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Review

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Crosstalk between Iron and Arteriosclerosis

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Iron is an important element for life; however, intracellular labile iron overload can lead to the generation of reactive oxygen species and cellular damage. Although iron is mainly utilized for heme synthesis and is incorporated into hemoglobin, body iron status is often implicated in the pathogenesis of cardiovascular diseases. In a cell, iron is used for basic processes such as cell growth, maintenance, and repair. Thus, iron is considered to be involved in the pathogenesis of arteriosclerosis. In fact, clinical and experimental studies have shown an association between iron and arteriosclerosis. These data suggest the crosstalk between iron and arteriosclerosis. However, iron metabolism in arteriosclerosis is often complicated, and the systemic and cellular mechanisms of iron homeostasis in arteriosclerosis remain completely unsolved. Thus, in this review, we aimed to examine the role of iron in arteriosclerosis.

Key words: **Iron, Arteriosclerosis, Atherosclerosis, Transferrin receptor 1**

Introduction

Iron is an important element for life and is known to be involved in oxidation-reduction reactions, changing between oxidation states its ferrous form (Fe^{2+}) and ferric form (Fe^{3+}). It has been determined to be involved in oxygen transport and storage and energy metabolism **(Fig. 1)**; however, intracellular labile iron overload can lead to the generation of reactive oxygen species. In fact, iron overload has been found to induce adverse health problems and is associated in the pathogenesis of several metabolic diseases[1, 2]. On the other hand, iron deficiency is also detrimental to health besides erythropoiesis such as cognitive development or birth defects[3]. Thus, cellular and tissue iron levels must be exquisitely governed to maintain systemic and cellular iron homeostasis. Iron is mainly utilized for heme synthesis and is incorporated into hemoglobin; however, body iron status is also implicated in the pathogenesis of cardiovascular diseases.

As regard to aortic diseases, both iron deficiency and iron overload can contribute to the pathogenesis of arteriosclerosis and atherosclerosis, respectively[4-7]. Iron metabolism in arteriosclerosis and atherosclerosis is often complicated, and the systemic and cellular mechanisms of iron homeostasis in arteriosclerosis and atherosclerosis remain to be largely unknown. Thus, in this review, we focus on the role of iron in arteriosclerosis and atherosclerosis.

Systemic Iron Transport

More than 70% of body iron exists as heme within hemoglobin. Further, 20% of body iron is stored in the liver and 5% in macrophages. Most of the iron is recycled as erythrocytes in the body. Macrophages phagocytize senescent erythrocytes, degrade hemoglobin-derived heme, and export to the circulation. The released iron is mainly used in hematopoiesis in the bone marrow, while excess body iron is stored in the liver[8].

Systemic iron homeostasis is tightly regulated by the peptide hormone hepcidin in the liver and maintained through dietary absorption in the duodenum. In the duodenum, dietary iron (Fe^{3+}) is transported into enterocyte via apical membrane iron

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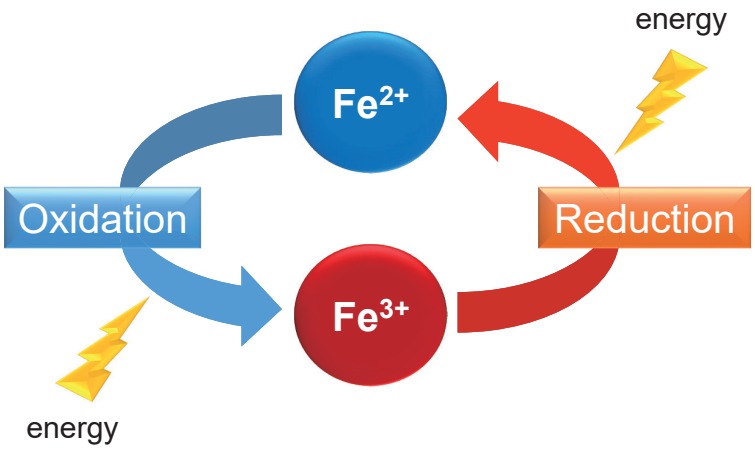

