———————————— *Review Paper* ————————————

Radiation-induced Cell Death and Its Mechanisms

Yunfei Jiao,[1,2,3] Fangyu Cao,[1,2] and Hu Liu[4]

Abstract—With rapid technical advances, ionizing radiation has been put into wider application in ordinary living, with the worst cytological effect on the human body being cell death. Moreover, according to the Nomenclature Committee on Cell Death, the method of radiation-induced cell death, usually classified as interphase and proliferative death, undergoes more detailed classifications oriented by its molecular mechanism. Elaborating its mode and molecular mechanism is crucial for the protection and treatment of radiation injury, as well as the radiotherapy and recovery of tumors. Varying with the changes of the radiation dose and the environment, the diverse targets and pathways of ionizing radiation result in various cell deaths. This review focuses on classifications of radiation-induced cell death and its molecular mechanism. We also examine the main characteristics of ionizing radiation-induced cell death. The modes of radiation-induced cell death can be classified as apoptosis, necrosis, autophagy-dependent cell death, pyroptosis, ferroptosis, immunogenic cell death, and non-lethal processes. Once the dose is high enough, radiation effects mostly appear as destructiveness ("destructiveness" is used to describe a situation in which cells do not have the opportunity to undergo a routine death process, in which case high-dose radiation works like a physical attack). This breaks up or even shatters cells, making it difficult to find responses of the cell itself. Due to diversities concerning cell phenotypes, phases of cell cycle, radiation dose, and even cellular subregions, various methods of cell death occur, which are difficult to identify and classify. Additionally, the existence of common initial activation and signaling molecules among all kinds of cell deaths, as well as sophisticated crossways in cellular molecules, makes it more laborious to distinguish and classify various cell deaths.
Health Phys. 123(5):376–386; 2022

INTRODUCTION

THE DIRECT effect of ionizing radiation on the human body is typically manifested as a cytological effect, the worst of which is cell death. It is important to identify the mode of cell death caused by ionizing radiation and its molecular mechanism for the protection and treatment of radiation injury, as well as radiotherapy and recovery of tumors.

Radiation-induced cell death is typically classified as interphase or proliferative death (Kondo 2012). The former refers to cells that cease to divide after radiation exposure and begin to die within hours. This is attributed to the damage of intracellular molecules and the activation of nuclease and proteolytic enzymes, etc., after high doses of radiation, which leads to degradation of chromatins as well as spill-over of histone. This is followed by shrinkage and lysis of cell nuclei, the rapid destruction of normal nuclear morphous, and ultimately cell death. Factors such as disruption of membrane structure and disorder of cell energy metabolism after irradiation are also important contributors to interphase death. Most cells undergo proliferative death after radiation, which results from mitotic catastrophe caused by accumulation of chromosomal aberrations and erroneous repair after radiation induces a DNA double-strand break. After one or several division cycles, cells lose their ability to proliferate and begin to die (Proskuryakov et al. 2002; Galluzzi et al. 2018). There is a consensus that cellular effects, including cell death, depend not only on radiation dose but cell type and a place in cell cycle.

The Nomenclature Committee on Cell Death (NCCD), sponsored by the Society of Toxicologic Pathology, proposes periodically unified criteria for the definition of cell death and its different morphologies according to the latest research, while formulating several caveats against the misuse of words and concepts that slow down progress in the area of cell death research. In accordance with NCCD recommendations in

[1]College of Basic Medicine, Second Military Medical University, Xiangyin Road, 200433 Shanghai, PR China; [2]Incubation Base for Undergraduates' Innovation Practice, Department of Radiation Medicine, Faculty of Naval Medicine, Naval Medical University, Shanghai, China; [3]Department of Gastroenterology, Changhai Hospital, Naval Medical University, Shanghai, China; [4]Department of Radiation Medicine, Faculty of Naval Medicine, Second Military Medical University, Shanghai, China.

Authors Yunfei Jiao and Fangyu Cao contributed equally to the preparation of this paper. The authors declare no conflicts of interest.

For correspondence contact: Hu Liu, Second Military Medical University Shanghai, China, or email at **gzsassliuhu@163.com**.

