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REVIEW

The correlation between iron homeostasis and telomere maintenance

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Abstract **Eukaryotic organisms require iron to sustain genome stability, cell proliferation and development. Chromosomes contain telomeres to ensure complete replications and avoid fusions. Numerous evidences reveal that iron can act directly or indirectly on telomere maintenance. In human, disruption of systemic or cellular iron homeostasis is reportedly to cause serious health problems such as iron overload (hereditary hemochromatosis), iron deficiency anemia, carcinogenesis and acceleration of aging process. These processes commonly associate with abnormal telomere length. Additionally, cells containing mutations in iron-containing proteins such as DNA polymerases (Polα, δ, and ε), regulator of telomere length 1 (RTEL1) and the small subunit of ribonucleotide reductases (RNRs) have abnormal telomere length. This review briefly summarizes current understandings on iron homeostasis and telomere maintenance in cancer and aging process, followed by discussing their direct and indirect correlation, and the possible regulatory mechanisms.**

Keywords iron homeostasis, telomere, telomere maintenance, cancer, aging

Introduction

Iron is an important micronutrient factor, which facilitates eukaryotic cell proliferation and growth (Torti S V and Torti F M, 2013). It also serves as the donor and acceptor of electrons in many metabolic processes (Ponka, 1997; Lill, 2009). Moreover, iron can be utilized as a cofactor in the formation of functional iron-sulfur (Fe-S) cluster proteins, heme-binding proteins, and diiron proteins (Dlouhy and Outten, 2013; Heath et al., 2013; Zhang, 2014), which extensively function in electron transfer, ribosome maturation, genome stability, as well as cell cycle control (Rouault and Klausner, 1997; Kaplan et al., 2006; Ye and Rouault, 2010; White and Dillingham, 2012; Zhang, 2014). In eukaryotes, iron overload and iron deficiency are the two main iron disorders. Of them iron overload may cause the generation of excess reactive oxygen species (ROS), which can damage lipids, proteins and DNA, eventually leading to genomic instability, cell death and organ dysfunction in almost all organisms (Turrens, 2003; Orrenius et al., 2011; Romero et al., 2014). In human, severe iron overload in vital organs increases the risk of many diseases such as liver disease, osteoporosis, diabetes mellitus, osteoarthritis, heart failure, and metabolic syndrome (Chung et al., 2013). In addition, iron deficiency generally leads to iron-deficiency anemia, anemia of chronic disease, and cancer (Denic and Agarwal, 2007; Miller, 2013).

Iron is reportedly involved in both carcinogenesis and aging process. For instance, iron is required for both tumor initiation and growth (Torti S V and Torti F M, 2013). The iron uptake, storage and regulation pathways participate in carcinogenesis (Lamy et al., 2014; Marques et al., 2014; Wang et al., 2014), suggesting the critical roles of iron homeostasis in tumor cell survival. Signal transduction through hypoxia-inducible factor (HIF) and Wnt pathways possibly contributes to disruption of iron homeostasis in cancer (Torti S V and Torti F M, 2013). Furthermore, excess iron can be toxic and accelerate the aging process (Pouillot et al., 2013). The fact that women have averagely longer life span than men possibly because of iron loss during reproductive life has been considered as a valid hypothesis (Jian et al., 2009).

Besides iron, telomeres also exhibit considerable correlation with cancer and aging process. Telomeres are the nucleoprotein-DNA complexes at the ends of linear chromosomes ensuring their replications (Denchi and de Lange,

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2007; Watson and Shippen, 2007). In normal cells, telomere shortening is commonly accompanied by cellular senescence or apoptosis (Cosme-Blanco et al., 2007). However, telomere length is greatly heterogeneous in cancer cells (Neumann et al., 2013). Additionally, in somatic cells, telomere length generally decreases with age, which forms a barrier to the growth of cancer cells but also contributes to the loss of cells with age (Aubert and Lansdorp, 2008).

Taken together, the fact that both iron and telomeres are involved in cancer and aging process provides indirect clues for their correlation. Additionally, some studies also have demonstrated that iron directly participates in telomeres maintenance in different organisms. For instance, depletion of some iron-containing proteins such as DNA polymerases (Polα, δ, and ε), RTEL1 and the small subunit of RNR, results in abnormal telomere length (Ohya et al., 2002; Askree et al., 2004; Uringa et al., 2011; Gupta et al., 2013). Moreover, patients with diseases caused by iron overload or iron deficiency also commonly have abnormal telomere length (Kozlitina and Garcia, 2012; Mainous et al., 2013).