Fig. 1. Ferrous iron (Fe^{2+}) and ferric iron (Fe^{3+})

Iron is involved in the oxidation-reduction reactions, changing between oxidation states Fe^{2+} and Fe^{3+}. Further, iron plays a role for oxygen transport and storage and energy metabolism.

transporter, divalent metal transporter 1 (DMT1) after reduction to iron (Fe^{2+}) by the ferrireductase, that is, duodenal cytochrome b (Dcyt-b). Iron is then stored or exported into the circulation by the basolateral membrane transporter, that is, ferroportin[9].

Iron Transport in the Cells

On a cellular level, iron is used for basic processes such as cell growth, maintenance, and repair. Thus, local iron must be tightly controlled for cellular homeostasis. Most cells regulate iron uptake via a cellular iron transporter, that is, transferrin receptor 1 (TfR1). TfR1 is ubiquitously expressed on the cell surface and has been found to be involved in cellular iron uptake through its interaction with transferrin. Transferrin has two iron-binding sites, the extracellular di-Fe^{3+} binds to transferrin in the circulation. Transferrin-bound di-Fe^{3+} is then transported into the cells by TfR1. Then, TfR1-transferrin di-Fe^{3+} complex is internalized; iron is then released into the cells by endocytosis. Transferrin is recycled back to the circulation, and TfR1 is back to cell membrane[10]. In cellular iron deficiency, TfR1 is upregulated; then, cellular iron uptake is accelerated. Meanwhile, in cellular iron overload, TfR1 is downregulated, and cellular iron uptake is suppressed **(Fig. 2)**. Iron is then stored in ferritin in the cells.

Until now, the role of TfR1 in cardiovascular diseases remains under investigation. For instance, cardiomyocyte-specific TfR1 deleted mice were created, and the role of TfR1 in the heart was examined. Cardiomyocyte-specific TfR1 deleted mice died by post-natal day 11 due to cardiac hypertrophy and dysfunction, caused by iron deficiency and associated with mitochondrial failure[11]. Previously, we have examined the role of TfR1 in the mechanism of limb ischemia and renal fibrosis, wherein in limb ischemia models study, blood flow recovery after limb ischemia was attenuated in TfR1 heterozygous deleted mice, along with decreased expression of ferritin and mitochondrial complex I in ischemic adductor muscles[12]. In renal fibrosis models study, we assessed the effects of heterozygous TfR1 deletion in the pathogenesis of renal fibrosis using obstructive nephropathy and diabetic kidney disease models. As per our findings, TfR1 heterozygous deleted mice exhibited attenuated renal fibrosis, along with reduced renal expression of ferritin and 4-hydroxynonenal in both models[13]. These results suggest that TfR1 is involved in the pathogenesis of cardiovascular diseases.

Cellular Iron Transport in Arteriosclerosis

Iron is reported to contribute to the mechanism of both arteriosclerosis and atherosclerosis. Impaired endothelial function and increased intima-media thickness of the carotid artery have been determined to be associated with iron overload in patients with hereditary hemochromatosis[6]. In a 64-slice coronary computed tomography scanning study, an association between increased serum ferritin levels and the presence of coronary artery calcium score, which is a marker of early coronary artery atherosclerosis, has been reported in 12,033 men[14]. In addition, a study using venous occlusion plethysmography has shown that deferoxamine, an iron chelator, improved nitric oxide-mediated, endothelium-dependent vasodilation in patients with coronary artery diseases[15]. Although