(*Manuscript accepted* 7 *May* 2022)

2018 (Galluzzi et al. 2018), this review provides more detailed classifications of radiation-induced cell death oriented by molecular mechanism, including apoptosis (intrinsic apoptosis and extrinsic apoptosis), necrosis (necroptosis, mitochondrial permeability transition /MPT-driven necrosis and parthanatos), autophagy-dependent cell death, pyroptosis, ferroptosis, immunogenic cell death, and non-lethal processes (mitotic catastrophe and cellular senescence).

Apoptosis

The term "apoptosis" was first coined by Kerr, Wyllie, and Currie in 1972 (Kerr et al. 1972), and subsequently we have a more comprehensive understanding (Luo et al. 1998; Elmore 2007; Yang et al. 2017): Apoptosis is a gene-regulated, energy-dependent, active, and programmed cell death process accompanied by contraction, pyknosis, and the formation of apoptotic bodies, which eventually ends with engulfment of surrounding cells. The metabolic activity and integrity of the plasma membrane are maintained to a certain extent without provoking inflammation around the cells thanks to the presence of apoptosis. The initiation of apoptosis is mainly activated by two different pathways, intrinsic and extrinsic, both of which ultimately complete apoptosis by activating the execution pathway (Fig. 1).

NCCD defined intrinsic apoptosis as a type of cell death initiated by perturbations of the intracellular or extracellular microenvironment, characterized by mitochondrial outer membrane permeabilization/MOMP and finally executed by caspases (mainly caspase-3).

Intrinsic apoptosis. Intrinsic apoptosis is triggered by microenvironmental perturbations including DNA damage, endoplasmic reticulum stress (ER stress), reactive oxygen species/ROS overload, microtubular alterations, and mitotic defects. In response to apoptotic stimuli, intracellular pro-apoptotic and anti-apoptotic members of the Bcl-2 family (especially those located on mitochondrial and ER membrane) are activated, of which Bax (BCL2 associated X, apoptosis regulator) and Bak (BCL2 antagonist/killer) play a pivotal role and form Bax-Bak holes (activated Bax and Bak form a dimer, which alters mitochondrial permeability) on the mitochondrial membrane directly, thus resulting in the irreversible and widespread mitochondrial outer membrane permeabilization (MOMP) and the release of mitochondrial pro-apoptotic factors including cytochrome c (CYCs), second mitochondria-derived activator of caspases (SMAC), etc. The released CYCs, Apaf 1, and caspase-9 precursor subsequently form an "apoptosome," which in turn activates caspase-9 and initiates the ultimate execution pathway of apoptosis (Yang et al. 2017).

Ionizing radiation, as a violent stimulation, may induce irreversible microenvironmental perturbations of MCF-7 cells in various ways, primarily including action on the mitochondrial membrane and endoplasmic reticulum membrane to induce apoptotic signals (Yang et al. 2017). This in turn may lead to extensive oxidation of multiple molecules and induce the massive accumulation of free radicals like ROS in IPEC-J2 cells (Kang et al. 2019) as well as destroy the plasma membrane or organelle membrane to induce changes in intracellular ions, potentials, and osmotic pressures, etc. These occurrences all can be detected by Bcl-2 family proteins localized on the mitochondrial membrane, thereby activating the intrinsic apoptotic pathway (Luo et al. 1998).