Telomeres, cancer, aging and iron

In recent years, a great number of studies have indicated that telomere maintenance associates with cancer and aging (Kim Sh et al., 2002; Donate and Blasco, 2011). The pancreatic, prostate, bone, lung, bladder, and kidney cancer cells have been reported to exhibit shortened telomeres (Ma et al., 2011). Moreover, shorter telomeres also have been found in aging process (Green and Mayeux, 2006; Moslehi et al., 2012). However, it is still controversial about the causality of shorter telomeres and aging. Moreover, carcinogenesis and aging process also associate with impaired iron absorption, storage and utilization, as well as abnormal protein levels or activities of some iron-containing proteins (Marques et al., 2014). This suggests a correlation between iron homeostasis and telomere length (Fig. 1).

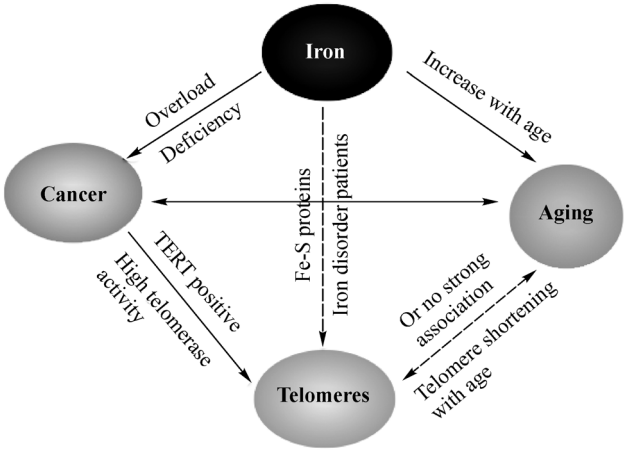

Figure 1 The relationships of iron, telomeres, cancer and aging. Iron overload or iron deficiency can cause carcinogenesis. Most human cancer cells possess short telomeres, upregulated telomerase activity and catalytic protein component (hTERT). Iron levels generally increase with age. However, the correlation between telomeres and aging are currently controversial. Commonly, the telomere length is gradually shortened as aging, but some studies also indicate there is no strong association between them. Moreover, abnormal telomere length also has been reported in mutants depleted iron-containing proteins and in iron disorder patients. Aging associates with many events at cellular and physiological levels that influence carcinogenesis and cancer growth.

Telomere length regulation in human

The integrity of telomere binding proteins is essential for telomere protection and telomere length regulation (Cong et al., 2002; Martínez and Blasco, 2011). The composition of telomeric protein complexes and function of individual telomere binding proteins exhibit considerable divergence across species (Palm and de Lange, 2008; de Lange, 2009; 2010). In human cells, six shelterin proteins, including TRF1, TRF2, Rap1, TIN2, TPP1 and POT1, comprise the protective telomere cap complex that allows cells to distinguish telomeres from DNA damage sites (de Lange, 2005; Simonet et al., 2011). TRF1, TRF2 and POT1 can directly recognize telomeric TTAGGG repeats (de Lange, 2005). Interestingly, shelterin components can negatively regulate telomere elongation (Diotti and Loayza, 2011). For instance, overexpression of TRF1 in the human HT1080 cancer cell line results in telomeres progressively shortening at a rate of 3–11 base pairs per population doubling, whereas telomerase activity is unaffected (van Steensel and de Lange, 1997; Smogorzewska et al., 2000). Conversely, the expression of a dominant negative truncated mutant of TRF1 leads to telomere elongation (Deng et al., 2002; Deng et al., 2003).

Iron homeostasis in human

The human body contains ~3–5 g of iron exclusively obtained from diet (Pantopoulos et al., 2012). The majority of iron exists in complex with heme cofactors in hemoglobin of erythroid cells (>2 g) or myoglobin of muscles (~300 mg) to carry oxygen through the blood (Pantopoulos et al., 2012). Most of the rest iron is stored in ferritin complexes that are present in all cells, especially in bone marrow, liver, and spleen (Pantopoulos et al., 2012; Lawen and Lane, 2013).

