The potential interplay between G-quadruplex and p53: their roles in regulation of ferroptosis in cancer

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Ferroptosis is a novel form of regulated cell death trigged by various biological processes, and p53 is involved in different ferroptosis regulations and functions as a crucial regulator. Both DNA and RNA can fold into G-quadruplex in GC-rich regions and increasing shreds of evidence demonstrate that G-quadruplexes have been associated with some important cellular events. Investigation of G-quadruplexes is thus vital to revealing their biological functions. Specific G-quadruplexes are investigated to discover new effective anticancer drugs. Multiple modulations have been discovered between the secondary structure G-quadruplex and p53, probably further influencing the ferroptosis in cancer. G-quadruplex binds to ferric iron-related structures directly and may affect the p53 pathways as well as ferroptosis in cancer. In addition, G-quadruplex also interacts with p53 indirectly, including iron-sulfur cluster metabolism, telomere homeostasis, lipid peroxidation, and glycolysis. In this review, we summarized the latent interplay between G-quadruplex and p53 which focused mainly on ferroptosis in cancer to provide the potential understanding and encourage future studies.

KEYWORDS
G-quadruplex, p53, ferroptosis, cancer, biological activities

Introduction

Ferroptosis is a newly identified type of regulated cell death that has attracted considerable attention in explaining the signaling pathways and defined effector mechanisms. Triggering cell death is one of the principal approaches to killing cancer cells. Emerging evidence shows cancer cells exhibit an increased iron demand compared with normal, non-cancer cells. This iron dependency can make cancer cells more vulnerable to ferroptosis. Therefore, exploiting how the ferroptosis are modulated could open new therapeutic avenues for eliminating cancer cells.

Although the precise molecular mechanism of ferroptosis has not been fully understood, many different genes involved in iron metabolism and lipid peroxidation,
such as GSH peroxidase 4 (GPX4) and solute carrier family 7 member 11 (SLC7A11), have been shown to be the key regulators in ferroptosis (Chen X. et al., 2021). Recently, studies have demonstrated that p53 regulates ferroptosis through transcription-dependent and -independent mechanisms (Kang et al., 2019; Liu et al., 2019; Liu J. et al., 2020; Liu and Gu, 2022). P53 was discovered to bind to the promoter region of SLC7A11 to repress its expression (Jiang et al., 2015; Ou et al., 2016). The binding of p53 to dipeptidyl-peptidase-4 (DPP4) protein decreased lipid peroxidation and ferroptosis (Xie et al., 2017). PTGS2 expression was demonstrated to be upregulated by ferroptosis in a p53-dependent manner (Jiang et al., 2015). Conversely, p53 acts as a positive regulator of ferroptosis via regulation of cytochrome c oxidase 2 (SCO2), glucose transporter (GLUT1), GLUT4 and glutaminase 2 (GLS2) (Schwartzenberg-Bar-Yoseph et al., 2004; Zhang et al., 2018). Besides, p53 suppresses the expression of RNA-binding protein ELAV-like RNA-binding protein 1 (ELAVL1), leading to impaired ELAVL1-LINC00336 interaction and further promoting ferroptosis (Wang et al., 2019).

Furthermore, p53’s role in the regulation of genes involved in metabolism has been implicated in its ability to regulate ferroptosis (Tarangelo et al., 2018; Liu and Gu, 2021; Yu et al., 2021). Arachidonate 12-lipoxygenase (ALOX12), a member of the lipooxygenase family that oxygenates polyunsaturated fatty acids (PUFAs), was identified as an important positive regulator for p53-mediated ferroptosis (Chu et al., 2019). The p53 suppresses ferroptosis through the induction of cyclin-dependent kinase inhibitor 1A (CDKN1A/p21) expression by suppressing the metabolic stress-induced ferroptosis (Tarangelo et al., 2018). The iPLA2β controls p53-driven ferroptosis by mediation detoxification of peroxidized lipids (Chen D. et al., 2021). Spermidine/spermine N1-acetyltransferase (SAT1) was also a direct p53 target that induced lipid peroxidation and sensitizes cells to undergo ferroptosis (Ou et al., 2016). Therefore, p53 represents a novel regulator of ferroptosis, an iron-catalyzed form of regulated necrosis that occurs through excessive peroxidation of PUFAs (Dixon et al., 2012) (Figure 1). An improved understanding of the molecular mechanisms and cellular factors of p53 in ferroptosis regulation will yield new therapeutic strategies for cancer.

