一个发现的通过单泛素化介导的

图3 铁转运体IRT1 细胞内运输和稳定性的调节^[45]

Figure 3 Regulation of intracellular trafficking and stability of IRT1^[45]

内吞作用的转运体。已被泛素化修饰后的IRT1通过内吞作用首先到达TGN，若条件需要停留着的IRT1会通过去泛素化作用回到质膜上继续发挥功能^[30]。因此，此时的单泛素化是调节IRT1上膜和下膜的信号。过量的IRT1会到达多囊泡结构/晚期内体(multivesicularbodies/late endosomes, MVBs/LEs)，然后进入液泡降解途径，而不是蛋白酶体依赖的降解途径^[30,53]。IDF1 (IRT1 degradation factor 1)作为E3，参与多点单泛素化IRT1-Ub4形成，进而直接调节IRT1的降解^[54]。IDF1具有RING结构域，需要与锌结合才能发挥，而且具有催化自身泛素化的活性。但是IRT1在突变体*idf1*中仍可被泛素化，说明IRT1还有其他的E3，共同介导IRT1的泛素化。从蛋白的定位看，IDF1在细胞质和质膜上均存在，说明有可能IDF1呈现出动态的分布以便招募其他的成员与其一起完成泛素化的功能。另外，MxIRT1也是通过多点单泛素进入液泡降解途径，且在铁过量情况下从内体小泡直接通过自噬作用进入液泡降解^[55]。

4 展望

IRT1的被调控是通过IRT1分子本身与调控者之间的相互作用：(i) 转录水平是转录因子与IRT1基因调节区的铁响应元件相互作用，FIT结合到*AtIRT1*基因的E-box序列上，IDEF1结合到*OsIRT1*的顺式响应元件IDE1上。大多数激素对IRT1的调控则是通过转录因子影响IRT1的转录表达。(ii) 蛋白水平是IRT1可变环上的Lys位点被单泛素化修饰后与内体相互作用再决定循环至质膜或液泡降解，调控IRT1的转录因子也可通过K48多聚泛素化修饰后与26S蛋白酶体相互作用被调控。(iii) 在细胞水平，质膜蛋白IRT1的蛋白分选首先是它的信号肽与内质网的信号肽假说的成员相互作用，如信号肽识别颗粒(SRP)、内质网膜上的SRP受体、易位子等。IRT1的分子解剖，以及与之重要的结构域相互作用的受体或成分的研究是亟待解决的问题。(i) 从蛋白分选的角度看，质膜蛋白IRT1的分选信号还不知道。(ii) IRT1能够在TGN/EE和PM中进行循环，而且同时可以进入液泡

图4 MxIRT1重要功能结构域分子解剖的研究方案示意图

Figure 4 The diagram of further research about the IRT1 vital domain

降解。而决定这个IRT1回到质膜还是进入液泡降解的信号来自于哪里还不得而知。(iii)已经报道的具有直接结合铁能力的蛋白有3类:转运体IRT1(推测,还需要直接的实验证据);水稻中转录因子IDEF1;具有泛素化酶活性的E3,拟南芥为BTS,水稻为HRZs。IDEF1和E3两种均定义为铁的感应元件,而IRT1作为铁离子吸收的最后执行者,对IRT1直接感应环境铁的变化还所知甚少。MxIRT1的组氨酸富集区域是铁转运所必需的(图4),共同存在于大可变环上的组氨酸富集区,是否作为铁的感应元件与泛素化位点之间进行信息的传递还有待于进一步证明。(iv)IRT1为多跨膜结构蛋白,然而IRT1在细胞中的

运输路径还不是很清楚,特别是对IRT1每个跨膜结构域在蛋白运输中的作用。(v)有报道称,双酸性、双疏水性位点、双芳香族位点通常作为蛋白出内质网的信号^[56],在IRT1可变环上也具有保守的双酸性区域(DQE)(图4),是否参与IRT1细胞水平的膜泡调控还有待研究。(vi)IRT1在根的外表皮层以极性的、斑点状的形式分布,发现在IRT1蛋白上存在两个与脂筏结合的区域CRAC(cholesterol recognition/interaction amino acid consensus sequence)和CARC(与CRAC恰好相反),且这两个区域为脂筏结合保守区域^[57]。所以脂筏对IRT1蛋白运输的介导将会是研究IRT1细胞内运输的重大创新点之一。

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Summary for “二价铁转运体 IRT1 的研究历程及最新进展”

Research of the iron-regulated transporter 1 (IRT1) in the past decades and its latest development

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Iron (Fe) is an essential element in organisms and plays a critical role in important biochemical processes. As a result, Fe deficiency limits plant growth and development and seriously affects human health. However, developing strategies to improve Fe content is challenging because Fe is also toxic at higher levels. In plants, IRT1, a ZIP family member, is the main Fe transporter. Therefore, there is an urgent need to study IRT1 to understand the mechanism of Fe absorption. Recent research has focused on three aspects: Firstly, investigation of the role of transcription factors in regulating IRT1 in response to Fe condition have identified. FER-like iron deficiency induced transcription factor (FIT), a basic helix-loop-helix (bHLH) protein, as the central transcriptional regulator of Fe uptake. Apparently, the FIT protein can form heterodimers with bHLH038, bHLH039, bHLH100, or bHLH101 in order to upregulate Fe-uptake genes, including *IRT1*, that affect Fe homeostasis via plant hormone signaling pathway. Secondly, recent studies have also investigated the modification of IRT1 proteins in regulating the intracellular traffic of IRT1. These studies have shown that IRT1 accumulates at the trans-Golgi network and then travels to the plasma membrane. For example, the monoubiquitination of lysine residues (K154 and K179) induces IRT1 to undergo clathrin-mediated endocytosis from the plasma membrane; IRT1 degradation factor 1 (IDF1) functions as a E3 ubiquitin ligase for the ubiquitination of IRT1; and the endosomal proteins SORTING NEXIN1 (SNX1) and FYVE1 (FYVE domain-containing protein) participate in recycling IRT1 to the plasma membrane. Thirdly, recent studies have investigated the use of IRT1 application in biofortification. Indeed, many IRT1s have been transformed into rice and have been shown to improve the micro-nutrition of the grain. Based on these studies, we first discussed the multi-transmembrane structure and important sites in metal transport. The signal peptide in the N-terminus of IRT1 directs the protein to the endoplasmic reticulum and initiates protein synthesis and trafficking. Key sites in the loop between transmembrane domains III and IV, such as lysines and histidines, are crucial for maintaining Fe homeostasis. The regulation network of IRT1 at the transcript level is also summarized. Briefly, gibberellin, ethylene, and nitric oxide regulate the expression of Fe-utilization genes by affecting FIT activity, whereas the COP9 signalosome subunit 6 (CSN6) is down-regulated during early stages of Fe deficiency, which ensures the rapid accumulation of IDEF1, and in turn, up-regulates Fe uptake- and utilization-related genes that help reduce the stress of Fe deficiency in rice. In contrast, BTS, an E3 ubiquitin ligase, negatively regulates Fe absorption by regulating the stability of downstream factors. In addition, we analyzed the intracellular trafficking of IRT1 at the subcellular level. Accordingly, we also present the route of intracellular IRT1 trafficking and describe the factors that affect IRT1 recycling between the plasma membrane and trans-Golgi network. Finally, we describe the persisting challenges with a focus on the additional unknown roles of the transmembrane domain in intracellular trafficking and of the membrane raft in Fe homeostasis, and propose future research directions. We hope this review provides insight into the regulation of Fe uptake by plants.

iron, iron transporter, IRT1, transcriptional regulation, protein traffic

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