Human cells have developed sophisticated mechanisms for assuring a balanced cellular and systemic iron homeostasis (Andrews and Schmidt, 2007; Pantopoulos et al., 2012). The systemic iron regulation is mainly determined by the following steps: (1) iron absorption from the intestine (Beaumont, 2010; Zhang, 2010); (2) iron recycling from senescent red blood cells (Soe-Lin et al., 2009; Pantopoulos et al., 2012); (3) iron utilization for erythropoiesis; and (4) iron efflux via ferroportin (Pantopoulos et al., 2012). For cellular

iron regulation, human cells complete this process mainly through: (1) the coordinated regulation of the transferrin receptor (TfR) and ferritin, which mediate iron uptake and storage, respectively; and (2) the posttranscriptional regulation of cytoplasmic iron regulatory proteins (IRPs) (Pantopoulos, 2004; Pantopoulos et al., 2012). Under iron decificiency, IRPs can stabilize the TfR and inhibit the translation of ferritin mRNAs by binding to RNA stem-loop of iron regulatory elements (IREs) (Oliveira and Drapier, 2000).

Telomeres, cancer and iron

Most human cancer cells possess shorter telomeres and upregulated telomerase activity, which is suggested to be critical for cancer cell immortalization and cancer progression (Shay et a., 2001). Telomerase activity is usually used as a potentially sensitive biomarker in cancer screening, early cancer detection and prognosis (Jakupciak et al., 2004). In most cases, reactivation or upregulation of telomerase activity and its template RNA (hTR) and catalytic protein component (hTERT) are associated with cancer cell types (Shay et al., 2001; Cong et al., 2002). In cancer cells with high telomerase activity, hTERT is positively detected, but not in cancer cells with low telomerase activity (Liu et al., 2004; Zavlaris et al., 2009).

Iron is considered to associate with carcinogenesis, either through inducing ROS generation or due to its critical roles in cellular proliferation (Marques et al., 2014). Experimental analyses indicate that iron induced oxidative stress may damage DNA, protein and organelle (Tang et al., 2011). Some studies have reported that cellular iron import, export and storage may affect cancer development, behavior and recurrence (Torti S V and TortiF M, 2013; Marques et al., 2014). In cancer cells, the expression of iron importers and exporters may also be different from normal cells. Cancer cells seem to have increased expression of iron importers and decreased expression of iron exporters (Brookes et al., 2006). The altered expression of some iron metabolism related proteins such as Tf, TfR1 and TfR2, Ferritin, and IRPs also has been found in cancer cells (Andrews and Schmidt, 2007; Pantopoulos et al., 2012).

Human red blood cells contain hemoglobin, an iron-rich protein that gives blood the red color. Telomere shortening shows marginally association with lower red blood cell counts, but exhibits significantly involvements with larger mean size of red blood cells, increased red blood cell distribution width, higher hemoglobin levels and lower platelet counts (Kozlitina and Garcia, 2012). In aplastic anemia, patients with the shortest telomeres are ~4–5-fold more possible than others to develop as myelodysplasia and leukemia (Calado and Young, 2012; Kozlitina and Garcia, 2012). Chromosomes and aneuploidy with telomere-free ends are obvious in patients' bone marrows in tissue culture years before clinical symptoms (Calado and Young, 2012). Furthermore, in acute myeloid leukemia without prior bone marrow failure, some patients have constitutional mutations in hTERT and hTERC (Xin et al., 2007; Koziel et al., 2011).

Telomeres, aging and iron

The correlation between telomeres and aging are currently controversial. Normally, telomeres are gradually shortened as we become old (Calado and Young, 2012; Ludlow et al., 2013). Telomere length indicates proliferation history of cells and their future propensity to apoptosis and senescence (Calado and Young, 2012; Ludlow et al., 2013). Studies have revealed that individuals around 60 years of age who have the longer telomeres live longer than those with the shorter telomeres (Rehkopf et al., 2013), but the most associated cause of death in patients with shorter telomeres is infection (Calado and Young, 2012; Rehkopf et al., 2013). Moreover, heart disease as the cause of death is also more common in patients with the shortest telomeres (Calado and Young, 2012). In cardiovascular disease patients over 65 years of age, individuals with shorter telomere length are 60% more likely to die than those with longer telomere length (Calado and Young, 2012). In contrast, the correlation between telomere and aging has not been confirmed in some studies. For instance, Dr. Hsueh and his colleagues reported that telomere length might not be a strong biomarker of survival in older individuals, but exhibited correlation with years of healthy life (Njajou et al., 2009). In a study of people aged 73 to 101 years, Dr. Christensen's group pointed out there's no association between telomere length and survival rate among these old people (Bischoff et al., 2006). After 7 years follow-up old people with a mean age of 78 years, Dr. Giltay and his colleagues concluded that telomere length eroded with aging but failed to correlate with mortality (Houben et al., 2011).