Four guanines bind together through eight Hoogsteen hydrogen bonds to form G-quartet, and two or more G-quartets stack to become G-quadruplex (Yuan et al., 2011). Both DNA and RNA can fold into G-quadruplex in GC-rich regions, such as protomer regions, telomere regions, or UTR regions, and increasing shreds of evidence demonstrate the involvement of G-quadruplexes in different biological pathways (Spiegel et al., 2020; Varshney et al., 2020). The correction between G-quadruplex and cancer can be mainly described in the following three aspects. First, the promoter regions contain numerous G-rich sequences which can form G-quadruplexes (Shen et al., 2021). The G-quadruplex on the coding strand blocks the transcription complex and inhibits transcription, while the G-quadruplex on the non-coding strand helps to unwind the duplex and facilitate the transcription (Hänsel-Hertsch et al., 2016), hence the G-quadruplex functions in oncogene promoters have been well studied as well as ligands investigation (Sidiqui-Jain et al., 2002; Nasiri et al., 2014; Zhang et al., 2017). Second, as nucleoprotein complexes at the ends of chromosomes, the telomere is essential for chromosome stability and genome integrity. The repetitive G-rich sequences in telomere fold into G-quadruplex and block the telomeric elongation in cancer cells, thus the G-quadruplex is an effective target for tumor suppression and different G-quadruplex ligands are being developed to inhibit telomerase activity in cancer (Tauchi et al., 2003; Zhu et al., 2012; Beniaminov et al., 2016). Third, the genome instability is regulated by G-quadruplex through DNA replication (Rhodes and Lipps, 2015), leading to apoptosis and autophagy of cancer cells, and the ligand study in this area has been well-developed (Bywater et al., 2012; Xu et al., 2017; Beauvarlet et al., 2019). All these regulations support G-quadruplex as the anti-cancer target using G-quadruplex binding ligands as a tool. Although the primary sequences of G-quadruplexes are all G-riched with similar lengths, the secondary structures in three-dimensional reveal diverse topologies, providing possibilities for targeting.

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**FIGURE 1**
Regulation of ferroptosis by p53. Various proteins involved in iron metabolism and lipid peroxidation are modulated by p53.
The p53 has been found to bind telomeric G-quadruplex directly through DNA binding domains (Adámik et al., 2016). Both full-length and C-terminal regions of p53 display strong binding with myc G-quadruplex in the NHEIII1 region (Petr et al., 2016). The binding between p53 and G-quadruplex participates in gene regulation, in addition, the G-quadruplex can in return modulate the p53 function. The p53 RNA G-quadruplex structure close to the poly(A) site recruits DHX36, RNA helicase maintaining pre-mRNA 3′-end processing after UV damage (Newman et al., 2017), and the G-quadruplex structures formed in the GC-riched region of p53 intron 3 can regulate the splicing of p53 intron 2 (Marcel et al., 2010). Moreover, as part of the non-B DNA structure suppression system, the defection of p53 promotes the influence of genetic instability by G-quadruplex and i-motif (AMPARO et al., 2020), and the G-quadruplex displays the function to be the labile heme pool in vivo (Kawai et al., 2022). Through dye-loaded hemin/G-quadruplex modification, the UiO-66 metal-organic framework nanoparticles can be used to detect microRNAs or genes including p53 and BRCA1 (Zhang et al., 2021). An extension of this study is the detection of more genes or RNAs based on sequence specificity. In brief, the G-quadruplex exhibits regulatory function through direct interaction with ferric ion or heme.

