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Biofortification Strategies to Improve Iron Concentrations in Potato Tubers: Lessons and Future Opportunities

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Abstract
Iron deficiency is a serious global issue, particularly in developing countries. Individuals are suffering from iron deficiency due to monotonous consumption of cereal based diets, which are unable to provide adequate amounts of iron. The majority of these people cannot afford a diversified diet, iron supplements and iron fortified food products. The development of iron biofortified potatoes could provide a sustainable solution to this problem. The leading strategies for crop biofortification include agronomic practices, plant breeding and transgenic approaches. Previous reports have highlighted that agronomic practices are not very effective for iron biofortification of potato. However, extensive genetic variability for iron content in potato gene pool makes it an ideal crop for iron biofortification through genetic approaches. Therefore, genotypes with high iron content could be used as parental lines in potato breeding programs. The screening of genes or QTLs responsible for high iron content in these genotypes could pave the way for the development of iron biofortified potatoes through marker-assisted selection, speed breeding and transgenic approaches.

Keywords Homeostasis · Iron deficiency · Iron uptake · Potato breeding · Transgenic approaches

Introduction

Micronutrient deficiencies (hidden hunger) have become a silent epidemic. More than 2 billion individuals are suffering from it worldwide (Gödecke et al. 2018). Among all micronutrients, iron (Fe) deficiency causes a significant threat to human health through

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anaemia. At present, more than 1.2 billion people are Fe deficient (Camaschella 2019). Fe deficiency is more prevalent in developing countries where plant-based food is the chief source of Fe (Pasricha et al. 2013). Children below the age five, adult girls and pregnant women are at severe risk of anaemia due to low dietary Fe bioavailability (Cappellini et al. 2020). Severe Fe deficiency results in impaired physical and mental health (Pivina et al. 2019). Current interventions such as the use of iron supplements and iron-fortified products have failed to reduce Fe deficiency due to high cost. In recent years, many efforts have been made to cut the cost of iron fortification and iron supplements (Horton 2006; Tripathi and Mishra 2020). Crop biofortification has emerged as a cost-effective and sustainable way to combat hidden hunger. Development of Fe rich staple food crops through biofortification has a tremendous potential to diminish this global issue (Connorton and Balk 2019; Masuda et al. 2020). Potato is an ideal target crop for Fe biofortification because it is a staple crop in many countries, where occurrence of Fe deficiency is most prevalent. Moreover, it is a short duration and easy to grow crop (Lutaladio and Castaldi 2009). A recent study shows that Fe bioavailability from potato is very high in comparison to cereals (Jongstra et al. 2020). The recommended dietary allowance (RDA) for iron is 1.8 times higher for vegetarians compared to non-vegetarians (NIH 2018). An in vitro gastrointestinal digestion procedure and a Caco2 cell lines based model of the human intestine showed that on an average, 70.6% of the potato iron is released from the potato matrix and is therefore available at the intestinal level (Andre et al. 2015). Hence, a high portion of the RDA could be obtained from potatoes. Furthermore, the presence of extensive natural variation in potato germplasm could be used for potato biofortification (Haynes et al. 2012; Paget et al. 2014; Singh et al. 2020b). During the last decade, many attempts have been made to develop Fe-rich biofortified potatoes using agronomic practices, traditional plant breeding and modern genetic engineering. However, knowledge of the various molecular mechanisms involved in Fe uptake, transportation and storage in potato tubers is still limited. This review discusses our current knowledge of molecular pathways involved in the determination of Fe concentrations in potato tubers. In addition, various biofortification strategies used to improve the nutritional value of potatoes are discussed with an emphasis on biofortification through genetic engineering tools.