Commonly, cellular and tissue iron levels increase with age (Killilea et al., 2004). The total content of iron increases significantly during cellular senescence, reaching ~10-fold higher levels relative to young cells (Killilea et al., 2004). Moreover, the increase of tissue iron levels is possible due to the failure regulation of iron absorption in enterocytes (Ganz, 2011). Interestingly, some studies give a positive relationship between cellular aging, the iron homeostasis disruption, and oxidative damage accumulation (Ghio et al., 2008). Iron chelators are suggested to use as alternative therapy drugs for diseases associated with aging and oxidative stress (Kaur and Andersen, 2002; Hatcher et al., 2009).

Iron overload and telomere length

Iron overload indicates excess iron accumulation in the body from any cause of which the most important factor is hereditary hemochromatosis (HHC) (Kremastinos and Farmakis, 2011). As a genetic disorder, HHC is generally caused by *HFE* gene mutations, which can lead to excess iron storage

and diseases (Hanson et al., 2001). However, the clinical penetrance of *HFE* gene mutations is low and many patients with excess iron storage lack *HFE* mutations (Hanson et al., 2001; Mainous et al., 2013). The recent results indicate that elevated iron phenotype, but not HFE genotype, is associated with shortened telomeres (Mainous et al., 2013).

However, in a rat iron overload model, telomerase activity increases three times relative to the control group, whereas the mean telomere length, TERT mRNA or protein level are same in both groups (Brown et al., 2007). The increased telomerase activity may contribute to the resistance of rodent liver to iron-induced damage (Brown et al., 2007). Furthermore, the distributions of telomere length are similar between the control and iron overload groups, while the iron overload livers appear to have fewer telomeres in the shortest range (Brown et al., 2007).

Iron deficiency and telomere length

Iron deficiency is very common in cardiovascular diseases patients (Carson and Adamson, 2010). Patients with heart failure typically have iron deficiency anemia or anemia of chronic inflammation (Tang and Katz, 2006). Clinically, the intravenous iron treatment in patients with congestive heart failure and iron deficiency can improve subjective and objective outcomes (Carson and Adamson, 2010).

Considerable amounts of clinical studies have shown that both cardiovascular risk factors and common cardiovascular diseases, such as atherosclerosis, heart failure and hypertension, are associated with telomere shortening (Serrano and Andrés, 2004; Fyhrquist et al., 2013). Cardiovascular diseases commonly accompany with short telomere length in white blood cells (WBCs), vascular endothelial cells (ECs), vascular smooth muscle cells (VSMCs) and myocardium cells, but the causality remains undermined (Fuster and Andrés, 2006; van der Harst et al., 2008; Wong et al., 2008). Moreover, thinning of myocardium always accompanies telomere shortening, TRF2 downregulation, Chk2 activation and increased apoptosis (Oh et al., 2003; Serrano and Andrés, 2004; Mourkioti et al., 2013). It is still unknown whether telomere shortening is the cause or consequence of cardiovascular disease.

Iron-sulfur cluster proteins and telomere maintenance

Over the past years, some iron-containing proteins have been found to involve telomere maintenance. The *Saccharomyces cerevisiae* DNA polymerases (Polα, δ, and ε), which utilize an iron-sulfur (Fe-S) cluster as cofactor in their holoproteins, are required for cell growth and chromosomal DNA replication (Kawasaki and Sugino, 2001). Polα and Polδ are necessary for lagging strand synthesis, whereas Polε is needed for leading strand synthesis (Jain et al., 2009). Importantly, the functions of DNA polymerases may influence telomerase activity (Adams Martin et al., 2000). Mutants of these three polymerases have been reported to exhibit abnormal telomere length (Ohya et al., 2002). Of them mutations in DNA Polε result in shortened telomeres, whereas mutations in DNA Polα and Polδ lead to longer telomeres relative to wild type (Ohya et al., 2002). The difference of telomere length in these three DNA polymerases may be caused by the disrupted coordination with telomere binding proteins (Ohya et al., 2002).