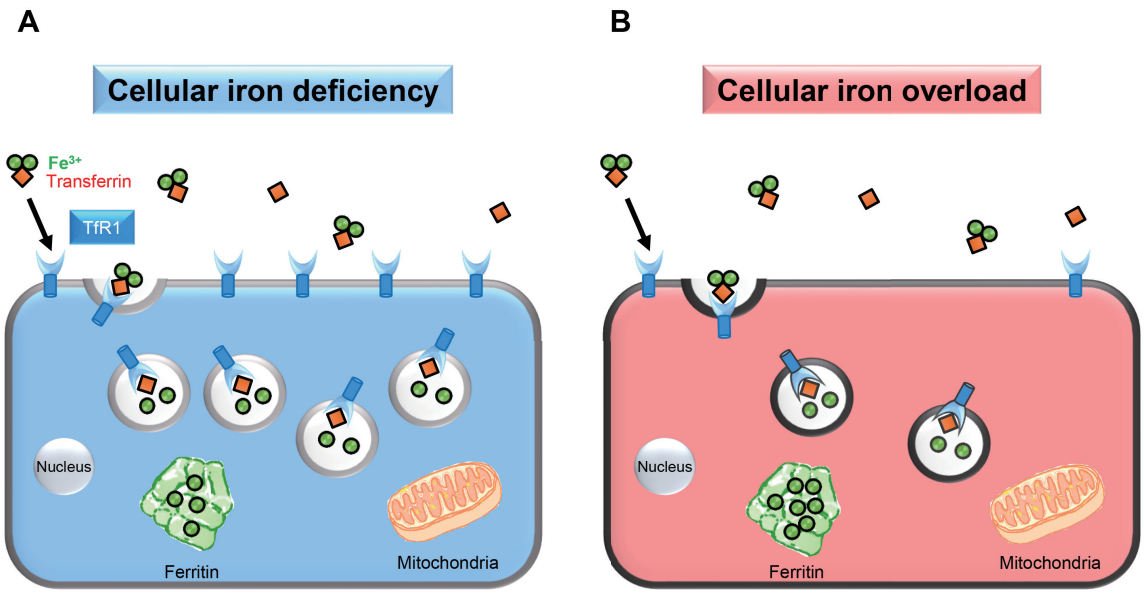

Fig. 2. A cellular iron transporter, transferrin receptor 1

TfR1-transferrin di-Fe^{3+} complex is transported into the cells by endocytosis after binding to transferrin receptor 1 (TfR1). (A) If cellular iron is deficient, TfR1 is upregulated, and cellular iron uptake is then accelerated. (B) If cellular iron is in excess, TfR1 is downregulated, and cellular iron uptake is inhibited.

several investigations on iron and aortic diseases have been performed, the causal relationship between iron and aortic diseases is yet to be fully understood. Also, it is almost unknown whether cellular iron regulating system is involved in the mechanisms of aortic diseases.

In this regard, we have investigated the iron regulating system using experimental model of arteriosclerosis and shown the impaired expression of aortic iron transporters in hypertensive model rats. In that study, we first confirmed iron deficiency and upregulated aortic TfR1 expression in rats given an iron-deficient diet. As per our immunohistochemical analysis, it was determined that TfR1 was expressed in the media layer of the aorta. The rats given an iron-deficient diet exhibited upregulated aortic TfR1 expression and downregulated ferritin heavy subunits (ferritin H) expression because of systemic iron deficiency. Of interest, we found that both aortic TfR1 and ferritin H expression were upregulated in Dahl salt-sensitive hypertensive rats with hypertension[16]. Dahl salt-sensitive hypertensive rats with hypertension showed anemia and decreased serum iron levels compared with rats given a normal diet[17]. These results suggested that dysregulated iron regulating system occurred in the aorta of hypertensive model rats. In addition, dietary iron restriction has attenuated the development of arteriosclerosis in these hypertensive rats, suggesting that cellular iron intake has contributed to the development of arteriosclerosis through upregulated aortic TfR1 expression[16]. Iron is required for cell growth, maintenance, and repair. Thus, augmented aortic TfR1 may have contributed to the mechanism of arteriosclerosis. Based on these data, we further investigated TfR1 expression in 5/6 nephrectomized chronic kidney disease (CKD) model rats. The CKD model rats showed hypertension and hypertensive arteriosclerosis. Of interest, aortic TfR1 expression was also upregulated in the media layer of aorta in CKD model rats, and dietary iron restriction suppressed the development of arteriosclerosis in CKD model rats[18]. Taken together, these results suggest that cellular iron intake contributes to arteriosclerosis through upregulated aortic TfR1 expression **(Fig. 3)**. Although further studies on cellular iron intake in the mechanism of arteriosclerosis are necessary, understanding the iron regulating system in arteriosclerosis may lead to a new therapeutic target in arteriosclerosis.