Fe Uptake Mechanisms

In nature, plants obtain Fe from the rhizosphere. Fe is present in ample amounts in the soil, but its availability to plant roots is limited (Morrissey and Guerinot 2009). As Fe is a vital mineral for plant growth and development, the higher plants have established two different strategies for Fe uptake. The non-graminaceous plants adopted the reduction-based strategy in which the plant roots excrete protons to the soil that converts less soluble Fe^{3+} to the more soluble Fe^{2+} form by reduction. The graminaceous plants such as wheat, rice, maize and barley have developed the chelation strategy, often called iron uptake strategy II (Kobayashi and Nishizawa 2012). Presently, iron uptake and homeostasis in potato is not well understood. However, potato being a non-graminaceous plant follows strategy I (Fig. 1). According to this strategy, plant roots excrete protons to the rhizosphere via a proton ATPase

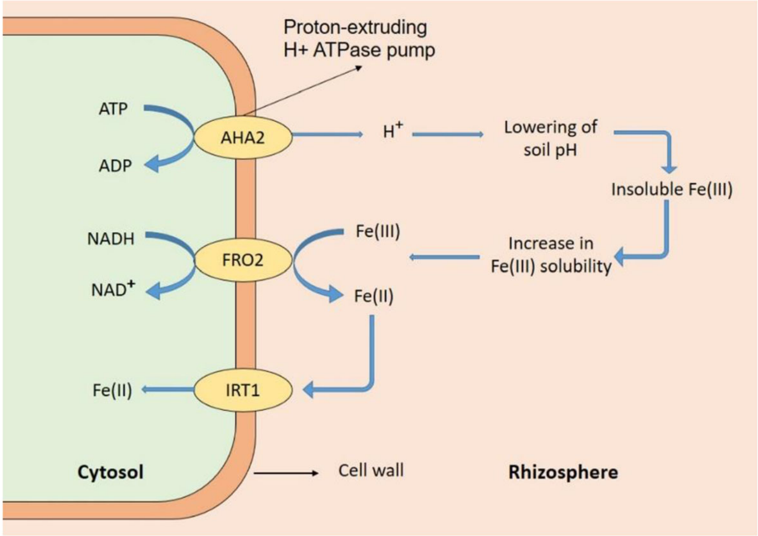

Fig. 1 Iron uptake strategy I adopted by non-graminaceous plants including potato

pump, which results in the reduction of Fe3+ to Fe2+ with the help of a ferric chelate reductase (FROs) (Jeong and Connolly 2009). The *FRO2* gene is chiefly responsible for the reduction of iron in *Arabidopsis* (Connolly 2003), whereas in potato roots, the *FRO1* gene showed elevated expression levels under iron deficient conditions (Legay et al. 2012). This indicates that *FRO* genes respond to iron deficiency in potato and reduce Fe3+ to Fe2+. Then Fe2+ is transported into the root epidermal cells by iron regulated transporter 1 (IRT1) (Barberon et al. 2014; Castaings et al. 2016). High expression levels of the *IRT1* gene were observed in potato roots (Legay et al. 2012). Inside the plant body, iron cannot move freely because of its poor solubility, high reactivity and excess iron cytotoxicity (Hell and Stephan 2003; Conte and Walker 2011; Kobayashi et al. 2019), and therefore must be linked to a chelating molecule. Various iron chelators have been reported in plants such as nicotinamide (Von Wiren et al. 1999), citrate (Durrett et al. 2007) and mugineic acid family phyosiderophores (Suzuki et al. 2008; Khan et al. 2018). It is expected that iron is transported to the shoots from the roots via the xylem (Durrett et al. 2007). The citrate transporters load the Fe-citrate complexes into the xylem in both non-graminaceous and graminaceous plants (Ariga et al. 2014). The ferric reductase defective3 (FRD3) citrate effluxer regulates iron translocation in the model plant *Arabidopsis* (Green and Rogers 2004; Durrett et al. 2007; Roschzttardtz et al. 2011). The high expression of the *FRD3* gene in in vitro potato plants grown on iron deficient media suggests its positive role in iron transportation in potato (Legay et al. 2012). During the last decade, our knowledge regarding iron transportation from roots to shoots and seeds has improved (Kobayashi and Nishizawa 2012; Brumbarova et al. 2015; Connorton et al. 2017; Jeong et al. 2017). However, our understanding of iron transportation and storage into the edible parts of tuber crops is still poor. Unlike other minerals (Mg, P, S, Cl and K), a significantly higher iron concentration in the surface layers compared to tuber flesh suggests that iron may not move easily through phloem. Another possible reason behind high iron content in the peridermal region is the direct uptake of iron across the epidermis of the developing tubers (Subramanian et al. 2011). However, the direct uptake of iron into the mature tubers via periderm is less likely because with maturity, the periderm becomes thick and suberized (Singh et al. 2020a). Nevertheless, several successful attempts have been made to increase the iron content in potato through better agronomic practices, utilization of diverse potato germplasm, traditional breeding and genetic engineering.