As the downstream protein of cytosolic iron-sulfur cluster assembly (CIA) machinery, MMS19 is required for the transfer of iron-sulfur (Fe-S) clusters to target proteins in *Saccharomyces cerevisiae* (Stehling et al., 2012). Interestingly, MMS119 has been identified to impact on telomere maintenance (Askree et al., 2004). The *mms19Δ* mutant exhibits extended telomere length relative to wild type, but the mechanism is still unknown (Askree et al., 2004).

RTEL1, an essential DNA helicase which possesses an iron-sulfur cluster, has been reported both in mice and human to be as a dominant factor that controls telomere length and integrity (Uringa et al., 2011; Le Guen et al., 2013). Mice lacking RTEL1 die in their early days with defects in multiple organs and their average telomere length in stem cells is decreased to 68% of that in wild-type cells (Uringa et al., 2011). In human, RTEL1 deficiency results in telomere shortening, anaphase bridges, sister telomere losses and terminal deletions (Le Guen et al., 2013). The telomere length reduction in RTEL1-deficient patients is possible due to the failure of active telomerase complex reaching the telomeres (Uringa et al., 2011; Le Guen et al., 2013).

Ribonucleotide reductases and telomere maintenance

Ribonucleotide reductases (RNRs) can use radical chemistry to reduce ribonucleotides to synthesize deoxyribonucleotides (dNTPs), and thereby providing the precursors needed for DNA replication and repair (Nordlund and Reichard, 2006). Iron is necessary for eukaryotic RNR activities because RNRs require iron to form a diferric tyrosyl radical (Fe_2^{III}-Y·) cofactor (Zhang, 2014). In iron deficient conditions, yeast cells control RNR function by redistributing the Rnr2-Rnr4 small subunit from the nucleus to the cytoplasm (Sanvisens et al., 2011).

In *Saccharomyces cerevisiae*, decreasing the overall pool sizes results in shortened telomeres, whereas increasing dNTP levels has no significant effect on telomere length (Gupta et al., 2013). Interestingly, alteration of the four dNTPs ratios dramatically affects telomere length homeostasis both in yeast and human (Gupta et al., 2013). The intracellular deoxyguanosine triphosphate (dGTP) levels positively correlate with both telomere length and telomerase nucleotide addition

processivity *in vivo*, while titration of deoxycytidine triphosphate (dCTP), deoxyadenosine triphosphate (dATP), or deoxythymidine triphosphate (dTTP) does not dramatically affect telomerase activity (Gupta et al., 2013). Similarly, human telomerase activity is greatly increased even with modestly elevated dGTP concentration, whereas it is dramatically decreased when dGTP concentrations are lowered (Gupta et al., 2013).

The possible mechanisms of iron regulating telomere maintenance

Although results have indicated that iron is required in maintaining telomere length, limited information is available regarding its functional mechanisms. Here, I presume some possible mechanisms based on the clues from the previous studies, as shown in Fig. 2.

DNA damage checkpoint activation

Disruption of iron homeostasis results in the activation of DNA damage checkpoints, which further affects the coordination of telomere binding proteins with telomeres, leading to abnormal telomere length. This hypothesis is strongly supported by the abnormal telomere length in DNA damage checkpoint kinase mutants. For instance, in yeast, the DNA damage checkpoint kinase cascade comprises Mec1/Tel1 (ATM/ATR in human), Rad53 (CHK1 and CHK2 in human) and Dun1. All their deficient mutants exhibit shorter telomere length relative to wild type (Ritchie et al., 1999; Takata et al., 2004; Gupta et al., 2013). Tel1 and Mec1 can be recruited to the telomeres at specific times during the cell cycle in a mutually exclusive manner (Takata et al., 2004). Mec1 can facilitate the loading of a telomere binding protein Cdc13 (Takata et al., 2005). Moreover, in human, telomere shortening triggers cell senescence through a pathway involving ATM, p53, and p21 (Herbig et al., 2004). In *Arabidopsis*, ATM and ATR kinases distinctly contribute to chromosome end protection and the maintenance of telomeric DNA (Vespa et al., 2005).