Extrinsic apoptosis. Extrinsic apoptosis is defined as a form of cell death that is initiated by detection of perturbations of the extracellular microenvironment by plasma membrane receptors and activates the ultimate execution pathway by means of mechanisms mediated by caspase-8 (with the optional involvement of MOMP). Extrinsic apoptosis is
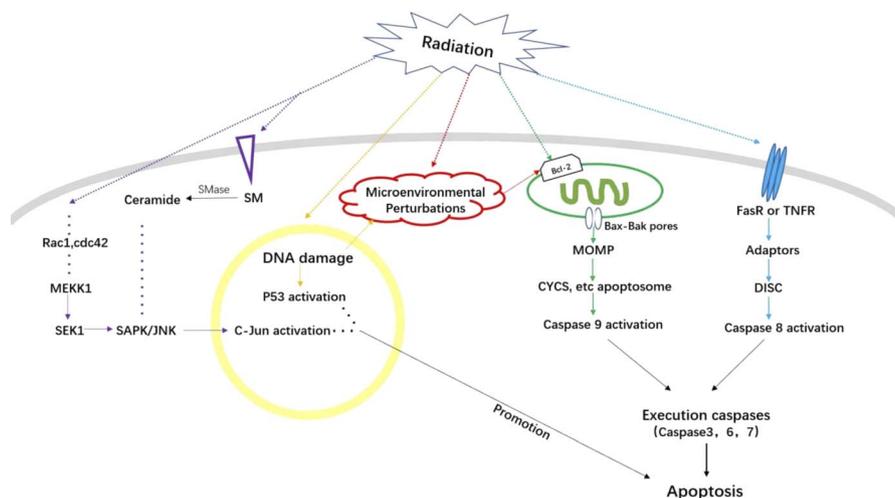
Fig. 1. Signaling pathways involved in radiation-induced apoptosis. After being induced by radiation, the initiation of apoptosis is mainly activated by two different pathways, intrinsic and extrinsic, both of which ultimately complete apoptosis by activating the execution pathway. Additionally, ionizing radiation can promote apoptosis in other two ways, P53 and SAPK/JNK pathways.

mostly driven by two different types of plasma membrane receptors: (1) death receptors, whose activation depends upon the binding to the cognate ligands, and (2) dependence receptors, which are activated when levels of their specific ligand drop below a specific threshold (Laubach et al. 2019). Death receptors include (but are not limited to) Fas cell surface death receptor (CD95/APO-1; the ligand is FasL) and the TNF receptor superfamily (the receptor is TNFSF-10). In physiological conditions, dependence receptors facilitate cell survival, proliferation, and differentiation (when their homologous ligands are available), while activating a lethal signal cascade once their ligands are below a distinct certain threshold level (the downstream executioner has not been clarified completely and usually affects the activation of caspases) (Contassot et al. 2007).

Under the stimulation of an extracellular microenvironment (binding to the ligand, etc.), death receptors are activated and induce partly intracellular conformational changes (death domain/DD activation), recruiting the downstream signals (adaptors). Subsequently, an apoptotic protein complex is formed by polymerizing caspase-8 by adaptors, including death-inducing signaling complex (DISC), complex I and complex II, which operate as molecular platforms to further activate caspase-8 and initiate the execution of extrinsic apoptosis (Contassot et al. 2007). It has been experimentally confirmed that Fas death receptors and TNF receptors would be up-regulated respectively following ionizing radiation, activating extrinsic apoptotic pathways (Wang and El-Deiry 2003).

The caspase-3,6,7-mediated execution pathway is the final step of apoptosis. Caspase-8 and caspase-9 are activated by intrinsic and extrinsic pathways, respectively, both of which result in the activation of the caspase-3 and execution pathway. Activated execution caspases induce activated proteases and endonucleases, degraded nuclear materials, nuclear proteins, and cytoskeleton, and finally apoptosis (Akpolat et al. 2020).

Other ways. Additionally, ionizing radiation can induce apoptosis in other ways:

1. The P53 gene plays a pivotal role in the regulation of cell cycle. In both cell experiments and animal (mice) experiments, the wild-type expression of P53 shows higher radiosensitivity than the defective type. Moreover, radiation-sensitive tissues usually have a higher basic P53 mRNA expression and are more prone to produce apoptosis-inducing responses to radiation exposure, indicating that radiation can promote cell apoptosis by activating P53-dependent pathways. Following radiation-induced DNA damage, the P53 pathway can be activated to repair DNA. While the damage is beyond repair, P53 directly provokes changes in Bcl-2 and Bax by activating the transcription of apoptotic genes to regulate the occurrence of apoptosis in the human leukemia cell lines U937 and Jurkat T. (Ruiter et al. 1999); and

2. SAPK/JNK pathway: the c-Jun N-terminal kinase (JNK), also known as stress-activated protein kinase (SAPK), is a member of mitogen-activated protein kinase (MAPK) family in mammalian cells. The JNK/SAPK signaling pathway can be initiated by stress to phosphorylate the serine 63 and 67 at the amino terminus of transcription factor c-Jun, which additionally activates c-Jun and enhances its transcriptional activity. Experiments demonstrated that SAPK/JNK-active cells are more prone to undergo apoptosis after radiation exposure, and the presence of SAPK/JNK in specific cells is even indispensable to radiation-induced apoptosis. Radiation may sequentially activate the Rho family and SPAK/JNK pathways by oxidizing the sphingomyelin on the plasma membrane into ceramide and other multiple pathways to regulate the occurrence of apoptosis in tumor cells. (Przybyszewski et al. 2008).

