nature reviews molecular cell biology

https://doi.org/10.1038/s41580-025-00842-3

Review article

Check for updates

p53-regulated non-apoptotic cell death pathways and their relevance in cancer and other diseases

Yanqing Liu[1], Brent R. Stockwell[2,3,4], Xuejun Jiang[5] & Wei Gu[1,4]

Abstract

Programmed cell death is a mechanism that is crucial for numerous physiological and pathological processes. Whereas p53-mediated apoptosis is a major cell death pathway in cancer, accumulating evidence indicates that p53 also has crucial roles in controlling different non-apoptotic cell death (NACD) pathways, including ferroptosis, necroptosis, pyroptosis, autophagy-dependent cell death, entotic cell death, parthanatos and paraptosis, and may regulate PANoptosis, cuproptosis and disulfidptosis. Notably, the function of p53 in these NACDs substantially contributes to its biological effects, particularly in cancer development and other pathological processes. In this Review, we discuss recent advances in understanding the roles and underlying mechanisms of p53-mediated NACDs, focusing on ferroptosis, necroptosis and pyroptosis. We discuss the complex and distinct physiological settings in which NACDs are regulated by p53, and potential targeting of p53-regulated NACDs for the treatment of cancer and other human diseases. Finally, we highlight several important questions concerning p53-regulated NACDs that warrant further investigation.

Sections

[1]Institute for Cancer Genetics, and Herbert Irving Comprehensive Cancer Center, Vagelos College of Physicians & Surgeons, Columbia University, New York, NY, USA. [2]Department of Chemistry, Columbia University, New York, NY, USA. [3]Department of Biological Sciences, Columbia University, New York, NY, USA. [4]Department of Pathology and Cell Biology, Vagelos College of Physicians & Surgeons, Columbia University, New York, NY, USA. [5]Cell Biology Program, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. e-mail: wg8@cumc.columbia.edu

Introduction

Since its discovery in 1979, the transcription factor p53 has been a focus of intensive study[1]. p53 is now recognized as one of the proteins most relevant to health, particularly owing to its potent tumour-suppressive function, but also through its involvement in normal physiology and in the pathogenesis of some non-cancer diseases[1]. Consequently, p53 has immeasurable therapeutic value and is capturing considerable attention from the pharmaceutical industry[2,3]. This 'star molecule' status of p53 stems from its powerful ability to regulate a wide range of functions in diverse biological processes. For example, p53 responds to DNA damage to induce cell-cycle arrest, apoptosis and senescence, which were previously thought to be the major mechanisms by which p53 suppresses tumorigenesis. However, research published in the past few years has suggested that these three classical p53 functions are not always indispensable for p53-mediated tumour suppression[4–6]. Furthermore, a major obstacle to therapeutically activating p53 is the side effects of its classical functions. Hence, discovering new functions of p53 will not only enhance our understanding of this crucial protein, but also benefit the development of p53-based therapeutics.

Homeostasis in multicellular organisms requires maintaining a balance between cell proliferation and cell death. Cell death is a common and important biological process: well-controlled cell death is vital for development and other physiological processes, but dysregulated cell death can result in diverse diseases. Apoptosis is the best-studied type of cell death and was once regarded as the only mode of regulated cell death (RCD). However, later studies have identified many new types of RCD, such as ferroptosis, necroptosis and pyroptosis[7] (Box 1). These RCDs may share similarities in their underlying mechanisms and morphology of dying cells, but each has unique characteristics, resulting in both overlapping and independent physiological or pathological functions[7–10]. Understanding the molecular mechanisms and identifying the essential regulators of these RCDs is of great importance for fundamental research and disease treatment.

In the past decade, p53 has been found to regulate many types of non-apoptotic cell death (NACD) pathways. In this Review, we discuss how p53 regulates multiple NACDs, focusing on ferroptosis, necroptosis and pyroptosis; we also consider other NACDs in which p53 may be involved. Next, we discuss the therapeutic potential of targeting p53-mediated NACD pathways in different disorders. Lastly, we discuss notable issues in p53–NACD research.

p53-regulated ferroptosis

Ferroptosis was identified and named by Brent Stockwell in a series of papers published between 2003 and 2012 (refs. 11–13), as a newly identified regulated NACD characterized by iron-dependent lipid peroxidation at cellular membranes (Box 2). Prior studies had observed features and elucidated key genetic drivers of what we now understand to be ferroptosis[14,15]. In the past decade, ferroptosis has become the most intensively studied NACD type, and it is the cell death mode most relevant to cellular metabolism, and which has been linked to ageing, ischaemic organ injury, neurodegenerative diseases and particularly cancer[16]. The canonical ferroptosis pathway revolves around the acyl-CoA synthetase long chain family member 4 (ACSL4)–glutathione peroxidase 4 (GPX4) axis[7]. However, recent research has revealed crucial non-canonical ferroptosis pathways[14].

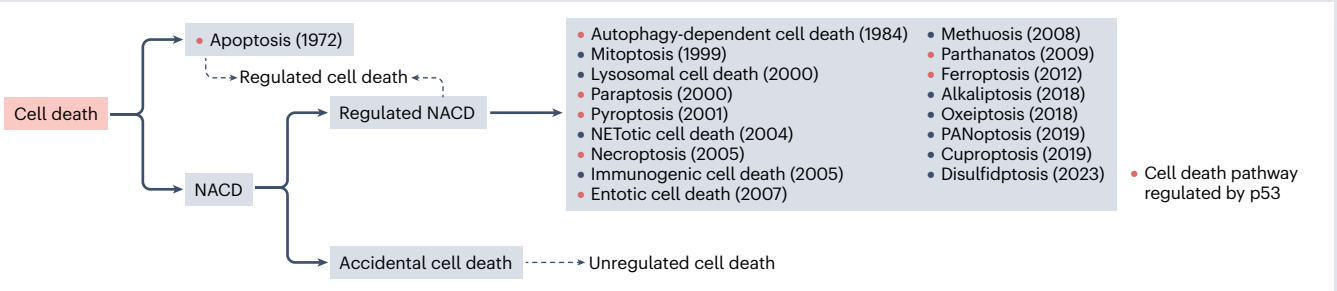
Role of p53 in ferroptosis

p53 is a master regulator of the three key components of ferroptosis[17] (Fig. 1 and Box 2). This activity of p53 primarily stems from its powerful ability to regulate the cellular metabolism of diverse biomolecules, such as amino acids, lipids, iron and reactive oxygen species (ROS)[18].

Solute carrier family 7 member 11 (SLC7A11; also known as cystine/glutamate transporter) is a subunit of the cystine/glutamate antiporter (system X_c^-) and is responsible for importing cystine into the cell for glutathione (GSH) synthesis. In initial reporting of p53 regulation of ferroptosis[19], p53 was found to suppress the transcription of *SLC7A11*, thereby reducing GSH levels and inhibiting GPX4 activity, leading to ferroptosis induction in vitro and in vivo (Fig. 1c). Importantly, the p53–SLC7A11 axis can also function independently of GPX4 inhibition. Arachidonate 12-lipoxygenase 12S type (ALOX12) can catalyse the peroxidation of lipids at the cytoplasmic membrane to trigger ferroptosis. However, it is sequestered from its substrates

Box 1 | Diverse cell death types

Cell death was observed and described as early as 1842 by Karl Vogt[170]. Today, dozens of cell death types are recognized, with apoptosis being the best-known and most extensively studied[7,8]. The different cell death modes can be categorized in various ways, including according to their trigger, mechanism and regulation, and the morphology of the dying cells. In this Review, we classify cell death into apoptosis and non-apoptotic cell death (NACD). The latter category includes accidental cell death, which is unregulated, and several regulated NACDs that have physiological or pathological relevance in humans. The figure lists several representative NACD types. The number following the cell death name is the year in which this pathway was termed. Notably, new cell death types are still being discovered.



by SLC7A11. As such, the downregulation of SLC7A11 by p53 releases ALOX12 to activate ferroptosis[20] (Fig. 1b,c). Notably, ALOX12 can be specifically recruited to phosphatidic acid (PA), a type of membrane phospholipid (PL) and a substrate for lipid peroxidation in ferroptosis, by interacting with pleckstrin homology like domain family A member 2 (PHLDA2)[21] (Fig. 1b). Glycerol-3-phosphate acyltransferase 3 (GPAT3) catalyses the biosynthesis of PL-containing polyunsaturated fatty acid phosphatidic acid (PUFA-PA), thereby providing substrates for ALOX12-mediated ferroptosis. This PHLDA2–ALOX12–PA-mediated ferroptosis has substantial pathological relevance and can be activated without common ferroptosis-inducing compound (FIN) treatments in both immunodeficient and immunocompetent mouse tumour models, thus being as a convincing example of the tumour-suppressive effect of ferroptosis in a natural background. In addition to ALOX12, p53-mediated SLC7A11 repression also enhances the lipoxygenase activity of ALOXE3 and ALOX15B to promote ferroptosis in glioblastoma and bladder cancer cells, respectively[22,23].

Regarding the substrates for lipid peroxidation, p53 regulates multiple lipid metabolism pathways that contribute to its ferroptosis-promoting effect[18] (Fig. 1a). For instance, p53 promotes Yes1 associated transcriptional regulator (YAP1)-mediated ACSL4 upregulation, thus enhancing the abundance of PUFAs in cellular membranes, which induces ferroptosis in colon cancer cells[24,25]. Monounsaturated fatty acids (MUFAs) can compete with PUFAs for incorporation into membrane PL. Thus, MUFAs are potent inhibitors of ferroptosis. p53 can suppress the expression of stearoyl-CoA desaturase 1 (SCD1) to reduce the composition of MUFAs in membrane phospholipids, thereby promoting the induction of ferroptosis in hepatocellular carcinoma cells[26,27]. p53-induced cell-cycle arrest increases the level of PUFA-PL by decreasing the expression of membrane bound O-acyltransferase domain containing 1 (MBOAT1) and epithelial membrane protein 2 (EMP2), thereby sensitizing cells to ferroptosis in diverse cell lines[28].

The execution of lipid peroxidation mainly depends on ROS, iron, and, in specific contexts, ALOXs[14] (Fig. 1b). Mitochondrial activity is a major source of ROS, production of which is enhanced by p53 activation of glutaminase 2 (GLS2) expression, which fuels the tricarboxylic acid (TCA) cycle and mitochondrial activity[29,30]. The resulting boost to ferroptosis limits the growth of hepatocellular carcinoma cells. Furthermore, the FINs erastin and RSL3 were reported to upregulate the expression of the long noncoding RNA (lncRNA) nuclear paraspeckle assembly transcript 1 (NEAT1), in a p53-dependent manner in hepatocellular carcinoma cells[31]. NEAT1 then increases ROS levels and promotes ferroptosis through the NEAT1–miR-362-3p–myo-inositol oxygenase (MIOX) axis. In rat hearts under ischaemia/reperfusion (I/R) stress, the level of ubiquitin specific peptidase 7 (USP7) is upregulated, resulting in p53 de-ubiquitilation[32]. The resulting stabilization of p53 activates its target gene transferrin receptor 1 (TfR1), a marker of active ferroptosis[33], which imports iron into the cell (Fig. 1b). The increased iron level promotes cardiac ferroptosis and causes myocardial injury. p53 regulates iron transport also independently of its activity as a transcription factor. In hepatic stellate cells, p53 localizes to the mitochondria, where it binds to SLC25A28 and supports iron import into the mitochondria[34]. The overload of mitochondrial iron leads to ROS production and ferroptosis. p53 transcriptionally regulates polyamine metabolism by inducing the expression of spermidine/spermine N1-acetyltransferase 1 (*SAT1*)[35]. SAT1 expression suppresses tumour growth by activating ALOX15-mediated ferroptosis both in vitro and in vivo. *SAT1* knockout partially diminishes p53-triggered ferroptosis, thereby linking polyamine metabolism with p53-mediated ferroptosis and tumour suppression. Interestingly, *ALOX5*, a known p53 target gene[36], has been shown to promote ferroptosis in Huntington disease[37] and bladder cancer cells[38], suggesting that p53 induces ferroptosis in these conditions through the transcriptional activation of *ALOX5*.