Agronomic Biofortification

Agronomic biofortification is potentially easy, cost-effective, efficient and applicable to most crops. Agronomic practices for potato biofortification comprise tuber priming (Vergara Carmona et al. 2019), foliar application and soil application of fertilizers (Kromann et al. 2017; White et al. 2017). Seed priming with different micronutrients has been shown to increase the micronutrient content of crop plants (Sundaria et al. 2019; Carmona et al. 2019) and to have several other growth benefits (Sharifi 2016; Reis et al. 2018). Carmona et al. (2019) reported an increase in the zinc concentration in the cortex of tubers by priming the seed tubers in zinc solution before planting. However, no such study has been performed for iron content in potato. Similarly, soil and foliar applications of zinc have improved the zinc content in tubers but the iron concentration does not increase with iron fertilization (Kromann et al. 2017; White et al. 2017). Foliar application of micronutrients (Fe, Zn, Cu and Mn) increased potato tuber yield and dry matter (Al-Jobori and Al-Hadithy 2014; Moinuddin et al. 2017). Apart from the soil and foliar fertilizer applications, agronomic biofortification can be performed by growing the plants in soilless media (Di Gioia et al. 2019; Giordano et al. 2019). For example, higher concentrations of Fe, Zn and Se have been observed in different cereal crops when grown in coal fly ash plant growth media in comparison to control plants grown in soil (Bilski et al. 2012). This method could be tested for iron biofortification in potato.

Genetic Biofortification

Genetic biofortification is a strategy that relies on traditional plant breeding techniques and modern biotechnological tools to develop nutrient rich crops. Crop biofortification through plant breeding is a globally accepted, cost-effective and sustainable method for the development of nutrient rich crops. The conventional breeding programs take advantage of naturally occurring genotypic variations for the trait of interest such as iron content in potato germplasm. Furthermore, mutagenesis can be used to induce promising genetic variations to increase iron concentrations. This technique has been used successfully for the functional characterization of various iron related genes (Rehman et al. 2020). For example, some mutant lines of wheat and rice exhibit increased levels of iron in grains (Tran and Ho 2017; Kenzhebayeva et al. 2019). The mutation breeding technique has been used to improve several qualitative and quantitative traits in tetraploid potato (Bado et al. 2016; Zia et al. 2018). This could also be employed to develop iron-rich potato varieties. Genetic biofortification can also involve the development of nutrient rich crops through the transgenic method. This method does not depend upon the genetic variation present in the germplasm of a particular crop as it can use beneficial genes from other plant species regardless of their evolutionary relationships (Garg et al. 2018; Kumar et al. 2019). The CRISPR-Cas9 gene-editing technology has become a routine practice in molecular biology labs. It has been used to improve various qualitative and quantitative traits in major food crops including potato (Dangol et al. 2019). It could take advantage of previously known regulators of iron metabolism. Moreover, this technique could be used as a reverse genetic approach to identify the key contributors of iron uptake from the rhizosphere and its allocation to the tubers.

Potato Biofortification by Breeding

The foremost requirement of plant breeders is the presence of natural variation in the germplasm of a crop for further breeding. Fortunately, potato germplasm is a rich source of natural variations in terms of tuber shape, size, skin texture and colour, and nutrient concentrations (Ashrafzadeh et al. 2017; Berdugo-Cely et al. 2017; de Haan et al. 2019). Different potato accessions have differential genetic variations for tuber iron content (Table 1). For example, some iron-rich potato accessions have been reported in *Solanum tuberosum* and in *Solanum tuberosum* ssp. *andigena* by Dalamu et al. (2017) and Singh et al. (2020a, 2020b), respectively. These accessions could be used as parental lines in the breeding programs aimed to develop iron-rich potato varieties, but more research is required on the heritability of the trait. Knowledge of genes responsible for iron uptake and accumulation in tubers could help the potato breeding programs aimed to enhance the iron content. Various types of molecular markers could be developed for iron related metabolism or markers associated with iron metabolism could be used in potato from other crops (Gupta et al. 2017). Moreover, genome wide association studies (GWAS) have emerged as a powerful tool for the identification of genes/markers associated with a complex phenotypic trait such as mineral concentrations (Arora et al. 2019; Cu et al. 2020). This approach has been used to dissect the potato genetics for different phenotypic traits. GWAS should be used to investigate the marker-trait associations liked to tuber iron content in diverse potato germplasm.