G-quadruplex and p53 in ferroptosis

G-quadruplex and iron-sulfur cluster biosynthesis in p53-regulated ferroptosis

The p53 participates in iron metabolism by regulating the transcriptional process of iron-sulfur cluster assembly enzyme (ISCU), and ISCU is critical for the biogenesis of iron-sulfur (Fe-S) cluster (Funauchi et al., 2015). The structure of the Fe-S cluster is first determined in the last century (Iwata et al., 1996) and it plays important role in cancer. In lung cancer, the overexpression of NFS1, one kind of iron-sulfur cluster biosynthetic enzyme, will sustain the iron-sulfur cluster expression, and inhibition of NFS1 leads to iron starvation and result in ferroptosis (Alvarez et al., 2017). In addition, sulfur transfer pathways also participate in the occurrence of ferroptosis (Yu et al., 2017). Fe-S cluster is involved in intracellular reduction/oxidation (REDOX) processes, FANCJ is one of the Fe-S cluster helicases, and the conserved Fe-S domain containing four cysteine residues is important for the cluster regulation (Bharti et al., 2013). Mutations in this FANCJ Fe-S domain would influence the cancer susceptibility (Paulo et al., 2018).

FANCJ is likely to be the only Fe-S cluster helicase to open the G-quadruplex structures to this day (Bharti et al., 2013). Human cells with FANCJ defecton exhibit increased sensitivity to the G-quadruplex specific ligand (Wu et al., 2008), and FANCJ mutated cells derived from patients enrich in genome regions...
along with G-quadruplex structures (London et al., 2008). A series of mutation designs demonstrate that FANCJ unwinds G-quadruplex in the genome through the Fe-S domain, correlating with the ability of ferric iron incorporation and metabolism. Therefore, based on ferric iron regulation and ferroptosis, drugs targeting G-quadruplexes should be reconsidered in clinical use in cancer patients with FANCJ deficiency (Odermatt et al., 2020).

In a word, the Fe-S cluster helicase FANCJ utilizes the Fe-S domain to regulate G-quadruplex and likely further influence p53-related iron metabolism and ferroptosis, as well as affect genomic instability by unwinding G-quadruplexes in cancer.

The p53-regulated telomere and the G-quadruplex function in ferroptosis

The regulatory relationship between telomere and p53 is complex. For example, telomere inactivation can activate p53, which leads to DNA damage and DNA repair at the end of chromosomes (Sahin et al., 2011), meanwhile, the p53–p21–DREAM–E2F/CHR pathway down-regulates telomere maintenance and influence telomere homeostasis in cancer (Engelang, 2018; Vodicka et al., 2021).

As a signature of ferroptosis, ROS plays a crucial role in cancer. ROS could generate 8-oxoguanine through in situ oxidation of guanine in telomere, and this oxidative telomeric DNA damage, as well as the increased TERT expression, appears to be one of the most important causes of telomere shortening, resulting in increased mortality and cancer recurrence (Ko et al., 2018; Kordowitzki, 2021). RSL3-mediated oxidative stress in ferroptosis drives a series of histone modifications, and H3K79me3/H2A.Z could regulate the telomeric regions (Logie et al., 2021). Telomerase reverse transcriptase (TERT) is involved in ferroptosis-related differential expression genes, indicating potential regulation between telomere and ferroptosis (Liu H.-J. et al., 2020).

G-quadruplex and lipid peroxidation in the p53-regulated ferroptosis

Accumulated iron triggers ferroptosis by producing excessive ROS and inducing lipid peroxidation (Liu et al., 2022; Ou et al., 2022; Qiao et al., 2022). As a critical component of the cellular antioxidant defense system, glutathione (GSH) prevents the accumulation of