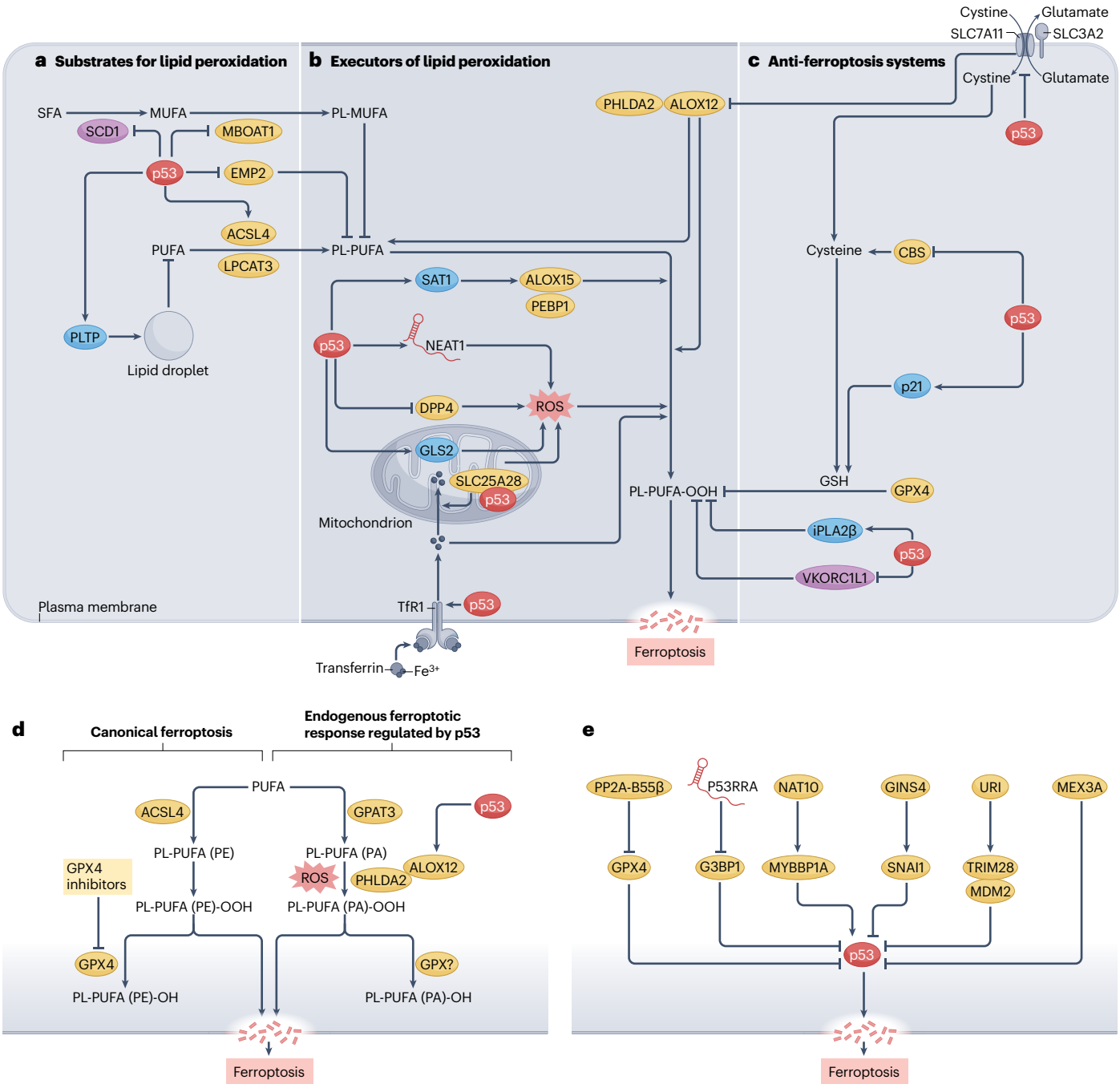
p53 influences ferroptosis also by regulating the cellular anti-ferroptosis systems (Fig. 1c). Beyond repressing SLC7A11, p53 can restrict serine and cysteine synthesis by inhibiting phosphoglycerate dehydrogenase (PHGDH) in melanoma cells and cystathionine β-synthase in lung cancer cells, respectively, which may ultimately lead to reduced GSH biosynthesis and to ferroptosis[39,40]. The reduced form of vitamin K is a metabolite with antioxidant activity and has been shown to inhibit ferroptosis[41]. p53 transcriptionally represses the expression of vitamin K epoxide reductase complex subunit 1 like 1 (VKORC1L1), an enzyme catalysing the reduction of vitamin K into vitamin K hydroquinone, to promote ferroptosis and suppress tumour

Box 2 | Mechanism of ferroptosis

Ferroptosis is an iron-dependent regulated cell death, which is triggered by lipid peroxidation at cell membranes[14]. The morphological features of ferroptotic cells include shrunken mitochondria, reduced mitochondrial cristae and increased mitochondrial-membrane density. Ferroptosis primarily results from disruptions in cellular metabolism and is modulated by three fundamental components: the substrates for lipid peroxidation, the executors of lipid peroxidation and the anti-ferroptosis systems[14,17,171,172]. The substrates for lipid peroxidation are polyunsaturated fatty acids (PUFAs), such as arachidonic acid (C20:4) and adrenic acid (C22:4), which are incorporated into cellular membrane phospholipids (PL). Enzymes such as acyl-CoA synthetase long chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) facilitate the assembly of PUFAs into membrane phospholipids. Metabolic processes that elevate PL-PUFA levels increase cellular sensitivity to ferroptosis.

Lipid peroxidation can occur through non-enzymatic Fenton reactions or through enzymatic pathways; both ways are iron-dependent. Many families of enzymes, including arachidonate lipoxygenase, cyclooxygenases and cytochrome p450 catalyse the peroxidation of PL-PUFA to PL-PUFA hydroperoxide (PL-PUFA-OOH). These lipid peroxides can propagate oxidative damage to nearby PL-PUFAs, amplifying the ferroptosis signal and leading to ferroptosis, or they can be detoxified by various anti-ferroptosis systems. Diverse metabolic enzymes can suppress ferroptosis through distinct mechanisms. Among them, glutathione peroxidase 4 (GPX4) is a well-characterized factor that utilizes glutathione to reduce PL-PUFA-OOH to PL-PUFA-OH, thereby protecting cells from ferroptosis[14]. GPX4 activity specifically counteracts ACSL4-mediated ferroptosis.

Ferroptosis-inducing compounds (FINs) are small molecules capable of inducing ferroptosis in vitro or in vivo through various mechanisms, primarily by inhibiting the activity of anti-ferroptosis systems. Some FINs inhibit GPX4 activity (for example, RSL3, ML162 and ML210), degrade GPX4 protein (for example, FIN56), or block cystine import by system X_C^- (for example, erastin and IKE). These compounds not only advance ferroptosis research, but also hold considerable therapeutic promise in triggering ferroptosis for cancer treatment[16].



growth in different cancer cell lines independently of the GSH system[42]. iPLA2β (also known as PLA2G6) removes the oxidized fatty acid chain from membrane phospholipids to terminate lipid peroxidation and ferroptosis. In contrast to p53-mediated promotion of ferroptosis, p53 activated by a low dose of doxorubicin (a DNA damaging drug) or nutlin (an inhibitor of the p53–MDM2 interaction), can suppress ferroptosis in melanoma and sarcoma cells by transcriptionally activating *PLA2G6*[43]. However, *PLA2G6* activation is lost when treating cells with a high dose of doxorubicin or following a long treatment with nutlin, and the cells die partly from ferroptosis.

These paradoxical results seem at odds with the ferroptosis-promoting role of p53. In fact, the regulation of iPLA2β fits well with the 'pro-survival or pro-death' mode of p53 activity: p53 is essentially a stress responder and a 'guardian of the cell'[1,44,45], and the outcome of p53 activation varies depending on the characteristics of the stress[46,47]. In the case of the p53–iPLA2β–ferroptosis axis, iPLA2β acts as a functional switch to dictate the consequence of the p53-elicited stress response. This dual role of p53 potentially circumvents some of the therapeutic concerns associated with inducing or suppressing cell death, as p53 can regulate the proper balance between cell survival and death.

Fig. 1 | p53-regulated ferroptosis. p53 regulates all three key components of ferroptosis through diverse mechanisms. **a**, Substrates for lipid peroxidation. Monounsaturated fatty acids (MUFAs) compete with polyunsaturated fatty acids (PUFAs) for incorporation into membrane phospholipids (PL). Ferroptosis is promoted by p53 reducing MUFA synthesis and incorporation into phospholipids by inhibiting the expression of stearoyl-CoA desaturase 1 (SCD1) in hepatocellular carcinoma cells and membrane bound O-acyltransferase domain containing 1 (MBOAT1) in diverse cell lines, respectively. Additionally, p53 promotes the synthesis of PUFA-containing phospholipids (PL-PUFAs) by downregulating the expression of epithelial membrane protein 2 (EMP2) in diverse cell lines and promoting the activity of acyl-CoA synthetase long chain family member 4 (ACSL4) in colon cancer cells. In liver cancer cells, p53 can suppress ferroptosis by activating phospholipid transfer protein (PLTP) and thus formation of lipid droplets, which sequester PUFAs. **b**, Executors of lipid peroxidation. Ferroptosis is promoted by p53 activation of arachidonate 12-lipoxygenase 12S type (ALOX12) and ALOX15 by suppressing solute carrier family 7 member 11 (SLC7A11) and by activating spermidine/spermine N1-acetyltransferase 1 (SAT1), respectively, in vitro and in vivo. p53 also increases the levels of reactive oxygen species (ROS) by transcriptionally activating glutaminase 2 (GLS2) and the long noncoding RNA (lncRNA) nuclear paraspeckle assembly transcript 1 (NEAT1) in hepatocellular carcinoma cells, and boosting the activity of SLC25A28 in hepatic stellate cells. Moreover, p53 induces the expression of transferrin receptor 1 (TfR1), which imports iron into the cell. p53 can suppress ferroptosis by inhibiting dipeptidyl peptidase 4 (DPP4) in colorectal cancer cells. **c**, Anti-ferroptosis systems. Ferroptosis is promoted by p53 repression of glutathione peroxidase 4 (GPX4) through downregulating SLC7A11 in vitro and in vivo in diverse cell types, and cystathionine β-synthase (CBS) in lung cancer cells. p53 also inhibits vitamin K epoxide reductase complex subunit 1 like 1 (VKORC1L1) in diverse cell types. p53 can suppress ferroptosis by activating p21 in fibrosarcoma cells and iPLA2β in melanoma and sarcoma cells. **d**, p53-regulated versus GPX4-regulated ferroptosis in vivo. GPX4 regulates canonical ferroptosis, which is enhanced by the treatment with ferroptosis-inducing compounds such as GPX4 inhibitors. By contrast, p53 modulates an endogenous ferroptosis response independently of ferroptosis-inducing treatment. This ferroptosis pathway involves PL-PUFA phosphatidic acid (PA), whose biosynthesis is catalysed by glycerol-3-phosphate acyltransferase 3 (GPAT3). In the presence of elevated ROS, p53 promotes ferroptosis through the pleckstrin homology like domain family A member 2 (PHLDA2)–ALOX12 complex, a process potentially terminated by an as-yet-unknown GPX family protein (GPX?). **e**, Regulation of p53-mediated ferroptosis. In hepatocellular carcinoma, protein phosphatase 2A-B55β subunit (PP2A-B55β) dephosphorylates mitochondrial GPX4, thereby facilitating the retrograde movement of mitochondrial p53 into the nucleus and ferroptosis induction. In lung cancer, the long noncoding RNA P53RRA promotes p53 accumulation in the nucleus by abrogating its cytoplasmic sequestration by G3BP stress granule assembly factor 1 (G3BP1), thereby activating ferroptosis. In cardiac ischaemia/reperfusion injury, *N*-acetyltransferase 10 (NAT10) increase the level of MYB binding protein 1a (MYBBP1A), which binds to p53 and enhances p53-induced ferroptosis. In lung adenocarcinoma, GINS complex subunit 4 (GINS4) destabilizes p53 by activating snail family transcriptional repressor 1 (SNAI1), thereby inhibiting ferroptosis. Additionally, unconventional prefoldin RPB5 interactor (URI) and mex-3 RNA binding family member A (MEX3A) promote p53 degradation to suppress ferroptosis in hepatocellular carcinoma and ovarian cancer, respectively. In panels **a**–**c**, direct transcriptional activation or repression targets of p53 are indicated in blue or light purple, respectively. GSH, glutathione; LPCAT3, lysophosphatidylcholine acyltransferase 3; PE, phosphatidylethanolamine; PEBP1, phosphatidylethanolamine binding protein 1; PL-PUFA-OOH, PL-PUFA hydroperoxide; SFA, saturated fatty acid.

In addition to upregulating iPLA2β, there are several sporadic reports showing that p53 can inhibit ferroptosis in certain conditions. For example, in colorectal cancer (CRC) cells, p53 binds to and sequesters dipeptidyl peptidase 4 (DPP4) in the nucleus, keeping it away from its interacting protein NADPH oxidase 1 (NOX1)[48] (Fig. 1b). This activity represses DPP4–NOX1-induced ferroptosis. In liver cancer cells, p53 negatively regulates ferroptosis by inducing the expression of phospholipid transfer protein (PLTP)[49]. PLTP stimulates the formation of lipid droplets, which sequester the substrate for ferroptosis-related lipid peroxidation (Fig. 1a). Another study has shown that p53 can delay the induction of cystine-deprivation-triggered ferroptosis by inducing p21 in a fibrosarcoma cell line, potentially protecting the cells from nutrient deprivation[50] (Fig. 1c). These counter-examples partly stem from the different cancer types and ferroptosis-inducing methods used in experiments[17]. They also reflect the complexity and context-dependency of p53 function[1,51].

The importance of p53-induced ferroptosis in tumour suppression has been corroborated by mouse models and human data. The p53-3KR (Lys-to-Arg) mutant protein retains the ability to suppress SLC7A11 and induce ferroptosis, which may explain why it still efficiently suppresses tumorigenesis[19]. Indeed, overexpression of SLC7A11 abolishes the ferroptosis-inducing and tumour-suppressing effect of the p53-3KR mutant. Acetylation of human p53 at Lys101 (corresponding to mouse Lys98) is crucial for p53-mediated SLC7A11 inhibition[52]. Further mutating p53-3KR to p53-4KR (3KR + K98R) significantly abrogates the ability of p53 to promote ferroptosis and tumour suppression. Consequently, p53-4KR mice develop tumours at a much higher rate compared with p53-3KR mice[53]. An African-specific SNP (p53-P47S) was found to be impaired in its ability to suppress tumorigenesis[54]. Subsequent studies have revealed that the S47 variant is less efficient at suppressing *SLC7A11* and activating *GLS2* compared with the P47 variant. p53-S47 cells have higher levels of two important antioxidants CoA and GSH[55]. These differences between P47 and S47 lead to a decreased ability of p53-S47 to induce ferroptosis and repress tumour growth. Indeed, the p53-P47S SNP is correlated with a higher risk of breast cancer in pre-menopausal African-American women[56].