Cellular Iron Transport in Pulmonary Arteriosclerosis

Pulmonary hypertension is a progressing vascular disease characterized by pulmonary vascular remodeling, which induces right ventricular failure and sudden death[19]. Iron is also considered to be implicated in the pathogenesis of pulmonary hypertension. Iron deficiency is often prevalent in patients with pulmonary hypertension[20-22]. Iron

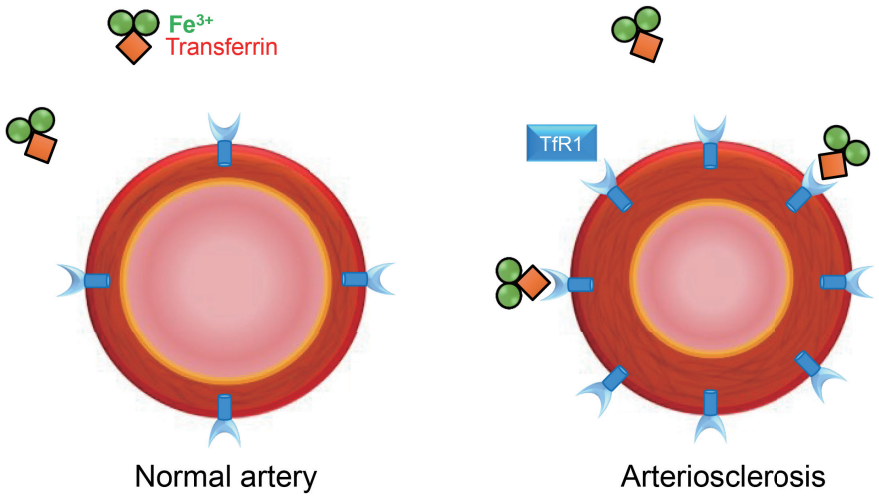

Fig. 3. Aortic transferrin receptor 1 in arteriosclerosis

Cellular iron intake contributes to the pathogenesis of arteriosclerosis through upregulated aortic transferrin receptor 1 (TfR1) expression.

deficiency without overt anemia, as defined by raised levels of soluble transferrin receptor, is common in patients with idiopathic pulmonary arterial hypertension; further, it is associated with disease severity and poor clinical outcome[20]. Another study also shows that iron deficiency is frequent in patients with idiopathic pulmonary arterial hypertension and associated with a lower exercise capacity regardless of the presence of anemia[21]. Also, the prevalence of unexplained iron deficiency is high in patients with idiopathic pulmonary arterial hypertension[22]. In addition, iron has been linked to the control of pulmonary vascular tone in response to acute hypoxic condition[23, 24]. An intravenous iron infusion reduced both the elevation in baseline pulmonary artery systolic pressure and the enhanced sensitivity of the pulmonary vasculature to acute hypoxia induced by exposure to sustained hypoxia in a study examining 16 healthy volunteers[23]. Also, two randomized controlled trials showed that approximately 40% of the pulmonary hypertensive response to hypoxia was reversed by an intravenous iron infusion, which reduced pulmonary artery systolic pressure in 22 healthy sea-level resident men[24].