### Table 1: The regulation and mechanism in ferroptosis related to G-quadruplex and p53.

| Process                        | Regulator | Targets                                      | Mechanism                                                                 | Reference                                                   |
|--------------------------------|-----------|----------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------|
| G-quadruplex-heme interaction  | labile heme | G-quadruplex in myc promoter region          | Labile heme binds to the G-quadruplex in the myc promoter region and blocks the transcription | Canesin et al. (2020)                                       |
| G-quadruplex                   | heme      |                                              | G-quadruplex could bind or release heme in different conditions          | Mestre-Fos et al. (2020); Gray et al. (2019)                 |
| iron-sulfur cluster biosynthesis | p53      | iron-sulfur assembly enzyme (ISCU)            | P53 regulates ISCU and affects the biosynthesis of Fe-S cluster         | Funauchi et al. (2015)                                      |
| Fe-S cluster helicase FANCJ    | G-quadruplex |                                              | FANCJ unwinds G-quadruplex through Fe-S domain                           | Wu et al. (2008); London et al. (2008); Odermatt et al. (2020) |
| telomere homeostasis           | p53      | p53                                          | Telomere inactivation could activate p53                                 | Sahin et al. (2011)                                         |
|                               | p53      | telomere                                     | P53–p21–DREAM–E2F/CHR pathway down-regulates telomere maintenance       | Engeland (2018); Vodicka et al. (2021)                      |
| ROS                            | G-quadruplex |                                              | ROS in ferroptosis destroys G-quadruplex and affect telomere homeostasis | Ko et al. (2018); Kordowitzki (2021)                        |
| lipid peroxidation             | MDM2      | p53, PPARα                                   | MDM2 promotes ferroptosis by p53 degradation and PPARα-mediated lipid remodeling | Bykov et al. (2018); Venkatesh et al. (2020)                 |
| G-quadruplex                   | MDM2      |                                              | G-quadruplex suppresses MDM2 transcription                               | Lago et al. (2021)                                         |
| Glycolysis                     | p53      | GLUT1, GLUT4, GLUT12                         | P53 inhibits the transcription of GLUT family, and imposes ferroptosis  | Schwartzenberg-Baz-Yoseph et al. (2004); Zawacka-Pankau et al. (2011); Yokoyama et al. (2014) |
| G-quadruplex                   | AMPK/SnRK, NrF2-related, and hypoxia-responsive transcription factors | G-quadruplex regulates transcription of target genes                  | Belmonte-Reche et al. (2022); Andorf et al. (2014)          |
ROS and constitutes the major cellular defense mechanism against ferroptosis. GSH is synthesized from L-cysteine, L-glutamate, and glycine; therefore, the cellular availability of these amino acids could directly affect the concentration of GSH. Several studies have developed a strategy based on G-quadruplex formation for the detection of glutathione and cysteine in the biological sample (Leung et al., 2013; Zhao et al., 2013). These methods were developed to investigate G-quadruplex prevalence in human cells and to study their biological functions, presenting the next key challenges that need to be addressed to fully unravel their biology and therapeutic potential. MDM2 can target and degrade p53, while oncogene activation could prevent MDM2 from binding to p53 and stimulate the p53 acetylation (Bykov et al., 2018). MDM2 also can promote ferroptosis by PPARα stimulated the p53 acetylation (Bykov et al., 2018). G-quadruplex structures are present in the MDM2 promoter and G-quadruplex ligands inhibit MDM2 expression and p53 degradation in the liposarcoma (Lago et al., 2021). Based on these published data, we have reasons to believe that G-quadruplex could be exploited to detect and modulate lipid peroxidation, probably reconstituting the p53-regulated ferroptosis signal.

G-quadruplex involved in p53-regulated glycolysis and ferroptosis

Under most circumstances, p53 inhibits glucose uptake via direct attenuating glucose transporters glucose transporter 1 (GLUT1), GLUT4, and GLUT12 gene transcription and then drives glycolysis inhibition (Schwartzenberg-Bar-Yoseph et al., 2004; Zawacka-Pankau et al., 2011; Yokoyama et al., 2014). Glucose-metabolism imbalance would activate the LKB1/AMPK regulatory axis to cause the phosphorylation of acetyl-CoA carboxylase (ACC) to inhibit its activity and impose a regulatory effect on tumor cell ferroptosis (Lee et al., 2020; Li et al., 2020). Glycosyl conjugation to drugs is a strategy being used to take advantage of GLUT overexpression in cancer cells in comparison with non-cancerous cells. Efes et.al have synthesized thiosugar naphthalene diimide conjugates as G-quadruplex ligand and proved their antiproliferative activity in colon cancer cells (Belmonte-Reche et al., 2022). Furthermore, G-quadruplex motifs are found in numerous genes encoding members of the AMPK/SnRK, Nrf2-realted, and hypoxia-responsive transcription factors (Andorf et al., 2014). Collectively, G-quadruplex may aid in energy status gene responses and provide a mechanistic basis for linking Glycolysis signals to ferroptosis.