Studying cancer-associated p53 mutants can provide more insights into how ferroptosis contributes to p53-mediated tumour suppression from a different angle. Mutant p53 may not only lose the ferroptosis-inducing activity of wild-type (WT) p53, but also gain new and often indirect functions that suppress ferroptosis, both of which facilitate tumour development. In lung cancer, *TP53* mutation abolishes the inhibition of forkhead box M1 (FOXM1)[57]. Increased FOXM1 confers cancer cells with resistance to ferroptosis. BTB and CNC homology 1 (BACH1) is a transcriptional repressor of SLC7A11. Interestingly, p53-R175H (a common, so-called 'hotspot', mutation that is equivalent to mouse p53-R172H), but not WT p53 and other p53 hotspot mutants, can bind to BACH1 (ref. 58). This interaction abrogates the repression of SLC7A11 by BACH1 and, therefore, reduces ferroptosis in different cancer cells. Knockout of *Bach1* in *Trp53*$^{R172H/+}$ mice extends the survival time of these mice, suggesting that BACH1-dependent ferroptosis inhibition contributes to the oncogenic effect of p53-R172H in mice. In triple-negative breast cancer (TNBC), mouse p53-R172H and p53-R245W (equivalent to human p53-R248W) protect cancer cells from ferroptosis by upregulating two antioxidant proteins, microsomal glutathione *S*-transferase 3 (MGST3) and peroxiredoxin 6 (PRDX6), in an NFE2 like bZIP transcription factor 2 (NRF2)-dependent manner[59]. Notably, depletion of either of these p53 mutants in established TNBC

results in tumour regression by activating ferroptosis, implying that eliminating mutant p53 may be an effective way to treat TNBC.

It is worth mentioning that, unlike the FIN-treatment-independent activity of p53 in promoting ferroptosis in vivo, activation of p53 alone is insufficient to trigger ferroptosis in vitro, which is likely to be due to the absence of in vivo stress signals in cultured cell lines[17]. Efficient induction of p53-mediated ferroptosis in vitro requires both p53 activation and treatment with FINs, such as GPX4 inhibitors or excessive ROS, which is consistent with the stress responder nature of p53. That is, p53 can fully execute its function only with a suitable stress[19,21,43]. This activity also aligns with the fact that tumorigenesis is accompanied by elevated ROS levels[60], and in this context the activation of p53 can more efficiently eradicate cancer cells (Fig. 1d). Unlike the p53-modulated ferroptosis pathway, GPX4-regulated ferroptosis primarily functions not in response to stress, but in a constitutive manner, to maintain cellular homeostasis[21,61,62]. GPX4-associated ferroptosis is enhanced by the application of FINs to suppress GPX4 activity both in vitro and in vivo (Fig. 1d). Therefore, to specifically focus on ferroptosis regulated by p53 without directly manipulating GPX4 activity, a ROS generator such as tert-butyl hydroperoxide can be used, as this type of ferroptosis primarily involves p53, but not GPX4 (refs. 19–21,43).

Regulation of p53-mediated ferroptosis

The regulation of p53 in ferroptosis is multi-faceted (Fig. 1e). Acetylation at p53 Lys351 stabilizes the protein in lung adenocarcinoma[63]. GINS complex subunit 4 (GINS4) antagonizes p53 Lys351 acetylation by activating snail family transcriptional repressor 1 (SNAI1), which destabilizes p53, thereby suppressing ferroptosis and promoting tumour progression[63]. Similarly, unconventional prefoldin RPB5 interactor (URI) and mex-3 RNA binding family member A (MEX3A) can also promote p53 degradation, which inhibits ferroptosis and accelerates tumour growth in hepatocellular carcinoma and in ovarian cancer, respectively[26,64]. In hepatocellular carcinoma, sorafenib treatment causes mitochondrial GPX4 dephosphorylation by protein phosphatase 2A-B55β subunit (PP2A-B55β), resulting in mitochondrial p53 retrograding into the nucleus and ferroptosis activation[65]. In lung cancer, the cytosolic p53-related lncRNA P53RRA binds to G3BP stress granule assembly factor 1 (G3BP1), which abrogates the sequestration of p53 protein in the cytosol[66]. The resulting augmented level of nuclear p53 stimulates ferroptosis and tumour suppression. In cardiac I/R injury, *N*-acetyltransferase 10 (NAT10) modifies and stabilizes the mRNA of MYB binding protein 1a (MYBBP1A), which increases MYBBP1A protein level[67]. MYBBP1A then binds to p53 and enhances p53-induced ferroptosis. Interestingly, p53 can transcriptionally activate NAT10 expression upon I/R stress. Therefore, the NAT10–MYBBP1A–p53 axis forms a positive feedback loop that amplifies ferroptosis in cardiac I/R injury. In addition, iron overload in dopaminergic cells, high glucose levels and interleukin-1β treatment in endothelial cells have been reported to induce p53-dependent ferroptosis[68,69].

p53-regulated necroptosis

Necroptosis was the first identified mode of regulated necrosis, which was formally named in 2005 (ref. 70) (Box 1). It was initially shown to be mediated by receptor interacting serine/threonine kinase 1 (RIPK1)[71], and later also by RIPK3 and mixed lineage kinase domain like pseudokinase (MLKL), independently of caspases[9]. Similarly to apoptosis, necroptosis can also be initiated by the activation of death receptors such as tumour necrosis factor receptor 1 (TNFR1), FAS (also known as TNFRSF6) and TRAIL receptor 1 (also known as TNFRSF10A). Nevertheless, necroptosis often occurs only when apoptosis is deficient. In such cases, RIPK1 is activated to interact with and activate RIPK3. Activated RIPK3 phosphorylates MLKL, which promotes its oligomerization and insertion into the cytoplasmic membrane, where it forms pores that lead to necroptotic cell death[9] (Fig. 2a). Additionally, other forms of necroptosis have been reported. Necroptosis mainly functions in inflammation, bacterial and viral infection, ischaemic injury and cancer.

Role of p53 in necroptosis

Given that necroptosis and apoptosis share many initiating factors, it could be reasoned that when apoptosis pathways are inhibited, p53 can switch to promoting necroptosis instead. Although this possibility requires more evidence to be proven, p53 is indeed a master regulator of necroptosis[72] (Fig. 2a). In cardiomyocytes from a mouse model of myocardial I/R injury, p53 transcriptionally induces the expression of the lncRNA necrosis-related factor (NRF)[73]. NRF functions as a competing endogenous RNA in titrating a microRNA, miR-873, thereby relieving its repression of RIPK1 and RIPK3 and promoting necroptosis and myocardial infarction. PUMA is a major target of p53 in inducing intrinsic apoptosis. Interestingly, PUMA also engages in necroptosis through a similar mechanism: in CRC cells, treatment with the chemotherapy drug 5-fluorouracil induces the p53–PUMA axis, which facilitates the release into the cytoplasm of mitochondrial DNA, thereby activating Z-DNA binding protein 1 (ZBP1)–RIPK3-mediated necroptosis[74]. Importantly, this PUMA–RIPK3-necroptosis axis can also invoke an antitumour immunogenic response that enhances the therapeutic effect of 5-fluorouracil. In intestinal epithelial cells, heat stress induces the phosphorylation and activation of p53, increasing the expression of Toll like receptor 3 (TLR3)[75]. TLR3 stimulates the binding between TIR domain containing adaptor-inducing interferon-β (TRIF) and RIPK3 to induce necroptosis. Consistently, *TP53* knockout can block necroptosis of intestinal epithelial cells that is triggered by heat stress.

Mitochondrial ROS (mtROS) have an important role in p53-mediated necroptosis[76–78] (Fig. 2a). In acute pancreatitis, p53 downregulates sulfiredoxin and peroxiredoxin 3 (PRDX3), which enhances the production of mtROS and necroptosis in pancreatic cells[79]. Moreover, mtROS also drives p53 translocation to mitochondria. The mitochondria-targeted antioxidant Mito-TEMPO blocks the mitochondrial accumulation of p53 and necroptosis, suggesting that (1) mtROS contribute to the occurrence of necroptosis and (2) mitochondrial p53 has a role in necroptosis. Both possibilities have been substantially supported. Consistent with the first possibility, mtROS promotes the formation of necrosomes — complexes that contain MLKL and RIPK3 (and RIPK1) — and the subsequent activation of necroptosis[80]. The TCA cycle and oxidative phosphorylation increase the production of mtROS, and RIPK3 can facilitate these processes to induce necroptosis[81,82]. The ability of p53 to promote the TCA cycle and oxidative phosphorylation may contribute to necroptosis induction[18]. Supporting the second possibility, mtROS stimulates the mitochondrial accumulation of p53, where it binds to cyclophilin D (CypD) and opens the mitochondrial permeability transition pore (PTP), leading to necrosis in diverse cell types[83] (Fig. 2a). This mitochondrial p53–CypD-induced necrosis is largely necroptosis[84]. The RIPK1–RIPK3 complex can drive the translocation of dynamin-related protein 1 (DRP1) to mitochondria, which enhances mtROS and necroptosis[85,86]. p53 also promotes DRP1 activity in mitochondria both directly and indirectly, which may subsequently bolster necroptosis in cardiomyocytes[87,88]. Interestingly, under oxidative stress, DRP1 boosts the stabilization and mitochondrial localization

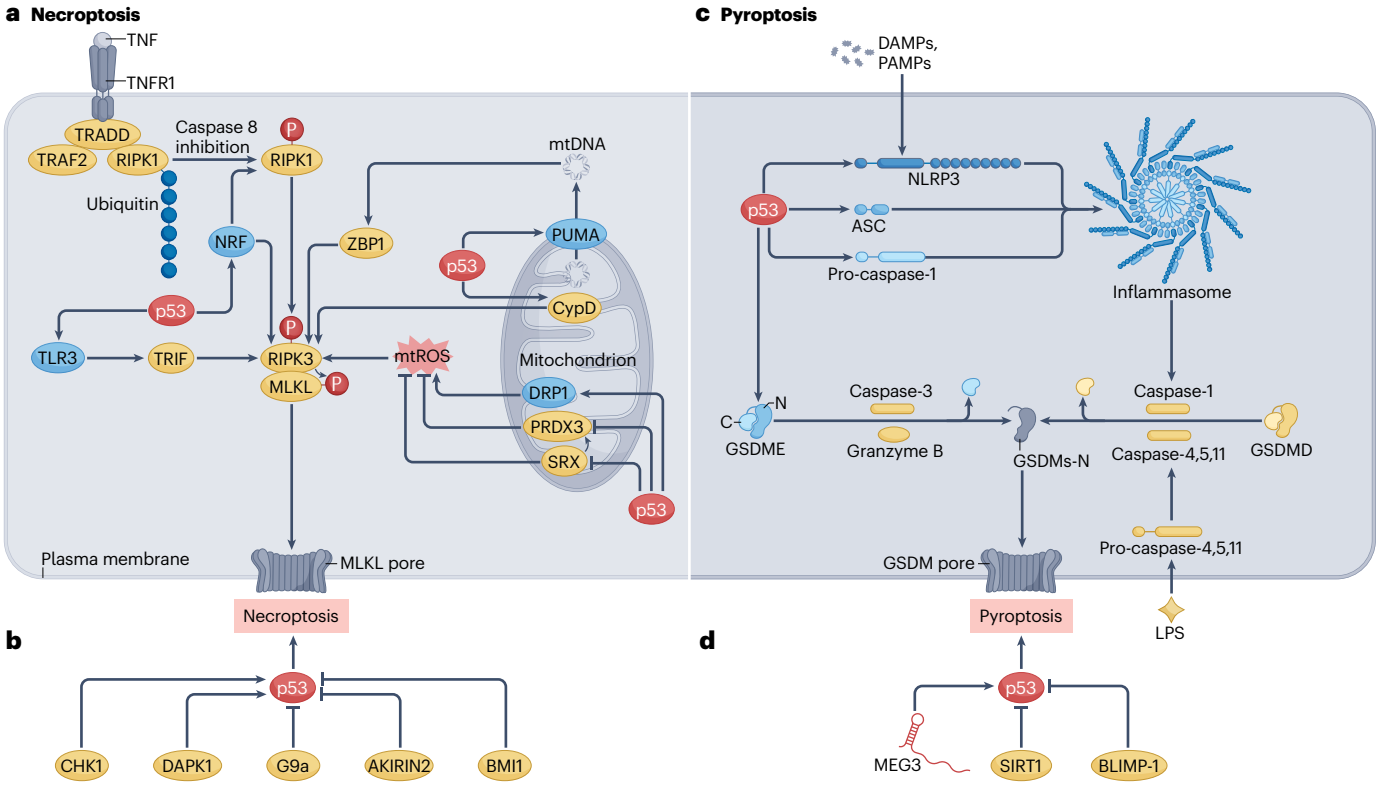


Fig. 2 | p53-regulated necroptosis and pyroptosis. a, Necroptosis. p53 indirectly activates receptor interacting serine/threonine kinase 1 (RIPK1) and RIPK3 by transcriptionally activating necrosis-related factor (NRF) in cardiomyocytes; it also increases the expression of Toll like receptor 3 (TLR3) in intestinal epithelial cells, thereby activating the TIR domain containing adaptor-inducing interferon-β (TRIF)–RIPK3 axis. In colorectal cancer cells, p53 activates p53 upregulated modulator of apoptosis (PUMA) to release mitochondrial DNA (mtDNA) into the cytosol, thereby activating the Z-DNA binding protein 1 (ZBP1)–RIPK3 axis. Activated RIPK3 then phosphorylates mixed lineage kinase domain like pseudokinase (MLKL) to form pores in the cytoplasmic membrane, leading to necroptosis. In addition, p53 can promote the production of mitochondrial reactive oxygen species (mtROS) by activating dynamin-related protein 1 (DRP1) in cardiomyocytes or by inhibiting sulfiredoxin (SRX) and peroxiredoxin 3 (PRDX3) in pancreatic cells. p53 also translocates to mitochondria, where it activates cyclophilin D (CypD) in diverse cell types. Both mtROS production and CypD activation can result in necroptosis. **b**, Regulation of p53-mediated necroptosis. In hepatocellular carcinoma, checkpoint kinase 1 (CHK1) activates p53 to induce necroptosis. During neuronal ischaemic stress, death associated protein kinase 1 (DAPK1) phosphorylates p53 in cortical neurons, resulting in p53-triggered necroptosis. G9a, AKIRIN2 and BMI1 polycomb ring finger oncogene (BMI1) suppress necroptosis by inhibiting p53 in breast cancer cells, cortical neurons and cone cells, respectively. **c**, Pyroptosis. p53 upregulates the expression of inflammasome components NLR family pyrin domain containing 3 (NLRP3) and pro-caspase-1 in diverse cell types, and ASC in non-small-cell lung cancer (NSCLC) cells. The inflammasome activates caspase-1 and facilitates the processing of gasdermin D (GSDMD). GSDMD cleavage releases its active N-terminal domain (N), which forms pores in the cytoplasmic membrane, causing pyroptosis. Additionally, p53 transcriptionally activates GSDME to promote pyroptosis in diverse cell types. p53 is also required for lipopolysaccharide (LPS)-triggered pyroptosis in NSCLC cells. **d**, Regulation of p53-mediated pyroptosis. In clear cell renal cell carcinoma, the long noncoding RNA maternally expressed 3 (MEG3) stabilizes p53 to promote pyroptosis. Conversely, sirtuin 1 (SIRT1) suppresses pyroptosis by inhibiting p53 in macrophages and liver cells. Similarly, B lymphocyte-induced maturation protein 1 (BLIMP1) represses p53, leading to reduced pyroptosis in *Leishmania donovani*-infected THP-1 and J774A.1 cell lines. In panels **a** and **c**, direct transcriptional activation targets of p53 are indicated in blue. DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; TNFR1, tumour necrosis factor receptor 1.

of p53 (ref. 89). Hence, p53 and DRP1 may form a positive feedback loop to enhance necroptosis.