Potato Biofortification via Transgenic Approaches

Potato iron biofortification by transgenic means can be a good alternative to conventional breeding. Potato plants obtain minerals primarily from soil through their roots (Karley and White 2009) and redistribute these minerals to the tubers via phloem, but iron is less mobile in the phloem (Subramanian et al. 2011). More knowledge is required on iron localization in potato tubers. Since the molecular players involved in the iron transportation into the tubers are poorly understood, the genes whose functionality linked to iron metabolism has been validated in other crops (Table 2) could be transferred into potato for testing. Sharma and Yeh (2020) suggested that the *iron deficiency tolerant1 (IDT1)* gene could be used for iron biofortification. Transgenic potatoes with increased provitamin A have been developed by incorporating *phytoene synthase* (*CrtB*), *phytoene desaturase* (*CrtI*) and *lycopene beta-cyclase* (*CrtY*) genes from *Erwinia herbicola* (Diretto et al. 2007). In a similar way, iron-rich potatoes can be

Table 1 Existing variability in potato germplasm for tuber iron content

Number of potato accessions	Sample type	Fe concentrations (mg/kg) of dry weight		Source
		Mean	Range	
74 potato cultivars	Whole tuber	54.95	29.87 to 157.96	(Andre et al. 2007)
37 native potato accessions	Peeled tuber	19.74	9.4 to 36.7	(Burgos et al. 2007)
33 clones, including varieties and advanced breeding selections	Whole tuber	34.03	17 to 62	(Brown et al. 2010)
18 potato clones	Whole tuber	46.9	41.5 to 53.0	(Haynes et al. 2012)
37 Andigena (*Solanum tuberosum* ssp. *andigena*) Accessions	Peeled tuber	32.29	18.03 to 45.97	(Singh et al. 2020)
48 potato varieties	Peeled tuber	28.49	19.96 to 49.51	(Sharma et al. 2017)
21 different potato varieties	Peeled tuber	53.52	17.13 to 164.83	(Abebe et al. 2012)
46 potato accessions	Peeled tuber	32.44	14.90 to 67.13	(Dalamu et al. 2017)
16 potato cultivars	Whole tuber	--	48.87 to 72.64	(Öztürk et al. 2011)
49 selected accessions of potato species	Whole tuber	22.0	12.2 to 43.6	(Subramanian et al. 2017)
17 full sib diploid families	Peeled tuber	20.0	7.0 to 42.5	(Paget et al. 2014)
13 red skinned advanced hybrids and varieties	Peeled tuber	33.03	19.28 to 63.94	(Dalamu et al. 2019)
36 potato breeding lines and varieties	Whole tuber	--	18 to 65	(Brown 2008)

Table 2 List of potential candidate genes along with their function(s) in iron uptake and homeostasis in non-graminaceous plants

Plant name	Gene	Function	References
Arabidopsis	*Fe-deficiency Induced Transcription Factor 1 (FIT1)*	Regulates FRO2 and IRT1	(Colangelo and Guerinot 2004)
Potato	*Ferritin (FER3)*	Associated with resistance to iron deficiency	(Boamponsem et al. 2017)
Arabidopsis thaliana	*Iron-regulated transporter (IRT1)*	Controls iron uptake in plants	(Vert et al. 2002; Barberon et al. 2011, 2014)
Arabidopsis thaliana	*Ferric reductase defective3 (FRD3)*	Controls iron localization	(Green and Rogers 2004; Roschzttardtz et al. 2011)
Arabidopsis thaliana	*Autoinhibited plasma membrane H+-ATPase 2 (AHA2)*	Rhizosphere acidification in response to Fe deficiency	(Santi and Schmidt 2009)
Sweet potato	*H+-pyrophosphatase (H+-PPase) gene (IbVP1)*	Fe acquisition	(Fan et al. 2017)
Arabidopsis thaliana	*Ferric reductase oxidase (FRO)*	Reduces Fe^{3+} to Fe^{2+}	(Jain et al. 2014; Satbhai et al. 2017)
Arabidopsis thaliana	*BHLH029/FER-like regulator of iron uptake (FRU)*	Induction of iron mobilization genes	(Jakoby et al. 2004)
Arabidopsis thaliana	*TF Basic helix-loop-helix (BHLH039)*	Forms a complex with FIT and activates it to upregulate Fe acquisition genes	(Trofimov et al. 2019)
Arabidopsis thaliana	*Vacuolar iron transporter 1 (VIT1)*	Catalyze iron transport and homeostasis	(Kim et al. 2006; Gollhofer et al. 2014)
Cassava	*Vacuolar iron transporter 1 (VIT1)*	Iron accumulation	(Narayanan et al. 2015)
Arabidopsis thaliana	*Iron deficiency tolerant1 (IDT1)*	Iron accumulation	(Sharma and Yeh 2020)
Arabidopsis thaliana	*POPEYE (PYE)*	Associated with resistance to iron deficiency	(Long et al. 2010)