Conclusion and perspectives

Ferroptosis is a new regulated cell death form and the mechanisms in cancer are still under exploration. As important regulatory elements, both G-quadruplex and p53 are involved in various ferroptosis-related processes, and the potential diversified interplay provides more understanding of ferric ion/heme, Fe-S cluster biosynthesis, telomere homeostasis, lipid peroxidation, and glucose metabolism.

The classic regulatory mode of p53 contains stabilization, antipression, and promoter-specific activation (Kruse and Gu, 2009), and recent research has highlighted the importance of the posttranslational modifications (Liu et al., 2019; Zhang L. et al., 2022). The p53 participates in regulating iron-sulfur cluster assembly enzyme activity, interacts with telomere, is involved in lipid peroxidation, and regulates glycolysis. The complicated models are tightly involved in p53-mediated ferroptosis. Targeting p53 pathways is a promising strategy for anticancer therapy, and various inhibitors are being developed, including ZNF498 (Zhang X. et al., 2022), and Eupaformosanin (Wei et al., 2022).

G-quadruplex acts as a vital regulator for gene activity based on its biological function thus attracting great enthusiasm from researchers in the field of drug discovery. G-quadruplex binding ligands, mostly small molecules, change the stabilization of this kind of secondary structure and further affect the gene activity, telomeric function, and genome instability in multiple cancers. Many small molecules have been discovered and several molecules have progressed to clinical trials, such as Quarflloxin/CX-3534 (Phase I/II) targeting different cancers (NCT00780663, NCT00955786) (Papadopoulos et al., 2007; Drygin et al., 2009), and CX-5461 (Phase I) targeting BRCA1/2 deficient cancer (NCT02719977) (Xu et al., 2017; Khot et al., 2019; Hilton et al., 2022).

However, the G-quadruplex regulation in cancer still remains unsolved problems. Many G-quadruplex ligands don’t exhibit selectivity between different G-quadruplexes (Chen J. et al., 2021; Galati et al., 2021), generating potential side effects or low efficiency. The binding affinity of some ligands still needs to be improved (Kosiol et al., 2021) to benefit clinical usage. The regulation of G-quadruplex and ligand function in cancer is yet not clear. Therefore it is necessary to explore new modulations, such as the direct/indirect interactions with p53 in ferroptosis regulation. Here we show that p53 might be an important regulator or target of the G-quadruplex, especially in ferroptosis of cancer research (Figure 2). It is still a challenge to figure out how p53 and G-quadruplex interplay in more stages such as posttranslational modifications or DNA binding, and if the crosstalk functions in other processes like cell cycle/apoptosis. More potential interactions need to be characterized with high resolution, thus methodologies including computational simulation and experimental tools are also required for robust molecular exploration. In addition, it will be interesting and crucial to study the direct interactions between p53 and G-quadruplex in the regulation of ferroptosis in cancer to achieve a clearer mechanism. Besides, diverse studies regarding p53 and G-quadruplex in ferroptosis are operated in vitro, and more in vivo validations are essential for future therapeutic investigations. Furthermore, more specific targeting strategies are required to evolve based on the potential interplay between p53 and G-quadruplex.
In conclusion, the G-quadruplex and p53 regulation network might be a potential target for cancer research in the future and the mechanisms will be better understood as the research attention increases, hopefully benefiting the clinical cancer treatment.

Author contributions

LZ: Conceptualization, Writing-Original Draft. YJ: Conceptualization, Supervision, Writing-Review and Editing. JS: Supervision, Writing-Review and Editing. YL, XM, and YX: Review and Editing. All authors contributed to the article and approved the submitted version.

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