In certain conditions, the autophagy machinery associates with the necrosome to promote necroptosis[90]. Mitophagy is a special type of autophagy that degrades damaged mitochondria. Theoretically, mitophagy can protect cells from necroptosis by reducing ROS levels. However, controversial results have been reported regarding the role of mitophagy in necroptosis[86,91,92]. As p53 can have a bidirectional — either promoting or inhibitory — effect on autophagy (including mitophagy)[18], whether and how p53 affects necroptosis through mediating autophagy requires further clarification. Additionally, p53 can be activated by metabolic stress and hypoxia[18], which also stimulate necroptosis[93,94]. Whether p53 has a role in metabolic-stress-associated and hypoxia-associated necroptosis remains elusive. Furthermore, it remains to be investigated whether p53 can inhibit necroptosis in specific conditions.

Regulation of p53-mediated necroptosis

Many factors can influence p53-mediated necroptosis (Fig. 2b). In cells of recurrent breast cancer, the activity of the histone methyltransferase G9a is required to suppress pro-inflammatory genes[95]. G9a ablation activates TNF-induced necroptosis that is dependent on p53 activity and

reduces the survival of tumour cells. Treatment of hepatocellular carcinoma with the chemotherapy drug actinomycin D stimulates necroptosis partly through checkpoint kinase 1 (CHK1)-activated p53, which underlies the antitumour effect of actinomycin D[96]. In cortical neurons, postnatal knockout of *Akirin2* triggers p53-dependent necroptosis and neurodegeneration, which can be rescued by reducing p53 protein levels[97]. Analogously, p53-induced necroptosis contributes to retinal degenerative disease by removing cone photoreceptors and bipolar neurons, which is repressed by BMI1 polycomb ring finger oncogene (BMI1)[98]. During neuronal ischaemic stress, death associated protein kinase 1 (DAPK1) interacts with and phosphorylates p53 Ser23 in cortical neurons[99]. This modification facilitates both nuclear-p53-activated apoptosis and mitochondrial-p53-triggered necroptosis[78,83], together causing neuronal injury.

p53-regulated pyroptosis

Pyroptosis was reported late in the twentieth century and was termed in 2001 (ref. 100) (Box 1). Pyroptosis is a pro-inflammatory form of NACD regulated by gasdermin proteins. It primarily functions as an innate immunity response to diverse types of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), and also has roles in organ injury and cancer[101]. Canonical pyroptosis is initiated by the recognition of PAMPs or DAMPs by inflammasome sensors such as NLR family pyrin domain containing 3 (NLRP3) (Fig. 2c). NLRP3 then recruits the adaptor ASC (also known as PYCARD) and pro-caspase-1 to form the inflammasome, in which caspase-1 is activated. Alternatively, lipopolysaccharide (LPS) can directly activate caspase-4 and caspase-5 in humans, or caspase-11 in mice without inflammasome assembly. Activated caspase-1, caspase-4, caspase-5 or caspase-11 cleave gasdermin D (GSDMD) to release its active N terminus (GSDMD-N), which oligomerizes and forms pores in the cytoplasmic membrane, eventually inducing cell death (Fig. 2c). Recent progress indicates that alternative pathways of pyroptosis activation exist[101].

Role of p53 in pyroptosis

The role of p53 in pyroptosis is less clear than its roles in ferroptosis and necroptosis (Fig. 2c). p53 has been discovered to activate the expression of several pyroptosis regulators, such as NLRP3, caspase-1 and GSDME in diverse cell types[102–104], which may promote pyroptosis. Consistent with these data, p53 was reported to promote pyroptosis in non-small-cell lung cancer[105]. The mRNA level of p53 positively correlated with those of NLRP3, ASC and caspase-1, and depletion of p53 abolished LPS-induced pyroptosis[105]. In another study, actinomycin D and nutlin-3a were used to synergistically activate p53, leading to upregulation of pro-caspase-1 and NLRP1 (ref. 106). However, no activated caspase-1 was detected, which could be explained by the possibility that activated p53 establishes a primed state for pyroptosis by increasing the levels of pyroptosis factors; pyroptosis would then be readily induced in response to a suitable trigger. This process may help cells prepare to respond to infections, and thus it could be relevant to study how p53 responds to pathogenic infection and inflammation. Interestingly, NLRP3 could stabilize and activate p53 (refs. 107,108). These results indicate that p53 and NLRP3 regulate each other in a positive feedback loop, potentially enhancing NLRP3-induced pyroptosis. Treatment of glioblastoma multiforme with benzimidazoles has a tumour-suppressive effect through activation of p53 followed by concurrent apoptosis and pyroptosis, this is likely to be because p53-mediated cell-cycle arrest facilitates benzimidazole-triggered pyroptosis[109]. However, the underlying mechanism requires further elucidation. The potential for p53 to suppress pyroptosis in certain conditions also warrants investigation.

Regulation of p53-mediated pyroptosis

Several regulators of p53 have been shown to influence p53-mediated pyroptosis (Fig. 2d). In macrophages, MUFAs can bind to fatty acid binding protein 4 (FABP4) and restrict the activity of the lysine deacetylase sirtuin 1, resulting in p53 acetylation and activation[110]. Activated p53 then promotes inflammasome assembly and pyroptosis by increasing the expression of ASC. Similarly, in an LPS–D-galactosamine-caused acute liver failure mouse model, sirtuin 1 inhibits both p53-induced ferroptosis and pyroptosis through the sirtuin 1–p53–GPX4–GSDMD pathway[111]. This study also reveals the crosstalk between p53-triggered ferroptosis and p53-triggered pyroptosis. The lncRNA maternally expressed 3 (MEG3) is able to stabilize p53 (ref. 112). In clear cell renal cell carcinoma, MEG3 is downregulated, leading to decreased p53 level, repressed p53-associated pyroptosis and increased cell proliferation[113]. A p53 aggregation inhibitor, ReACp53, rescues the phenotypes caused by MEG3 depletion, suggesting that triggering pyroptosis may be an effective way to treat tumours with aggregated p53. Of note, by activating p53, MEG3 can also promote ferroptosis[114].

In *Leishmania donovani*-infected THP-1 and J774A.1 cell lines, B lymphocyte-induced maturation protein 1 (BLIMP1) is responsible for repressing p53 expression, reducing ROS production and NLRP3 activation, and repressing pyroptosis[115] (Fig. 2d). These results explain how *L. donovani* avoids innate immunity and pyroptosis during infection, informing the development of treatments for visceral leishmaniasis. In an asthma mouse model, depletion of kinesin family member 23 (KIF23) suppresses inflammation and pyroptosis in bronchial epithelial cells, thereby alleviating asthma symptoms[116]. Interestingly, p53 level is reduced along with KIF23 depletion. Whether the decrease in p53 level contributes to pyroptosis repression requires more investigation. Finally, KIF23 is a repressed transcriptional target of p53 (ref. 117). The pathological relevance of the p53–KIF23 negative feedback loop is worthy of additional study.

Other modes of p53-regulated non-apoptotic cell death

Besides ferroptosis, necroptosis and pyroptosis, p53 is involved in other NACDs, such as autophagy-dependent cell death, entotic cell death, parthanatos and paraptosis (Fig. 3), and may regulate PANoptosis, cuproptosis and disulfidptosis.

p53-regulated autophagy-dependent cell death

Autophagy is a conserved catabolic process that degrades cytoplasmic materials for reuse. Autophagy begins with an isolated membrane, which gradually expands to form a phagophore, and finally forms an autophagosome. During this process, autophagy cargos are encapsulated and then delivered to lysosomes for degradation. Generally, autophagy promotes cell survival under stress (particularly nutrient starvation). However, dysregulated or excessive autophagy can result in the demise of a cell through autophagy-dependent cell death[7,8,118] (Fig. 3a).

As p53 regulates autophagy through multiple mechanisms[18], it is also involved in autophagy-dependent cell death. When HCT116 cells are treated with an inhibitor of sphingosine kinase 1 (SPHK1), p53 activates autophagy-dependent cell death, which is rescued by the depletion of two crucial regulators of autophagy, beclin 1 and autophagy related 5 (ref. 119). p53 also induces autophagy-dependent cell death in colon cancer cells by activating BCL2 interacting protein 3 like (BNIP3L)-triggered

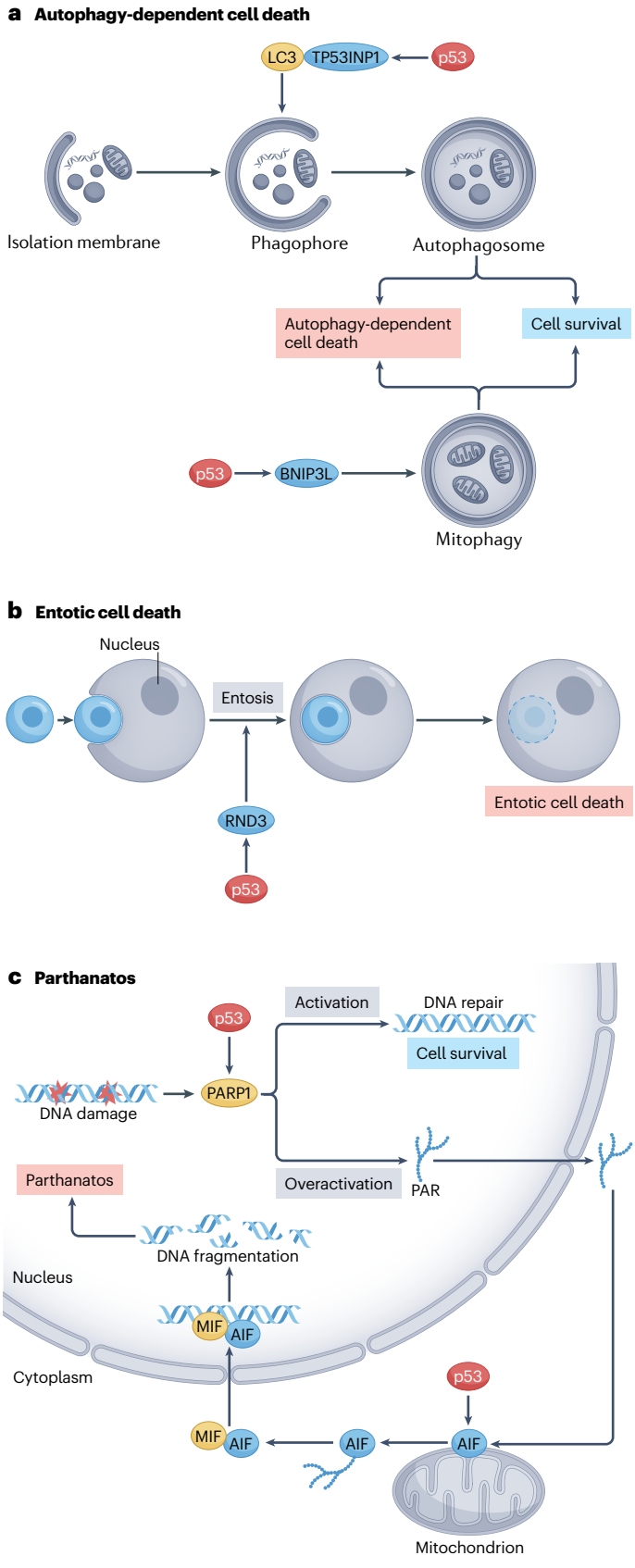


Fig. 3 | Other modes of p53-regulated non-apoptotic cell death. a, Autophagy-dependent cell death. p53 transcriptionally activates BCL2 interacting protein 3 like (BNIP3L), which can induce mitophagy and trigger autophagy-dependent cell death in colon cancer cells. p53 also activates the expression of tumour protein p53 inducible nuclear protein 1 (TP53INP1) in diverse cell types. TP53INP1 promotes autophagy-dependent cell death by interacting with microtubule-associated protein 1 light chain 3 (LC3). **b**, Entotic cell death. p53 transactivates Rho-family GTPase 3 (RND3) in mitotic epithelial cells, thereby facilitating the clearance of aneuploid cells through entotic cell death. **c**, Parthanatos. p53 activates poly(ADP-ribose) polymerase 1 (PARP1) to generate poly(ADP-ribose) (PAR) polymers, thereby facilitating the release of apoptosis-inducing factor (AIF) from mitochondria. In the cytoplasm, AIF binds to macrophage migration inhibitory factor (MIF), thus forming a complex that translocates into the nucleus to cleave genomic DNA into large fragments, resulting in parthanatos in human colorectal and breast cancer cells, and in mouse embryonic fibroblasts. p53 may also promote parthanatos by transcriptionally inducing AIF expression. Direct transcriptional activation targets of p53 are indicated in blue.

mitophagy[120] (Fig. 3a). p53 may promote autophagy-dependent cell death by transcriptionally activating tumour protein p53 inducible nuclear protein 1 (TP53INP1) in diverse cell types[121]. The antitumour drugs ginsenoside Rh4 and resveratrol activate p53 and induce autophagy-dependent cell death in colorectal cancer cells and in lung adenocarcinoma cells, respectively[122,123]. It should be emphasized that autophagy-mediated cell death is not necessarily 'autophagy-dependent cell death', it may involve other cell death modalities, such as apoptosis[118] and ferroptosis[124,125]. Hence, it is crucial to distinguish which type of cell death is occurring when p53-regulated autophagy contributes to cell demise.

p53-regulated entotic cell death

Entosis is a process in which a viable cell is engulfed by a non-phagocytic cell, forming a cell-in-cell structure. Cytoskeleton-rearrangement-mediated cell invasion has a vital role in entosis. Usually (but not always), the internalized cell will die by entotic cell death[7,8] (Fig. 3b).