Based on the experimental results of hypertensive arteriosclerosis, we have investigated the involvement of cellular iron intake in the mechanisms of vascular lesions of pulmonary hypertension (pulmonary vascular remodeling). Of note, TfR1 expression was increased in the remodeled pulmonary artery of monocrotaline-injected pulmonary hypertension model rats. In addition, dietary iron restriction has prevented the development of pulmonary vascular remodeling in monocrotaline-injected pulmonary hypertensive model rats[25]. We have also found that TfR1 heterozygous deleted mice attenuated pulmonary vascular remodeling in hypoxia-induced pulmonary hypertension model mice[26]. Moreover, the depletion of TfR1 by RNA interference has attenuated human pulmonary artery smooth muscle cells proliferation induced by platelet-derived growth factor-BB *in vitro*[26]. Taken together, these results suggest that cellular iron intake via TfR1 in pulmonary artery may be associated with the pathophysiology of pulmonary vascular remodeling.

Chronic severe iron deficiency can lead to pulmonary vascular remodeling in normal Sprague–Dawley rats[27]. Clinical studies have shown that iron deficiency is noted to be frequent in patients with idiopathic pulmonary arterial hypertension[20-22]. In cellular iron deficiency, TfR1 is upregulated; then, cellular iron uptake is accelerated. Collectively, TfR1 in pulmonary artery in response to iron deficiency may contribute to the development of pulmonary vascular remodeling in pulmonary hypertension. As iron deficiency is associated with a poor prognosis in patients with idiopathic pulmonary arterial hypertension[20], iron deficiency is expected as a therapeutic target for pulmonary hypertension. As regards iron repletion for patients with pulmonary hypertension, recent two randomized, double-blind studies of intravenous iron versus placebo showed that iron repletion to pulmonary hypertension patients with iron deficiency without overt anemia provided no significant clinical benefit at 12 weeks after intravenous iron administration[28]. Besides systemic

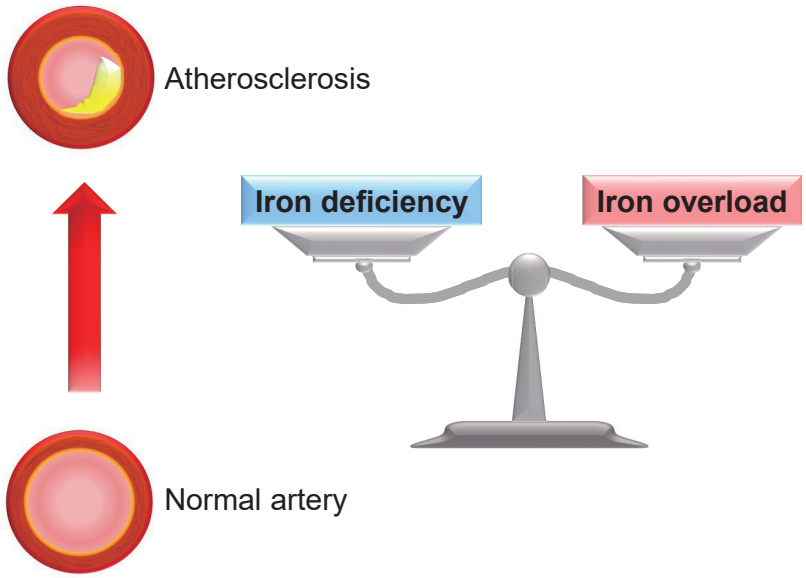

Fig. 4. Crosstalk between iron and atherosclerosis

Both iron deficiency and iron overload are associated with the pathogenesis of atherosclerosis. The appropriate body iron status should be considered in patients with atherosclerosis.

iron repletion, modulation of TfR1 expression in pulmonary artery might contribute to preventing or treating pulmonary vascular remodeling.