The reduction of dNTP pools

Unbalanced iron results in dysfunction of RNR holoproteins or their interaction proteins, which further lead to the reduction of dNTP pools, eventually causing shortened telomere length. In yeast, RNR contains two different R1 subunits (Rnr1-α and Rnr3-α′) and two different R2 subunits (Rnr2-β and Rnr4-β′), in which Rnr2 requires iron to sustain an active differric-Y· cofactor (Zhang, 2014). It has been reported that some iron-sulfur (Fe-S) cluster proteins such as Dre2-Tah18 and Grx3/Grx4 can directly or indirectly influence RNR activity (Zhang et al., 2008; Li et al., 2009). Thus, disruption of iron homeostasis may also affect the expression and stability of these iron-requiring proteins,

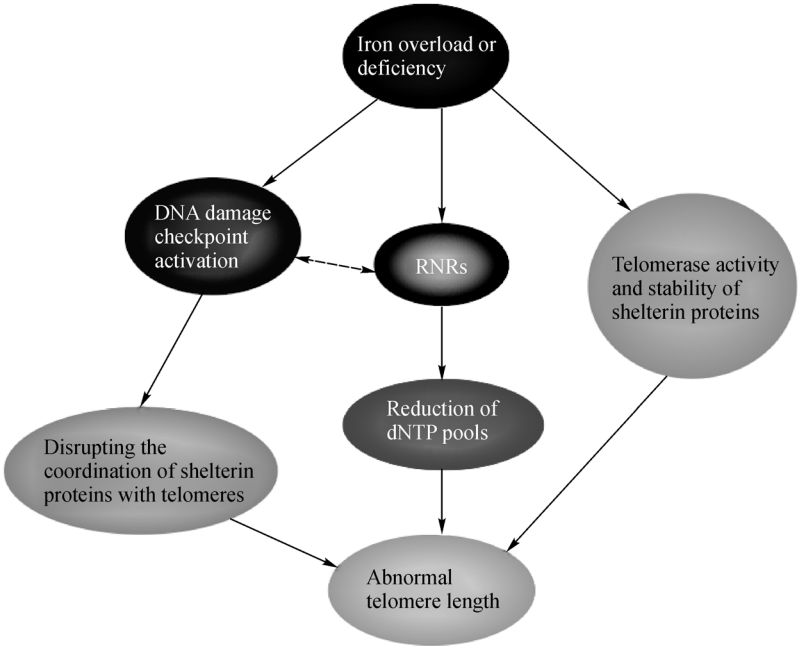

Figure 2 The possible mechanisms that iron involves in telomere maintenance. Firstly, disruption of iron homeostasis results in the activation of DNA damage checkpoint pathway, which further affects the coordination of telomere binding proteins with telomeres, and consequently leads to abnormal telomere length. Secondly, impaired iron homeostasis results in dysfunction of RNRs or their interaction proteins, which lead to the reduction of dNTP pools, eventually causing shortened telomere length. Moreover, iron homeostasis may also directly regulate telomerase activity and the stability of telomere binding proteins.

causing the decrease of dNTP pools. Interestingly, the four subunits of RNRs can extensively interact with DNA damage checkpoint kinases (Mec1, Rad53 and Dun1) (Huang and Elledge, 1997; Fikus et al., 2000) and DNA polymerases (Polα and Polε) (Lis et al., 2008). These results strongly suggest that the DNA damage checkpoint pathway may correlate with dNTP pools pathway.

Iron directly regulate telomerase activity and the stability of telomere binding proteins

Iron homeostasis may also regulate telomerase activity and the stability of telomere binding proteins. A variety of studies have indicated that telomerase activity is markedly increased either in iron overload or iron deficient condition (Brown et al., 2007; Zhu et al., 2010; Mainous et al., 2013). In human, mutations in TERT have been implicated in predisposing patients to aplastic anemia, a disorder in which the bone marrow fails to produce blood cells (Calado and Young, 2012). In yeast, Cdc13 can interact with Polα, and Pol32 (a subunit of Polδ) (Addinall et al., 2011; Sun et al., 2011), which possess an iron-sulfur (Fe-S) cluster and need iron for their activities. It is possible that there are other mechanisms involved in the regulation of telomere length under iron sufficient and deficient conditions.

Conclusions

More and more evidences indicate that iron performs critical roles in telomere maintenance. However, the regulation mechanisms are poorly understood. Further studies are still needed to uncover their relationships in the following aspects: (1) examining the iron levels and telomere length in cancer cells, senescent cells, and iron deficient anemia cells; (2) testing the stability of shelterin proteins in iron sufficient and deficient conditions; (3) checking the protein interactions between shelterin proteins and DNA replication/repair related proteins such as DNA polymerases and DNA helicases. As such, it would help us know more about the correlation between iron homeostasis and telomere maintenance, and also would explore our knowledge about iron, cancer and aging.

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Compliance with ethics guidelines

The author declares no conflict of interest. This article does not contain any studies with human or animal as subjects performed by the author.

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