In mitotic epithelial cells with DNA damage, p53 promotes entotic cell death by activating Rho-family GTPase 3 (RND3)[126,127] (Fig. 3b). This action eliminates aneuploid daughter cells to maintain genome integrity. Interestingly, mutant p53 was also reported to promote the morphological feature of entosis — the cell-in-cell structure — which can be pro-tumorigenic because the internalized cell may somehow evade cell death[128]. In addition, p53-driven entotic cell death of cortical progenitor cells is related to PALS1-associated microcephaly[129].

p53-regulated parthanatos

Following mild DNA damage, poly(ADP-ribose) polymerase 1 (PARP1) is activated to repair the DNA and promote cell survival. However, when DNA damage is widespread, PARP1 is overactivated and generates excessive poly(ADP-ribose) (PAR) polymers, which facilitate the release of apoptosis-inducing factor (AIF) from mitochondria. In the cytoplasm, AIF binds to macrophage migration inhibitory factor (MIF), and the AIF–MIF complex translocates into the nucleus to cleave genomic DNA into large fragments, leading to parthanatos[7,8] (Fig. 3c).

In both human CRC and breast cancer cells, and in mouse embryonic fibroblasts, p53 can activate parthanatos in response to ROS-induced DNA damage by promoting the enzymatic activity of PARP1 (ref. 130) (Fig. 3c). In CRC, when the kinase AKT is inhibited, p53 also activates parthanatos by directly interacting with PARP1 to facilitate the polymerization of PAR, which impedes the growth of CRC cells[131]. In addition, p53 may promote parthanatos by

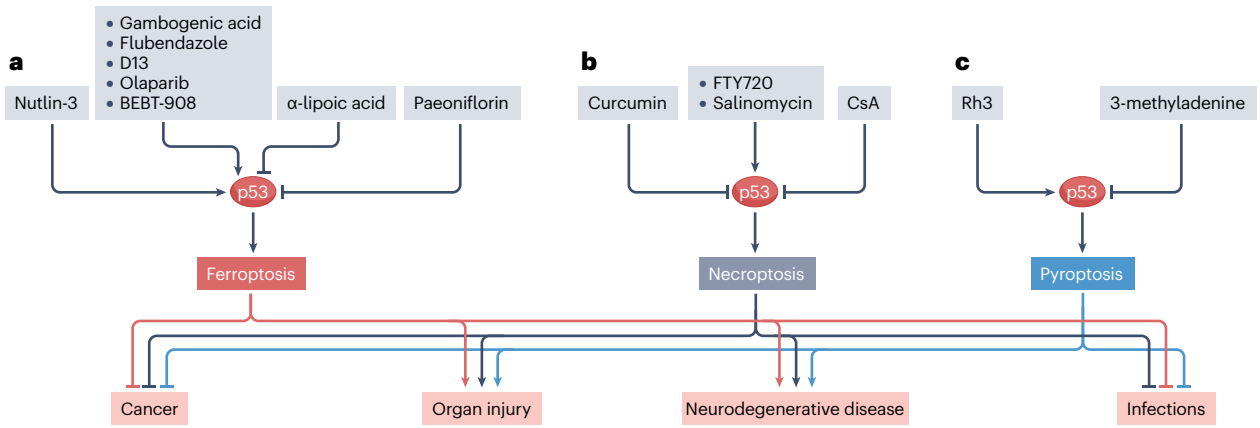


Fig. 4 | Targeting p53-regulated non-apoptotic cell death for disease treatment. Numerous drugs have been developed that target p53-mediated non-apoptotic cell death pathways for the treatment of various diseases, including cancer, organ injury, neurodegenerative disease and infections. **a**, Targeting p53-regulated ferroptosis. Gambogenic acid, flubendazole, D13, olaparib and BEBT-908 exhibit antitumour effects by activating p53-mediated ferroptosis in melanoma, castration-resistant prostate cancer, multidrug-resistant cancer cells, ovarian cancer, and diverse cancer cell lines, respectively. In hepatocytes, nutlin-3 can activate p53-driven ferroptosis to block liver stage *Plasmodium* spp. infection. In folic-acid-induced acute kidney injury, α-lipoic acid mitigates renal damage by inhibiting p53-mediated ferroptosis. In an Alzheimer disease mouse model, paeoniflorin represses p53-mediated ferroptosis, thereby improving cognitive behaviours. **b**, Targeting p53-regulated necroptosis. FTY720 and salinomycin suppress tumour growth by triggering p53-mediated necroptosis in glioblastoma and glioma, respectively. In hepatocytes, curcumin improves alcoholic liver disease through inhibiting p53-modulated necroptosis. Cyclosporin A (CsA) holds potential for treating neurodegenerative diseases by suppressing p53-induced necroptosis. **c**, Targeting p53-regulated pyroptosis. In colorectal cancer cells, ginsenoside Rh3 activates p53-mediated pyroptosis, thereby inhibiting the growth of cancer cells. In proximal tubular cells, 3-methyladenine protects against hyperuricemic nephropathy by mitigating p53-induced pyroptosis.

transcriptionally activating AIF[132] (Fig. 3c). However, there is a report showing that, in the presence of the *BRAF* V600E mutation, *TP53* loss sensitizes tumour cells to parthanatos induced by an inhibitor of E26 transformation-specific (ETS)[133]. Therefore, whether p53 is activated or inhibited in parthanatos-triggered tumour suppression is likely to be context-dependent.

p53-regulated paraptosis

Paraptosis is a caspase-independent NACD that can be induced by many chemical compounds and various stresses, such as oxidative stress and endoplasmic reticulum stress. The details of molecular mechanism underlying paraptosis are still elusive. Key morphological features of paraptosis include cytoplasmic vacuolization that are usually associated with the swelling of the endoplasmic reticulum and/or of mitochondria[134].

In CRC cells, ginsenoside Rh2 treatment induces both p53-dependent apoptosis and paraptosis, together achieving an anti-tumour effect[135]. Nevertheless, the exact mechanism of p53-induced vacuole formation and paraptosis is still unknown.

Potential role of p53 in regulating PANoptosis, cuproptosis and disulfidptosis

PANoptosis is an innate immunity inflammatory type of cell death, which involves crosstalk between pyroptosis, apoptosis and necroptosis (hence PAN). As such, it has characteristics of all three cell death modalities, but it cannot be explained by any of them alone. The molecular mechanism of PANoptosis revolves around the formation of diverse PANoptosomes, which are platforms that integrate pyroptosis, apoptosis and necroptosis signals[136]. As p53 is a potent regulator of all three, it is reasonable to speculate that p53 can also modulate PANoptosis[137].

Cuproptosis is a copper-dependent NACD. Aberrant increase in cellular copper levels promotes the aggregation of lipoylated proteins, particularly dihydrolipoamide *S*-acetyltransferase (DLAT), in the TCA cycle, resulting in proteotoxic stress and eventually cuproptotic cell death[138,139]. Although direct evidence is lacking, p53 is thought to have an important role in modulating cuproptosis[140].

Disulfidptosis is a form of NACD triggered by excessive disulfides under glucose starvation in cells with high SLC7A11 expression[141,142]. p53 may enhance cellular resistance to disulfidptosis by inhibiting SLC7A11 expression. In p53-deficient cancer cells, elevated SLC7A11 levels may sensitize cells to disulfidptosis, presenting a potential therapeutic vulnerability for treating these cancers.

Targeting p53-regulated non-apoptotic cell death for disease treatment

As p53-mediated NACD is associated with the pathology of diverse disorders, considerable efforts have been devoted to developing therapeutic agents that target p53-NACDs. In this section, we use p53-regulated ferroptosis, necroptosis and pyroptosis as examples to demonstrate how this approach holds great potential for clinical use (Fig. 4).

Targeting p53-regulated ferroptosis

Cancer is the most relevant disease for targeting ferroptosis (Fig. 4a). Many drugs have been found to elicit p53-mediated ferroptosis to kill cancer cells. For instance, gambogenic acid suppresses melanoma metastasis by activating p53 to trigger ferroptosis in cells undergoing epithelial-to-mesenchymal transition[143]. Flubendazole, an antiparasitic drug, effectively suppresses tumour growth in castration-resistant prostate cancer by activating p53 to simultaneously induce ferroptosis and cell-cycle arrest[144]. D13, a triterpenoid saponin derivative, exhibits strong efficacy in killing multidrug-resistant cancer cells by

activating p53-regulated ferroptosis and apoptosis[145]. p53-activated ferroptosis can also be used to treat cancer in combination with other drugs. PARP inhibition is less effective in treating ovarian cancer that retains WT *BRCA1* and *BRCA2* genes. Interestingly, a study found that olaparib, a PARP inhibitor, induces ferroptosis in *BRCA*-proficient ovarian cancer by activating p53 (ref. 146). Co-treatment of olaparib with FINs has a synergistic effect in eliminating these cancer cells. A dual phosphoinositide 3-kinase (PI3K) and histone deacetylase (HDAC) inhibitor, BEBT-908, can hyperacetylate p53 to promote ferroptosis[147]. Importantly, ferroptosis induction may establish a pro-inflammatory tumour microenvironment that boosts immunotherapy. However, ferroptosis in pathologically activated neutrophils can negatively regulate antitumour immunity[61]. Therefore, it is crucial to achieve cancer-cell-specific delivery of p53-activating drugs in clinical practice. Additionally, ferroptosis underlies the antitumour effect of p53 in radiotherapy[148]. Cancer cells expressing mutant p53 may be resistant to radiotherapy owing to the loss of p53-elicited ferroptosis, and thus FINs can be used in combination with radiotherapy to treat these cancers.

Other than cancer, activating p53-regulated ferroptosis by nutlin-3 is beneficial for blocking the liver stage infection of *Plasmodium* parasites[149,150] (Fig. 4a).

Whereas p53-mediated ferroptosis confers health benefits in the aforementioned contexts, its aberrant induction in normal cells may lead to organ injury or neurodegenerative diseases (Fig. 4a). In these cases, ferroptosis should be avoided. In folic-acid-induced acute kidney injury, supplementation with α-lipoic acid effectively inhibits p53-mediated ferroptosis, thereby mitigating renal damage[151]. In a mouse model of Alzheimer disease, administration of paeoniflorin fosters the improvement of cognitive behaviours by directly binding to p53 and suppressing ferroptosis[152].

It is important to point out that most of the above-mentioned drugs invoking p53-mediated ferroptosis function through the repression by p53 of the canonical SLC7A11–GPX4 pathway. However, as we have discussed, non-canonical ferroptosis pathways have vital roles in p53 function. Thus, attention should be paid also to these non-canonical ferroptosis pathways regulated by p53 and their therapeutic potential.

Targeting p53-regulated necroptosis

Necroptosis can have both tumour-suppressive and tumour-promoting effects[76]. However, recent studies have suggested that p53-mediated necroptosis is primarily tumour-suppressive. It is possible that p53-activated necroptosis cooperates with other functions of p53 to eliminate cancer cells (Fig. 4b). In glioblastoma, the immunomodulating drug FTY720 suppresses tumour growth by inducing necroptosis through a ROS–c-Jun N-terminal kinase (JNK)–p53 pathway[153]. In glioma, salinomycin mediates the translocation of p53 to mitochondria, where it interacts with CypD and induces mitochondrial-PTP-associated necroptosis[84].

In human T cell leukaemia virus type 1-transformed adult T cell leukaemia cells, the dihydroorotate dehydrogenase inhibitor BAY2402234 shows therapeutic value by inducing various cell death modes, including apoptosis, ferroptosis and necroptosis[154]. Intriguingly, p53 is also activated upon BAY2402234 treatment. Whether p53 contributes to BAY2402234-triggered necroptosis requires further investigation. To treat neuroblastoma, activation of p53 may be a promising approach[155]. It was also suggested that the induction of necroptosis can have a newly identified treatment effect in neuroblastoma[155]. Hence, it would be interesting to investigate whether evoking p53-regulated necroptosis can efficiently eradicate neuroblastoma cells.