Cellular Iron Transport in Atherosclerosis

Epidemiologic and experimental studies have shown an association between iron and atherosclerosis. Prospective results from the Bruneck study show the potential association between increased serum ferritin levels and the 5-year progression of carotid atherosclerosis assessed by ultrasonography[4]. From the Kuopio Ischaemic Heart Disease Risk Factor Study in Eastern Finland, high stored iron levels, as assessed by elevated serum ferritin levels, have been identified to be a risk factor for coronary heart disease[5]. Also, associations between increased iron load and endothelium-dependent dilation of the brachial artery and intima-media thickness of the carotid artery are reported in patients with hereditary hemochromatosis[6]. By contrast, a Mendelian randomization study has shown that higher iron status reduces coronary artery disease risk[7]. In experimental studies, iron accumulation is observed in the atherosclerotic lesions of apolipoprotein E-deficient mice[29]. In addition, we have previously reported that iron is involved in the pathophysiology of abdominal aortic aneurysm (AAA) formation in angiotensin II injected apolipoprotein E-deficient mice[30]. Iron deposition was accumulated in AAA walls with the increments of oxidative stress and inflammation. Also, dietary iron restriction has reduced the incidence of AAA formation with attenuation of oxidative stress and inflammation in angiotensin II-induced AAA mice[30]. Iron is known to bind to transferrin in the circulation. When iron exceeds the carrying capacity of transferrin, non-transferrin-bound iron then circulates and promotes organ damage such as vascular endothelial cell dysfunction. Indeed, crossing hereditary haemochromatosis mice with apolipoprotein E-deficient mice was associated with iron accumulation on the aorta and an increase in atherosclerotic lesion compared with control mice[31]. Atherosclerotic plaques contain iron, and this may promote atherosclerotic plaque progression[32]. Iron may also accumulate in atherosclerotic lesions, and the hydroxyl radical is thought to promote the formation of oxidized low-density lipoprotein cholesterol and pro-inflammatory intermediates. In contrast, an earlier study has reported that dietary iron overload decreased atherosclerosis in apolipoprotein E-deficient mice[33], and iron deficiency is reported to be associated with a risk of coronary artery disease (CAD)[7, 34]. These are supports to the hypothesis that both iron overload and iron deficiency are associated with the pathogenesis of atherosclerosis **(Fig. 4)**. These findings suggest the importance of appropriate body iron status in the pathogenesis of atherosclerosis. However, the detailed mechanism of this U-shaped association of iron and atherosclerosis remains unknown. In experimental studies reporting a link between iron overload and

atherosclerosis, iron deposits appear in atherosclerotic lesions, particularly in the endothelium, intima enriched in foam cells, and smooth muscle cells of the media layer of aorta in apolipoprotein E-deficient mice[29]. Further, iron is mainly present in the media layer of aorta in hereditary haemochromatosis mice crossed with apolipoprotein E-deficient mice[31]. The investigation focusing on cellular iron metabolism may lead to uncover the mechanism of these cellular iron distributions in atherosclerosis and a U-shaped association of iron and atherosclerosis.

In patients with heart failure (HF), iron deficiency has been associated with a poor prognosis[35]. Thus, iron deficiency is expected as a therapeutic target for HF. The European Society of Cardiology guideline 2016 has recommended iron repletion for symptomatic patients with HF with reduced ejection fraction with iron deficiency as class IIa[36]. Also, intravenous iron supplementation has been recommended for symptomatic patients with HF with reduced ejection fraction (NYHA II/III) with iron deficiency as class IIb in American College of Cardiology/American Heart Association/Heart Failure Society of America 2017 guidelines[37]. In fact, iron is necessary to maintain mitochondrial functions in organs with high-energy demands such as the heart. However, iron repletion could be harmful to HF patients complicated with arteriosclerosis. Considering the total iron balance for the body, the risks and benefits of iron repletion should be considered cautiously in patients with arteriosclerosis.

Conclusion

Iron has been determined to contribute to the development of arteriosclerosis and atherosclerosis. Thus, understanding the iron regulating system in these aortic diseases may lead to a new therapeutic target in aortic diseases. However, future studies are needed to address the clinical significance of cellular iron metabolism in aortic diseases.

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Disclosures

None.

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