developed by incorporating the already known positive regulators of iron metabolism from other crops. The potato orthologues of these genes could be used to develop iron rich over-expressor lines. One study suggests that overexpression of *ferritin* (*FER3*) and *iron-regulated transporter (IRT1)* genes can help potato plants grow normally without exhibiting any Fe deficiency symptoms in calcareous soils (Boamponsem et al. 2017). Likewise, *MT* (*metal transporter*), *oligopeptide transporter*, *plasma membrane H+-ATPase* and *germin* genes showed significantly increased expression levels in potato plants grown in iron deficient soil and complemented the iron uptake (Xiao et al. 2015). Potato follows a reduction-based strategy for iron uptake, which is different from other major crops such as wheat, rice and maize. Therefore, currently not much information is available about the genes regulating the iron homeostasis in potato. Moreover, the chances of achieving success by incorporating the positive regulators of iron metabolism from graminaceous crops into potato are doubtful. However, the overexpression of candidate genes present in potato and the introduction of iron-associated genes from other tuber crops could play a pivotal role in the generation of iron-rich potatoes.

Lessons from Other Tuber Crops

There are many candidate genes that are well studied in the model plant *Arabidopsis* and also in other non-graminaceous plants, which can be used for iron biofortification in tuber crops including potato. A few attempts to enhance iron concentrations have been made in cassava using these candidate genes. For example, transgenic cassava plants overexpressing *AtVIT1* showed significantly higher iron content in cassava roots and stems in comparison to control (Narayanan et al. 2015). Likewise, overexpression of an algal gene *FEA1* in cassava roots increased the iron accumulation by threefold in its storage roots (Ihemere et al. 2012). Another study reported that co-expression of a mutated *AtIRT1* gene and *AtFER1* gene in transgenic cassava increased the iron accumulation 7–18 times higher than non-transgenic controls (Narayanan et al. 2019). These genes might play important roles in the development of iron-rich potato varieties. In addition, H^+-pyrophophatase gene *IbVP1* could also be used in potato biofortification for iron deficient soils as it promotes soil acidification in transgenic sweet potato plants (Fan et al. 2017).

Conclusion and Future Perspectives

Potato is a highly nutritious crop feeding the poor throughout the world. Previous studies suggest that 100 g of potatoes can deliver up to 8% of the RDA for iron for adult males (Camire et al. 2009; King and Slavin 2013). However, wide variations in the iron concentrations in potato germplasm (Table 1) suggest that iron rich genotypes can provide a much higher portion of RDA for iron than previously thought. The genetic variability in the potato gene pool could be used to increase the iron content in potato by using traditional breeding and selection methods. Genotypes with high iron concentration should be incorporated into potato breeding programs. Identification of genes/markers/QTLs associated with iron uptake, translocation and storage may speed up the breeding programs or could be used in the transgenic studies (Bradshaw 2019).

GWAS is a powerful tool that can decipher the genetic variation linked to a complex phenotypic trait. As there is always a risk of transferring undesirable genes along with desirable genes while crossing with wild genotypes, the development of iron-rich potatoes through transgenic approaches is a good alternative option. At present, iron deficiency is a global issue, which could be reduced by the development of iron-rich potato varieties. Potato biofortification requires integrated approaches comprising the most effective agronomic practices, modern plant breeding strategies and advanced genetic engineering tools.

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