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Research review paper

Dissecting plant iron homeostasis under short and long-term iron fluctuations

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ABSTRACT

A wealth of information on the different aspects of iron homeostasis in plants has been obtained during the last decade. However, there is no clear road-map integrating the relationships between the various components. The principal aim of the current review is to fill this gap. In this context we discuss the lack of low affinity iron uptake mechanisms in plants, the utilization of a different uptake mechanism by graminaceous plants compared to the others, as well as the roles of riboflavin, ferritin isoforms, nitric oxide, nitrosylation, heme, aconitase, and vacuolar pH. Cross-homeostasis between elements is also considered, with a specific emphasis on the relationship between iron homeostasis and phosphorus and copper deficiencies. As the environment is a crucial parameter for modulating plant responses, we also highlight how diurnal fluctuations govern iron metabolism. Evolutionary aspects of iron homeostasis have so far attracted little attention. Looking into the past can inform us on how long-term oxygen and iron-availability fluctuations have influenced the evolution of iron uptake mechanisms. Finally, we evaluate to what extent this homeostastic road map can be used for the development of novel biofortification strategies in order to alleviate iron deficiency in human.

Contents

1. Introduction . . . 0
2. Iron and its importance in the story of life . . . 0
3. Iron uptake mechanisms in plants . . . 0
4. Long-distance transport of iron in plants . . . 0
5. Intracellular iron reserves in plants . . . 0
    5.1. Vacuoles . . . 0
    5.2. Ferritin . . . 0
6. Regulatory mechanisms for iron homeostasis in plants . . . 0
    6.1. Transcription factors regulating iron homeostasis . . . 0
    6.2. Hormonal regulation of iron homeostasis . . . 0
    6.3. Citrate metabolism interplay with iron homeostasis . . . 0
    6.4. Interactions between iron and other elements . . . 0
    6.5. Diurnal regulation of iron homeostasis . . . 0
7. Conclusions . . . 0
Acknowledgments . . . 0
Appendix A. . . . 0
References . . . 0

1. Introduction

Iron is the most common element by mass in the Earth's outer and inner core and the fourth most common element in the crust. Naturally occurring iron consists of four stable isotopes with ^{56}Fe as the

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most abundant (Holleman et al., 1985). Iron is a transition metal with the ability to change its oxidation state in both hydrated free states, $[Fe(H_2O)_6]^{2+}$ and $[Fe(H_2O)_6]^{3+}$, and in complexes with different organic molecules. This gives iron its catalytic character and makes it an essential micronutrient for photosynthesis, respiration, sulphate assimilation, hormone synthesis, and nitrogen fixation, as well as DNA synthesis and repair (Le and Richardson, 2002; Rains, 1976). Iron availability is also of the utmost importance for pathogenesis where hosts and pathogens compete for the iron reserves by producing high affinity ferric chelators (Miethke and Marahiel, 2007; Smits and Duffy, 2011). Iron is an indispensable micronutrient in the redox reactions for virtually all organisms. However, exceptions are lactic acid bacteria where manganese and cobalt replace iron and the two pathogenic bacteria, *Borrelia burgdorferi* and *Treponema pallidum1* which as obligate intracellular parasites rely on the iron-dependent metabolic processes of their hosts (Posey and Gherardini, 2000; Weinberg, 1997).

In spite of the high iron content in the planet and that elaborate high affinity iron uptake mechanisms have been developed in all kingdoms organisms can still suffer from iron deficiency under certain conditions. Today up to 12% of the world's human population suffers from iron deficient anemia (IDA) and iron deficiency is categorized as being among the most important disease precursors (WHO, 2001, 2002, 2008). Different strategies have been applied to overcome this nutritional problem in the human population (reviewed by Bhullar and Gruissem, 2013; Galera et al., 2010; Murgia et al., 2012). The most promising solution would be the development and application of a sustainable approach which provides an easy distribution and accessibility of iron enriched final products without increased price. Therefore, a non-profit biofortification of the major crops might be the optimal strategy for alleviating iron deficiency in human. In this context a deeper insight into the plant iron homeostasis, including evolutionary and regulatory aspects, is of the utmost importance. Since, plants are also sensitive to low bioavailability of iron this can clarify why organisms have not been more successful in overcoming the low bioavailability of iron and pave the way to further develop the current iron biofortification strategies.