Like p53-activated ferroptosis, p53-induced necroptosis can cause damage to normal organs (Fig. 4b). For instance, p53 promotes necroptosis that aggravates alcoholic liver disease[156]. Curcumin improves alcoholic liver disease by increasing the expression of NRF2, which impedes the activity of p53. Necroptosis induced by CypD is related to various brain diseases, such as neurodegenerative diseases. Cyclosporin A (CsA) and other ligands can disrupt the CypD–p53 complex[157]. These inhibitors of mitochondrial CypD–p53 interaction may be useful in treating diseases caused by the CypD–p53–necroptosis axis.

Targeting p53-regulated pyroptosis

In CRC, ginsenoside Rh3 simultaneously activates pyroptosis and ferroptosis through the signal transducer and activator of transcription 3 (STAT3)–p53–NRF2 pathway, inhibiting the growth of cancer cells[158] (Fig. 4c). p53-activated autophagy contributes to pyroptosis, which may result in hyperuricemic nephropathy[159]. The autophagy inhibitor 3-methyladenine can effectively protect the kidney from pyroptosis and ameliorate hyperuricemic nephropathy in proximal tubular cells (Fig. 4c). Following *Escherichia coli* infection, p53-induced cell-cycle arrest and apoptosis may lead to pyroptosis in bovine mammary epithelial cells[160]. Specific inhibitors targeting p53 or pyroptosis may hold therapeutic potential in preventing *E. coli*-induced bovine mastitis. Curaxin CBL0137 is a p53-activating drug. CBL0137 induces caspase-3–GSDME-dependent pyroptosis that kills ovarian cancer cells[161]. This effect depends on the accumulation of BAX, a p53 target gene, at the mitochondrial membrane. It is probable that the p53–BAX axis partly underlies pyroptosis caused by CBL0137 treatment.

In summary, currently diverse therapeutics exist that target p53-mediated NACDs in different pathological conditions. It is hopeful that in the future, more drugs with this activity will benefit individuals suffering from related diseases.

Conclusions and future perspectives

Over the past years, numerous insights have been gained into the mechanisms, regulation and therapeutic implications of p53-regulated ferroptosis, necroptosis, pyroptosis and other NACDs. Nevertheless, there are still many questions to address, a few of which we discuss below.

Conceptually, why does p53 regulate so many cell death pathways? One possibility is that, as the guardian of the cell, p53 must efficiently eliminate damaged cells and induction of different types of cell death can ensure the accomplishment of this mission. The role of p53 in ferroptosis has been intensively studied. However, our understanding of the mechanisms of p53 function in other NACDs and their physiological or pathological relevance is still rather preliminary. More efforts are required to elucidate these issues. An intriguing point is that many p53-repressed targets, such as SLC7A11 (ref. 19), VKORC1L1 (ref. 42) and PHGDH[39], substantially contribute to p53-modulated NACD. Research has focused on the activated targets of p53, and more attention should be given to the repressed targets in NACD[1]. It is important to note that many targets influenced by p53 in NACDs are not direct p53 transcriptional targets.

Mechanistically, a major endeavour is to identify specific factors that dictate the specific NACD type(s) that p53 activates in different conditions. Stresses and other upstream signals have crucial roles in this process. However, some stresses (such as DNA damage and ROS) and signalling pathways (such as TNF and TLR pathways) can affect distinct cell death modes. A pertinent issue is that certain regulatory effects of p53 on NACDs exhibit cell-type-specificity or tissue-specificity[162]. Distinct

stresses and signals in cooperation with other cell-type-specific or tissue-specific regulators, converge on p53 to promote specific NACD(s) in a context-dependent manner. For example, in response to acute stresses such as DNA damage or ROS, p53 can induce both apoptosis and ferroptosis to remove stressed cells. The question about which cell death pathway predominates under these stress conditions is indeed a complex one that warrants further investigation. It seems that p53 is particularly adept at inducing ferroptosis in response to oxidative stress, as seen with tert-butyl hydroperoxide treatment in cultured cancer cells, where p53-regulated ferroptosis may precede apoptosis temporally[20,21,43]. Besides apoptosis and ferroptosis, which have been relatively well-studied, do some PTMs or cofactors of p53 specifically affect certain types of cell death? Defining the regulatory mechanisms and context-dependency of p53-mediated NACD is a prerequisite for developing therapeutic agents targeting these pathways.

Recent research has demonstrated that distinct cell death pathways can interact with one another[163–165]. Given that p53-regulated cell death pathways may share common upstream triggers or overlapping molecular mechanisms, crosstalk among these pathways is likely. Further exploration of this possibility will be of substantial importance in the future.

Therapeutically, targeting p53–NACD pathways not only supplements existing clinical treatments, such as apoptosis-inducing drugs in cancer therapy, but also holds unique advantages in some specific situations. It is worth noting that most of the aforementioned therapeutic agents target cancer cells that are expressing unmutated p53. However, these cancer cells often use multiple mechanisms to attenuate WT p53 activity[166], posing challenges to achieving optimal p53 activation. More importantly, *TP53* is frequently mutated or deleted in cancers[1]. Developing therapies targeting p53–NACD in these conditions is of invaluable importance. Unfortunately, current strategies to restore WT p53 activity in such cancer cells are not yet fully satisfactory[1–3]. Combination therapies provide a promising avenue to overcome these obstacles[1,146–148,167]. In addition, p53–NACD pathways only partially contribute to the therapeutic effects of the majority of the targeting agents mentioned above. These agents also influence other functions of p53 or even involve p53-independent mechanisms. Therefore, a crucial goal remains to specifically target p53–NACD axes.

Ferroptosis, necroptosis, pyroptosis and PANoptosis are often considered forms of immunogenic cell death, a process in which cell death can stimulate an immune response. In recent years, modulating immunity has emerged as a p53 function[1,168]. Determining whether p53-regulated immunogenic cell death can contribute to local or systemic immune responses is crucial, as it may have important implications for cancer therapy, including the potential combination of p53 activation with immunotherapy[169].

It will not be a surprise if p53 is found to regulate other NACDs in the future. Much work will be required to fully understand the p53–NACD connection and leverage the power of p53 in these cell death modalities for disease treatment.

Published online: 09 April 2025

References

1. Liu, Y. Q., Su, Z. Y., Tavana, O. & Gu, W. Understanding the complexity of p53 in a new era of tumor suppression. *Cancer Cell* **42**, 946–967 (2024).
2. Hassin, O. & Oren, M. Drugging p53 in cancer: one protein, many targets. *Nat. Rev. Drug Discov.* **22**, 127–144 (2023).
3. Tuval, A., Strandgren, C., Heldin, A., Palomar-Siles, M. & Wiman, K. G. Pharmacological reactivation of p53 in the era of precision anticancer medicine. *Nat. Rev. Clin. Oncol.* **21**, 106–120 (2024).
4. Brady, C. A. et al. Distinct p53 transcriptional programs dictate acute DNA-damage responses and tumor suppression. *Cell* **145**, 571–583 (2011).
5. Li, T. Y. et al. Tumor suppression in the absence of p53-mediated cell-cycle arrest, apoptosis, and senescence. *Cell* **149**, 1269–1283 (2012).
6. Valente, L. J. et al. p53 efficiently suppresses tumor development in the complete absence of its cell-cycle inhibitory and proapoptotic effectors p21, Puma, and Noxa. *Cell Rep.* **3**, 1339–1345 (2013).
7. Galluzzi, L. et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death Differ.* **25**, 486–541 (2018).
8. Tang, D., Kang, R., Berghe, T. V., Vandenabeele, P. & Kroemer, G. The molecular machinery of regulated cell death. *Cell Res.* **29**, 347–364 (2019).
9. Yuan, J. & Ofengeim, D. A guide to cell death pathways. *Nat. Rev. Mol. Cell Biol.* **25**, 379–395 (2024).
10. Hadian, K. & Stockwell, B. R. The therapeutic potential of targeting regulated non-apoptotic cell death. *Nat. Rev. Drug Discov.* **22**, 723–742 (2023).
11. Dolma, S., Lessnick, S. L., Hahn, W. C. & Stockwell, B. R. Identification of genotype-selective antitumor agents using synthetic lethal chemical screening in engineered human tumor cells. *Cancer Cell* **3**, 285–296 (2003).
12. Yang, W. S. & Stockwell, B. R. Synthetic lethal screening identifies compounds activating iron-dependent, nonapoptotic cell death in oncogenic-RAS-harboring cancer cells. *Chem. Biol.* **15**, 234–245 (2008).
13. Dixon, S. J. et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell* **149**, 1060–1072 (2012).
14. Stockwell, B. R. Ferroptosis turns 10: emerging mechanisms, physiological functions, and therapeutic applications. *Cell* **185**, 2401–2421 (2022).
15. Seiler, A. et al. Glutathione peroxidase 4 senses and translates oxidative stress into 12/15-lipoxygenase dependent- and AIF-mediated cell death. *Cell Metab.* **8**, 237–248 (2008).
16. Lei, G., Zhuang, L. & Gan, B. Y. The roles of ferroptosis in cancer: tumor suppression, tumor microenvironment, and therapeutic interventions. *Cancer Cell* **42**, 513–534 (2024).
17. Liu, Y. & Gu, W. p53 in ferroptosis regulation: the new weapon for the old guardian. *Cell Death Differ.* **29**, 895–910 (2022).
18. Liu, Y. Q. & Gu, W. The complexity of p53-mediated metabolic regulation in tumor suppression. *Semin. Cancer Biol.* **85**, 4–32 (2022).
19. Jiang, L. et al. Ferroptosis as a p53-mediated activity during tumour suppression. *Nature* **520**, 57–62 (2015).
20. Chu, B. et al. ALOX12 is required for p53-mediated tumour suppression through a distinct ferroptosis pathway. *Nat. Cell Biol.* **21**, 579–591 (2019).
21. Yang, X. et al. PHLDA2-mediated phosphatidic acid peroxidation triggers a distinct ferroptotic response during tumor suppression. *Cell Metab.* **36**, 762–777.e9 (2024).
22. Yang, X. Z. et al. miR-18a promotes glioblastoma development by down-regulating ALOXE3-mediated ferroptotic and anti-migration activities. *Oncogenesis* **10**, 15 (2021).
23. Li, X. R. et al. p53 activates the lipoxygenase activity of ALOX15B via inhibiting SLC7A11 to induce ferroptosis in bladder cancer cells. *Lab Invest.* **103**, 100058 (2023).
24. Ye, S. Z. et al. Cytoglobin promotes sensitivity to ferroptosis by regulating p53–YAP1 axis in colon cancer cells. *J. Cell Mol. Med.* **25**, 3300–3311 (2021).
25. Wu, J. et al. Intercellular interaction dictates cancer cell ferroptosis via NF2-YAP signalling. *Nature* **572**, 402–406 (2019).
26. Ding, Z. W. et al. URI alleviates tyrosine kinase inhibitors-induced ferroptosis by reprogramming lipid metabolism in p53 wild-type liver cancers. *Nat. Commun.* **14**, 6269 (2023).
27. Sen, U., Coleman, C. & Sen, T. Stearoyl coenzyme A desaturase-1: multitasker in cancer, metabolism, and ferroptosis. *Trends Cancer* **9**, 480–489 (2023).
28. Rodencal, J. et al. Sensitization of cancer cells to ferroptosis coincident with cell cycle arrest. *Cell Chem. Biol.* **31**, 234–248.e13 (2024).
29. Suzuki, S. et al. GLS2 is a tumor suppressor and a regulator of ferroptosis in hepatocellular carcinoma. *Cancer Res.* **82**, 3209–3222 (2022).
30. Gao, M. H., Monian, P., Quadri, N., Ramasamy, R. & Jiang, X. J. Glutaminolysis and transferrin regulate ferroptosis. *Mol. Cell* **59**, 298–308 (2015).
31. Zhang, Y., Luo, M. Y., Cui, X. H., O'Connell, D. & Yang, Y. F. Long noncoding RNA NEAT1 promotes ferroptosis by modulating the miR-362-3p/MIOX axis as a ceRNA. *Cell Death Differ.* **29**, 1850–1863 (2022).
32. Tang, L. J. et al. Ubiquitin-specific protease 7 promotes ferroptosis via activation of the p53/TfR1 pathway in the rat hearts after ischemia/reperfusion. *Free. Radic. Biol. Med.* **162**, 339–352 (2021).
33. Feng, H. et al. Transferrin receptor is a specific ferroptosis marker. *Cell Rep.* **30**, 3411–3423 (2020).
34. Zhang, Z. L. et al. The BRD7–P53–SLC25A28 axis regulates ferroptosis in hepatic stellate cells. *Redox Biol.* https://doi.org/10.1016/j.redox.2020.101619 (2020).
35. Ou, Y., Wang, S. J., Li, D., Chu, B. & Gu, W. Activation of SAT1 engages polyamine metabolism with p53-mediated ferroptotic responses. *Proc. Natl Acad. Sci. USA* **113**, E6806–E6812 (2016).
36. Gilbert, B. et al. 5-Lipoxygenase is a direct p53 target gene in humans. *BBA Gene Regul. Mech.* **1849**, 1003–1016 (2015).
37. Song, S. J. et al. ALOX5-mediated ferroptosis acts as a distinct cell death pathway upon oxidative stress in Huntington's disease. *Genes Dev.* **37**, 204–217 (2023).