2. Iron and its importance in the story of life

The fact that iron-mediated redox reactions are essential parts of photosynthesis and aerobic respiration implies that iron has been important in biological systems from the very early beginning of life. The timeline of evolution of life outlines two major periods in global development of the biosphere each with very different cellular iron-demands (Fig. 1). The first period ended 2–2.5 billion years ago with the evolution of photosynthetic bacteria. In this early period the atmosphere was anoxic and iron was mainly present in its reduced and more bioavailable ferrous form, Fe^{2+} (Crichton and Pierre, 2001). In agreement with this, the bacterial high affinity ferrous uptake system (FEO) is generally associated with bacteria living anaerobicaly or at low pH (Cartron et al., 2006; Kammler et al., 1993; Rodionov et al., 2004).

Anaerobic cells do not have a great demand for iron (see Box 1) (Romano and Conway, 1996). The substantial change in iron uptake and homeostasis came with the evolution of photosynthetic bacteria leading to the development of an aerobic atmosphere that completely changed global life (Crichton and Pierre, 2001; Knowles, 1980). Ferric became the most common form of iron, with a much lower solubility and bioavailability than the ferrous form. The increased oxygen level triggered the evolution of organisms with aerobic respiration, which came to be the dominant life form. Photosynthesis and respiration increased the cellular demand for iron and also the need for improved homeostatic mechanisms to control iron toxicity in an aerobic environment. Metals and specifically iron can catalyze the Haber-Weiss reaction leading to the production of extremely active hydroxyl radicals that damage macromolecules (Buonocore et al., 2010; Haber and Weiss, 1934; Kehrer, 2000). During the course of evolution, therefore, tight regulation of iron homeostasis has been favored in order to have the necessary minimum of iron available. A higher availability of iron would have been deleterious by decreasing the fitness of organisms. Therefore, iron-mediated oxidative stress, the increased iron-demand through iron utilization by respiration, and the decreased iron bioavailability under oxygenic environment seem to be the main reasons of the current status of iron deficiency (see Fig. 1). Oxidative stress does not favor excess iron inside the cells and is one of the key reasons for a tightly regulated iron homeostasis. In agreement with this, organisms have not developed highly efficient iron uptake mechanisms and the major part of iron reserves, both in foods and soils, is not usable by them. These iron sources are in different ferric complexes formed because of the oxygenic environment and refereed as low bioavailable sources. That is why switching from high bioavailable iron diets towards low bioavailable iron diets easily results in iron deficiency which in human

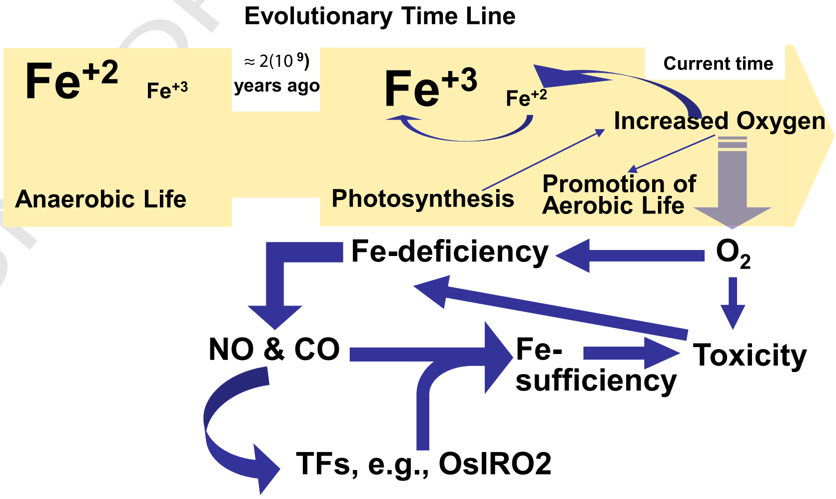

Fig. 1. A model for iron availability and demand in the evolution. As the consequence paradox of evolution of aerobic life, iron-toxicity and also the demand for iron have been increased by evolving the processes of photosynthesis and respiration. The oxygen-mediated toxicity and low bioavailability of iron decrease the iron uptake-rate and subsequently induce the iron deficiency response. For example, the plant iron-deficiency response involving heme-degradation mediated NO and CO production and downstream regulatory transcription factors (TFs) upregulate the iron uptake mechanisms. This can be repressed by iron-mediated oxidative stress which again leads to iron deficiency. Therefore, the decreased fitness caused by iron-mediated oxidative stress seems to be one of the main reasons for the tightly regulated iron homeostasis mechanisms adapted to avoid excess iron under normal conditions. This explains why diets/soils which are nutritionally poor in iron but not poor in iron content, result in iron deficiency. NO: Nitric oxide, CO: Carbon monoxide.

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