38. Liu, T. Y. et al. ALOX5 deficiency contributes to bladder cancer progression by mediating ferroptosis escape. *Cell Death Dis*. **14**, 800 (2023).
39. Ou, Y., Wang, S. J., Jiang, L., Zheng, B. & Gu, W. p53 Protein-mediated regulation of phosphoglycerate dehydrogenase (PHGDH) is crucial for the apoptotic response upon serine starvation. *J. Biol. Chem.* **290**, 457–466 (2015).
40. Wang, M. et al. Long noncoding RNA LINC00336 inhibits ferroptosis in lung cancer by functioning as a competing endogenous RNA. *Cell Death Differ.* **26**, 2329–2343 (2019).
41. Mishima, E. et al. A non-canonical vitamin K cycle is a potent ferroptosis suppressor. *Nature* **608**, 778–783 (2022).
42. Yang, X. et al. Regulation of VKORC1L1 is critical for p53-mediated tumor suppression through vitamin K metabolism. *Cell Metab.* **35**, 1474–1490, (2023).
43. Chen, D. L. et al. iPLA2β-mediated lipid detoxification controls p53-driven ferroptosis independent of GPX4. *Nat. Commun.* **12**, 3644 (2021).
44. Liu, Y., Tavana, O. & Gu, W. p53 modifications: exquisite decorations of the powerful guardian. *J. Mol. Cell Biol.* **11**, 564–577 (2019).
45. Kruiswijk, F., Labuschagne, C. F. & Vousden, K. H. p53 in survival, death and metabolic health: a lifeguard with a licence to kill. *Nat. Rev. Mol. Cell Biol.* **16**, 393–405 (2015).
46. Vousden, K. H. & Lane, D. P. p53 in health and disease. *Nat. Rev. Mol. Cell Biol.* **8**, 275–283 (2007).
47. Liu, Y., Leslie, P. L. & Zhang, Y. Life and death decision-making by p53 and implications for cancer immunotherapy. *Trends Cancer* **7**, 226–239 (2021).
48. Xie, Y. C. et al. The tumor suppressor p53 limits ferroptosis by blocking DPP4 activity. *Cell Rep.* **20**, 1692–1704 (2017).
49. Gnanapradeepan, K. et al. PLTP is a p53 target gene with roles in cancer growth suppression and ferroptosis. *J. Biol. Chem.* **298**, 102637 (2022).
50. Tarangelo, A. et al. p53 suppresses metabolic stress-induced ferroptosis in cancer cells. *Cell Rep.* **22**, 569–575 (2018).
51. Kastenhuber, E. R. & Lowe, S. W. Putting p53 in context. *Cell* **170**, 1062–1078 (2017).
52. Wang, S. J. et al. Acetylation is crucial for p53-mediated ferroptosis and tumor suppression. *Cell Rep.* **17**, 366–373 (2016).
53. Kon, N. et al. mTOR inhibition acts as an unexpected checkpoint in p53-mediated tumor suppression. *Genes Dev.* **35**, 59–64 (2021).
54. Jennis, M. et al. An African-specific polymorphism in the TP53 gene impairs p53 tumor suppressor function in a mouse model. *Genes Dev.* **30**, 918–930 (2016).
55. Leu, J. I., Murphy, M. E. & George, D. L. Mechanistic basis for impaired ferroptosis in cells expressing the African-centric S47 variant of p53. *Proc. Natl Acad. Sci. USA* **116**, 8390–8396 (2019).
56. Murphy, M. E. et al. A functionally significant SNP in TP53 and breast cancer risk in African-American women. *npj Breast Cancer* **3**, 5 (2017).
57. Peng, M. et al. Mutation of TP53 confers ferroptosis resistance in lung cancer through the FOXM1/MEF2C axis. *Am. J. Pathol.* **193**, 1587–1602 (2023).
58. Su, Z. et al. Specific regulation of BACH1 by the hotspot mutant $p53^{R175H}$ reveals a distinct gain-of-function mechanism. *Nat. Cancer* **4**, 564–581 (2023).
59. Dibra, D. et al. Mutant p53 protects triple-negative breast adenocarcinomas from ferroptosis in vivo. *Sci. Adv.* **10**, eadk1835 (2024).
60. Liou, G. Y. & Storz, P. Reactive oxygen species in cancer. *Free Radic. Res.* **44**, 479–496 (2010).
61. Kim, R. et al. Ferroptosis of tumour neutrophils causes immune suppression in cancer. *Nature* **612**, 338–346 (2022).
62. Seibt, T. M., Proneth, B. & Conrad, M. Role of GPX4 in ferroptosis and its pharmacological implication. *Free Radic. Biol. Med.* **133**, 144–152 (2019).
63. Chen, L. et al. GINS4 suppresses ferroptosis by antagonizing p53 acetylation with Snail. *Proc. Natl Acad. Sci. USA* **120**, e2219585120 (2023).
64. Wang, C. K. et al. MEX3A mediates p53 degradation to suppress ferroptosis and facilitate ovarian cancer tumorigenesis. *Cancer Res.* **83**, 251–263 (2023).
65. Qian, B. et al. Protein phosphatase 2A-B55β mediated mitochondrial p-GPX4 dephosphorylation promoted sorafenib-induced ferroptosis in hepatocellular carcinoma via regulating p53 retrograde signaling. *Theranostics* **13**, 4288–4302 (2023).
66. Mao, C. et al. A G3BP1-interacting lncRNA promotes ferroptosis and apoptosis in cancer via nuclear sequestration of p53. *Cancer Res.* **78**, 3484–3496 (2018).
67. Qu, Z. et al. The positive feedback loop of the NAT10/Mybbp1a/p53 axis promotes cardiomyocyte ferroptosis to exacerbate cardiac I/R injury. *Redox Biol.* **72**, 103145 (2024).
68. Zhang, P. et al. Ferroptosis was more initial in cell death caused by iron overload and its underlying mechanism in Parkinson's disease. *Free Radic. Biol. Med.* **152**, 227–234 (2020).
69. Luo, E. F. et al. Role of ferroptosis in the process of diabetes-induced endothelial dysfunction. *World J. Diabetes* **12**, 124–137 (2021).
70. Degterev, A. et al. Chemical inhibitor of nonapoptotic cell death with therapeutic potential for ischemic brain injury. *Nat. Chem. Biol.* **1**, 112–119 (2005).
71. Degterev, A. et al. Identification of RIP1 kinase as a specific cellular target of necrostatins. *Nat. Chem. Biol.* **4**, 313–321 (2008).
72. Fridman, J. S. & Lowe, S. W. Control of apoptosis by p53. *Oncogene* **22**, 9030–9040 (2003).
73. Wang, K. et al. The long noncoding RNA NRF regulates programmed necrosis and myocardial injury during ischemia and reperfusion by targeting miR-873. *Cell Death Differ.* **23**, 1394–1405 (2016).
74. Chen, D. et al. PUMA/RIP3 mediates chemotherapy response via necroptosis and local immune activation in colorectal cancer. *Mol. Cancer Ther.* **23**, 354–367 (2024).
75. Zhou, J. et al. Heat stress-induced intestinal epithelial cells necroptosis via TLR3–TRIF–RIP3 pathway was dependent on p53. *Int. Immunopharmacol.* **122**, 110574 (2023).
76. Gong, Y. et al. The role of necroptosis in cancer biology and therapy. *Mol. Cancer* **18**, 100 (2019).
77. Rius-Pérez, S. p53 at the crossroad between mitochondrial reactive oxygen species and necroptosis. *Free Radic. Biol. Med.* **207**, 183–193 (2023).
78. Dashzeveg, N. & Yoshida, K. Cell death decision by p53 via control of the mitochondrial membrane. *Cancer Lett.* **367**, 108–112 (2015).
79. Rius-Pérez, S., Pérez, S., Toledano, M. B. & Sastre, J. p53 drives necroptosis via downregulation of sulfiredoxin and peroxiredoxin 3. *Redox Biol.* **56**, 102423 (2022).
80. Zhang, Y. Y. et al. RIP1 autophosphorylation is promoted by mitochondrial ROS and is essential for RIP3 recruitment into necrosome. *Nat. Commun.* **8**, 14329 (2017).
81. Zhang, D. W. et al. RIP3, an energy metabolism regulator that switches TNF-induced cell death from apoptosis to necrosis. *Science* **325**, 332–336 (2009).
82. Yang, Z. T. et al. RIP3 targets pyruvate dehydrogenase complex to increase aerobic respiration in TNF-induced necroptosis. *Nat. Cell Biol.* **20**, 186–197 (2018).
83. Vaseva, A. V. et al. p53 opens the mitochondrial permeability transition pore to trigger necrosis. *Cell* **149**, 1536–1548 (2012).
84. Qin, L. S., Jia, P. F., Zhang, Z. Q. & Zhang, S. M. ROS-p53-cyclophilin-D signaling mediates salinomycin-induced glioma cell necrosis. *J. Exp. Clin. Cancer Res.* **34**, 57 (2015).
85. Wang, X. Q. et al. RNA viruses promote activation of the NLRP3 inflammasome through a RIP1–RIP3–DRP1 signaling pathway. *Nat. Immunol.* **15**, 1126–1133 (2014).
86. Wang, P. et al. Necroptosis signaling and mitochondrial dysfunction cross-talking facilitate cell death mediated by chelerythrine in glioma. *Free Radic. Biol. Med.* **202**, 76–96 (2023).
87. Li, J. C. et al. miR-30 regulates mitochondrial fission through targeting p53 and the dynamin-related protein-1 pathway. *PLoS Genet*. **6**, e1000795 (2010).
88. Wang, J. X. et al. miR-499 regulates mitochondrial dynamics by targeting calcineurin and dynamin-related protein-1. *Nat. Med.* **17**, 71–78 (2011).
89. Guo, X., Sesaki, H. & Qi, X. Drp1 stabilizes p53 on the mitochondria to trigger necrosis under oxidative stress conditions in vitro and in vivo. *Biochem. J.* **461**, 137–146 (2014).
90. Goodall, M. L. et al. The autophagy machinery controls cell death switching between apoptosis and necroptosis. *Dev. Cell* **37**, 337–349 (2016).
91. Mizumura, K. et al. Mitophagy-dependent necroptosis contributes to the pathogenesis of COPD. *J. Clin. Invest.* **124**, 3987–4003 (2014).
92. Tait, S. W. et al. Widespread mitochondrial depletion via mitophagy does not compromise necroptosis. *Cell Rep.* **5**, 878–885 (2013).
93. Zhang, T. et al. Metabolic orchestration of cell death by AMPK-mediated phosphorylation of RIPK1. *Science* **380**, 1372–1380 (2023).
94. Zhang, T. et al. Prolonged hypoxia alleviates prolyl hydroxylation-mediated suppression of RIPK1 to promote necroptosis and inflammation. *Nat. Cell Biol.* **25**, 950–962 (2023).
95. Mabe, N. W. et al. G9a promotes breast cancer recurrence through repression of a pro-inflammatory program. *Cell Rep.* **33**, 108341 (2020).
96. Guijarro, L. G. et al. Actinomycin D arrests cell cycle of hepatocellular carcinoma cell lines and induces p53-dependent cell death: a study of the molecular mechanism involved in the protective effect of IRS-4. *Pharmaceuticals* **14**, 845 (2021).
97. Peek, S. L. et al. p53-mediated neurodegeneration in the absence of the nuclear protein Akirin2. *iScience* **12**, 103814 (2022).
98. Barabino, A. et al. Loss of *Bmi1* causes anomalies in retinal development and degeneration of cone photoreceptors. *Development* **143**, 1571–1584 (2016).
99. Pei, L. et al. DAPK1–p53 interaction converges necrotic and apoptotic pathways of ischemic neuronal death. *J. Neurosci.* **34**, 6546–6556 (2014).
100. Cookson, B. T. & Brennan, M. A. Pro-inflammatory programmed cell death. *Trends Microbiol.* **9**, 113–114 (2001).
101. Elias, E. E., Lyons, B. & Muruve, D. A. Gasdermins and pyroptosis in the kidney. *Nat. Rev. Nephrol.* **19**, 337–350 (2023).
102. Gong, L. J. et al. Nuclear SPHK2/S1P induces oxidative stress and NLRP3 inflammasome activation via promoting p53 acetylation in lipopolysaccharide-induced acute lung injury. *Cell Death Discov.* **9**, 12 (2023).
103. Gupta, S., Radha, V., Furukawa, Y. & Swarup, G. Direct transcriptional activation of human caspase-1 by tumor suppressor p53. *J. Biol. Chem.* **276**, 10585–10588 (2001).
104. Masuda, Y. et al. The potential role of *DFNA5*, a hearing impairment gene, in p53-mediated cellular response to DNA damage. *J. Hum. Genet.* **51**, 652–664 (2006).
105. Zhang, T. et al. Transcription factor p53 suppresses tumor growth by prompting pyroptosis in non-small-cell lung cancer. *Oxid. Med. Cell Longev.* **2019**, 8746895 (2019).
106. Krzesniak, M. et al. Synergistic activation of p53 by actinomycin D and nutlin-3a is associated with the upregulation of crucial regulators and effectors of innate immunity. *Cell Signal.* **69**, 109552 (2020).
107. Bodnar-Wachtel, M. et al. Inflammasome-independent NLRP3 function enforces ATM activity in response to genotoxic stress. *Life Sci. Alliance* **6**, e202201494 (2023).
108. Licandro, G. et al. The NLRP3 inflammasome affects DNA damage responses after oxidative and genotoxic stress in dendritic cells. *Eur. J. Immunol.* **43**, 2126–2137 (2013).
109. Ren, L. W. et al. Benzimidazoles induce concurrent apoptosis and pyroptosis of human glioblastoma cells via arresting cell cycle. *Acta Pharmacol. Sin.* **43**, 194–208 (2022).
110. Huang, Y. et al. Inflammasome activation and pyroptosis via a lipid-regulated SIRT1-p53-ASC axis in macrophages from male mice and humans. *Endocrinology* **163**, bqac014 (2022).

111. Zhou, X. N. et al. Silent information regulator sirtuin 1 ameliorates acute liver failure via the p53/glutathione peroxidase 4/gasdermin D axis. *World J. Gastroenterol.* **30**, 1588–1608 (2024).
112. Zhou, Y. et al. Activation of p53 by MEG3 non-coding RNA. *J. Biol. Chem.* **282**, 24731–24742 (2007).
113. Zhu, A. et al. Silence of linc00023 inhibits pyroptosis and promotes cell proliferation via regulating p53. *Gene* **882**, 147628 (2023).
114. Chen, C. et al. Long noncoding RNA Meg3 mediates ferroptosis induced by oxygen and glucose deprivation combined with hyperglycemia in rat brain microvascular endothelial cells, through modulating the p53/GPX4 axis. *Eur. J. Histochem.* **65**, 3224 (2021).
115. Saha, G. et al. BLIMP-1 mediated downregulation of TAK1 and p53 molecules is crucial in the pathogenesis of *Kala-Azar*. *Front. Cell Infect. Microbiol.* **10**, 594431 (2020).
116. Rao, X., Lei, Z., Zhu, H., Luo, K. & Hu, C. Knockdown of KIF23 alleviates the progression of asthma by inhibiting pyroptosis. *BMJ Open Respir. Res.* **11**, e002089 (2024).
117. Fischer, M. et al. p53 and cell cycle dependent transcription of kinesin family member 23 (KIF23) is controlled via a CHR promoter element bound by DREAM and MMB complexes. *PLoS ONE* **8**, e63187 (2013).
118. Denton, D. & Kumar, S. Autophagy-dependent cell death. *Cell Death Differ.* **26**, 605–616 (2019).
119. Lima, S. et al. TP53 is required for BECN1-and ATG5-dependent cell death induced by sphingosine kinase 1 inhibition. *Autophagy* **14**, 942–957 (2018).
120. Wilfinger, N. et al. Novel p53-dependent anticancer strategy by targeting iron signaling and BNIP3L-induced mitophagy. *Oncotarget* **7**, 1242–1261 (2016).
121. Seillier, M. et al. TP53INP1, a tumor suppressor, interacts with LC3 and ATG8-family proteins through the LC3-interacting region (LIR) and promotes autophagy-dependent cell death. *Cell Death Differ.* **19**, 1525–1535 (2012).
122. Wu, Q. et al. Ginsenoside Rh4 induces apoptosis and autophagic cell death through activation of the ROS/JNK/p53 pathway in colorectal cancer cells. *Biochem. Pharmacol.* **148**, 64–74 (2018).
123. Fan, Y. M. et al. Resveratrol modulates the apoptosis and autophagic death of human lung adenocarcinoma A549 cells via a p53-dependent pathway: integrated bioinformatics analysis and experimental validation. *Int. J. Oncol.* **57**, 925–938 (2020).
124. Gao, M. H. et al. Ferroptosis is an autophagic cell death process. *Cell Res.* **26**, 1021–1032 (2016).
125. Hou, W. et al. Autophagy promotes ferroptosis by degradation of ferritin. *Autophagy* **12**, 1425–1428 (2016).
126. Liang, J. Q. et al. p53-dependent elimination of aneuploid mitotic offspring by entosis. *Cell Death Differ.* **28**, 799–813 (2021).
127. Rizzotto, D. & Villunger, A. P53 clears aneuploid cells by entosis. *Cell Death Differ.* **28**, 818–820 (2021).
128. Mackay, H. L. et al. Genomic instability in mutant p53 cancer cells upon entotic engulfment. *Nat. Commun.* **9**, 3070 (2018).
129. Sterling, N. A., Park, J. Y., Park, R., Cho, S. H. & Kim, S. An entosis-like process induces mitotic disruption in Pals1 microcephaly pathogenesis. *Nat. Commun.* **14**, 82 (2023).
130. Montero, J., Dutta, C., van Bodegom, D., Weinstock, D. & Letai, A. p53 regulates a non-apoptotic death induced by ROS. *Cell Death Differ.* **20**, 1465–1474 (2013).
131. Zhang, Y. Z. et al. Inhibition of AKT induces p53/SIRT6/PARP1-dependent parthanatos to suppress tumor growth. *Cell Commun. Signal.* **20**, 93 (2022).
132. Stambolsky, P. et al. Regulation of AIF expression by p53. *Cell Death Differ.* **13**, 2140–2149 (2006).
133. Dinhof, C. et al. p53 loss mediates hypersensitivity to ETS transcription factor inhibition based on PARylation-mediated cell death induction. *Cancers* **12**, 3205 (2020).
134. Chen, F. et al. Targeting paraptosis in cancer: opportunities and challenges. *Cancer Gene Ther.* **31**, 349–363 (2024).
135. Li, B. H. et al. Ginsenoside Rh2 induces apoptosis and paraptosis-like cell death in colorectal cancer cells through activation of p53. *Cancer Lett.* **301**, 185–192 (2011).
136. Pandian, N. & Kanneganti, T. D. PANoptosis: a unique innate immune inflammatory cell death modality. *J. Immunol.* **209**, 1625–1633 (2022).
137. He, W. J. et al. The role of p53 in regulating chronic inflammation and PANoptosis in diabetic wounds. *Aging Dis.* **16**, 373–393 (2025).
138. Tsvetkov, P. et al. Mitochondrial metabolism promotes adaptation to proteotoxic stress. *Nat. Chem. Biol.* **15**, 681–689 (2019).
139. Tsvetkov, P. et al. Copper induces cell death by targeting lipoylated TCA cycle proteins. *Science* **375**, 1254–1261 (2022).
140. Xiong, C., Ling, H., Hao, Q. & Zhou, X. Cuproptosis: p53-regulated metabolic cell death? *Cell Death Differ.* **30**, 876–884 (2023).
141. Liu, X. G. et al. Actin cytoskeleton vulnerability to disulfide stress mediates disulfidptosis. *Nat. Cell Biol.* **25**, 404–414 (2023).
142. Liu, X., Zhuang, L. & Gan, B. Disulfidptosis: disulfide stress-induced cell death. *Trends Cell Biol.* **34**, 327–337 (2024).
143. Wang, M. et al. Gambogenic acid induces ferroptosis in melanoma cells undergoing epithelial-to-mesenchymal transition. *Toxicol. Appl. Pharm.* https://doi.org/10.1016/j.taap.2020.115110 (2020).
144. Zhou, X. M. et al. Flubendazole, FDA-approved anthelmintic, elicits valid antitumor effects by targeting P53 and promoting ferroptosis in castration-resistant prostate cancer. *Pharmacol. Res.* https://doi.org/10.1016/j.phrs.2020.105305 (2021).
145. Wei, G. F. et al. Novel antitumor compound optimized from natural saponin Albiziabioside A induced caspase-dependent apoptosis and ferroptosis as a p53 activator through the mitochondrial pathway. *Eur. J. Med. Chem.* **157**, 759–772 (2018).
146. Hong, T. et al. PARP inhibition promotes ferroptosis via repressing SLC7A11 and synergizes with ferroptosis inducers in BRCA-proficient ovarian cancer. *Redox Biol.* https://doi.org/10.1016/j.redox.2021.101928 (2021).
147. Fan, F. S. et al. A dual PI3K/HDAC inhibitor induces immunogenic ferroptosis to potentiate cancer immune checkpoint therapy. *Cancer Res.* **81**, 6233–6245 (2021).
148. Lei, G. et al. Ferroptosis as a mechanism to mediate p53 function in tumour radiosensitivity. *Oncogene* **40**, 3533–3547 (2021).
149. Kaushansky, A. et al. Suppression of host p53 is critical for *Plasmodium* liver-stage infection. *Cell Rep.* **3**, 630–637 (2013).
150. Kain, H. S. et al. Liver stage malaria infection is controlled by host regulators of lipid peroxidation. *Cell Death Differ.* **27**, 44–54 (2020).
151. Li, X. et al. A-lipoic acid alleviates folic acid-induced renal damage through inhibition of ferroptosis. *Front. Physiol.* https://doi.org/10.3389/fphys.2021.680544 (2021).
152. Zhai, L. P. et al. Paeoniflorin suppresses neuronal ferroptosis to improve the cognitive behaviors in Alzheimer's disease mice. *Phytother. Res.* **37**, 4791–4800 (2023).
153. Zhang, L., Wang, H. D., Ding, K. & Xu, J. G. FTY720 induces autophagy-related apoptosis and necroptosis in human glioblastoma cells. *Toxicol. Lett.* **236**, 43–59 (2015).
154. Ishikawa, C. & Mori, N. Pivotal role of dihydroorotate dehydrogenase as a therapeutic target in adult T-cell leukemia. *Eur. J. Haematol.* **113**, 99–109 (2024).
155. Nicolai, S., Pieraccioli, M., Peschiaroli, A., Melino, G. & Raschellà, G. Neuroblastoma: oncogenic mechanisms and therapeutic exploitation of necroptosis. *Cell Death Dis.* **6**, e2010 (2015).
156. Lu, C. F., Xu, W. X., Zhang, F., Shao, J. J. & Zheng, S. Z. *Nrf2* knockdown disrupts the protective effect of curcumin on alcohol-induced hepatocyte necroptosis. *Mol. Pharm.* **13**, 4043–4053 (2016).
157. Fayaz, S. M. & Rajanikant, G. K. Modelling the molecular mechanism of protein–protein interactions and their inhibition: CypD–p53 case study. *Mol. Divers.* **19**, 931–943 (2015).
158. Wu, Y. C. et al. Ginsenoside Rh3 induces pyroptosis and ferroptosis through the Stat3/p53/NRF2 axis in colorectal cancer cells. *Acta Biochim. Biophys. Sin.* **55**, 587–600 (2023).
159. Hu, Y. et al. Blockade of autophagy prevents the progression of hyperuricemic nephropathy through inhibiting NLRP3 inflammasome-mediated pyroptosis. *Front. Immunol.* https://doi.org/10.3389/fimmu.2022.858494 (2022).
160. Zhuang, C., Zhao, J., Zhang, S. & Shahid, M. *Escherichia coli* infection mediates pyroptosis via activating p53–p21 pathway-regulated apoptosis and cell cycle arrest in bovine mammary epithelial cells. *Microb. Pathog.* **184**, 106338 (2023).
161. Yang, C., Wang, Z. Q., Zhang, Z. C., Lou, G. & Jin, W. L. CBL0137 activates ROS/BAX signaling to promote caspase-3/GSDME-dependent pyroptosis in ovarian cancer cells. *Biomed. Pharmacother.* **161**, 114529 (2023).
162. Pant, V., Sun, C. & Lozano, G. Tissue specificity and spatio-temporal dynamics of the p53 transcriptional program. *Cell Death Differ.* **30**, 897–905 (2023).
163. Snyder, A. G. & Oberst, A. The antisocial network: cross talk between cell death programs in host defense. *Annu. Rev. Immunol.* **39**, 77–101 (2021).
164. Bertheloot, D., Latz, E. & Franklin, B. S. Necroptosis, pyroptosis and apoptosis: an intricate game of cell death. *Cell Mol. Immunol.* **18**, 1106–1121 (2021).
165. Chen, X. et al. International consensus guidelines for the definition, detection, and interpretation of autophagy-dependent ferroptosis. *Autophagy* **20**, 1213–1246 (2024).
166. Wasylishen, A. R. & Lozano, G. Attenuating the p53 pathway in human cancers: many means to the same end. *Cold Spring Harb. Perspect. Med.* **6**, a026211 (2016).
167. Abraham, S. A. et al. Dual targeting of p53 and c-MYC selectively eliminates leukaemic stem cells. *Nature* **534**, 341–346 (2016).
168. Munoz-Fontela, C., Mandinova, A., Aaronson, S. A. & Lee, S. W. Emerging roles of p53 and other tumour-suppressor genes in immune regulation. *Nat. Rev. Immunol.* **16**, 741–750 (2016).
169. Galluzzi, L., Buque, A., Kepp, O., Zitvogel, L. & Kroemer, G. Immunogenic cell death in cancer and infectious disease. *Nat. Rev. Immunol.* **17**, 97–111 (2017).
170. Clarke, P. G. H. & Clarke, S. Nineteenth century research on naturally occurring cell death and related phenomena. *Anat. Embryol.* **193**, 81–99 (1996).
171. Jiang, X. J., Stockwell, B. R. & Conrad, M. Ferroptosis: mechanisms, biology and role in disease. *Nat. Rev. Mol. Cell Biol.* **22**, 266–282 (2021).
172. Dixon, S. J. & Olzmann, J. A. The cell biology of ferroptosis. *Nat. Rev. Mol. Cell Biol.* **25**, 424–442 (2024).

Acknowledgements

This work was supported by the National Cancer Institute (NCI) of the National Institutes of Health under Award R35CA253059, R01CA258390 and R01CA254970 to W.G., and award R35CA209896 to B.R.S., and R01CA204232, R01CA258622, and R01CA166413 to X.J. This work was also supported by NCI Cancer Centre core grant P30 CA008748 to Memorial Sloan-Kettering Cancer Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author contributions

Y.L. researched data for the article. Y.L., W.G., B.R.S. and X.J. contributed substantially to discussion of the content. Y.L. and W.G. wrote the article. Y.L., W.G., B.R.S. and X.J. reviewed and/or edited the manuscript before submission.

Competing interests

B.R.S. is an inventor on patents and patent applications involving ferroptosis; he has co-founded and serves as a consultant to ProJenX, Inc. and Exarta Therapeutics; holds equity in Sonata Therapeutics; serves as a consultant to Weatherwax Biotechnologies Corporation and Akin Gump Strauss Hauer & Feld LLP. X.J. is an inventor on patents related to autophagy and cell death, and holds equity of and consults for Exarta Therapeutics and Lime Therapeutics. The other authors declare no competing interests.

Additional information

Peer review information *Nature Reviews Molecular Cell Biology* thanks Boyi Gan, Xiang Zhou and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.