Although different cell types have different radiation sensitivities, the pattern of cell death following radiation is generally radiation dose-dependent. Low doses tend to induce apoptosis, while high doses are more inclined to induce cell necrosis (Przybyszewski et al. 2008).

Necrosis

The mechanisms of cell necrosis mainly include cytokines, ion channels, redox reactions, mitochondria, Bc-l 2 family, heat shock proteins, various proteases, and nucleases. Increased permeability of the necrotic cell membrane provokes cell swelling, organelle deformation, and ultimately rupture, which releases pro-inflammatory contents. The ATP level in necrotic cells is so decreased that cellular physiological activities cannot be maintained; chromatin is randomly degraded to DNA fragments of varying sizes rather than agglutinate during necrosis (Ying and Padanilam 2016). Necrosis is considered as an active form of controllable death (Fig. 2).

Cell necrosis can be divided into "MPT (mitochondrial permeability transition)-driven necrosis," "necroptosis," and "Parthanatos."

MPT-driven necrosis. MPT-driven necrosis is a CYPD (cyclophilin D)-dependent death mode triggered by severe oxidative stress, calcium iron overload, and other changes in the intracellular microenvironment. MTP means that the IMM abruptly loses its impermeability to small solutes, leading to the rapid dissipation of the transmembrane potential/$\Delta\psi$m and the osmotic destruction of the mitochondrial membrane, which in turn leads to dysfunction of ATP generation and release of pro-necrotic factors into cytoplasm. At the biochemical level, the realization of MPT relies on the formation of a "permeable transition pore complex" (PTPC, a supramolecular complex assembled at the junction of IMM and
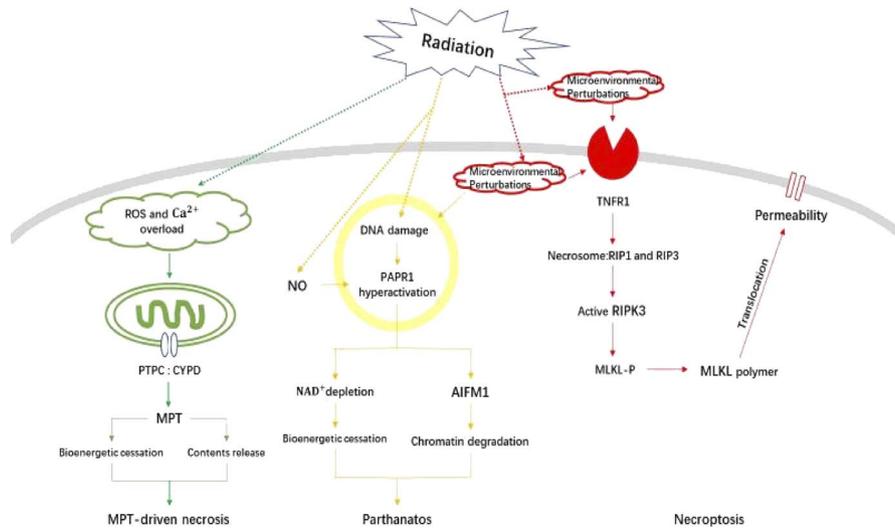
Fig. 2. Signaling pathways involved in radiation-induced necroptosis. According to the key executive molecules, cell necrosis can be divided into "MPT (mitochondrial permeability transition)-driven necrosis," "necroptosis," and "Parthanatos."

OMM). The key molecule in this subroutine is peptidyl prolyl isomerase F (PPIF), and the most widely known is cyclophilin D/CYPD, a central component of the PTPC which is assembled at the junction of the inner and outer mitochondrial membranes and induced by MPT. Serving as the only protein indispensable for inducing MPT in vivo as well, CYPD is capable of regulating the occurrence of necrosis together with other MPT-inducing molecules, such as F0ATP. Radiation can trigger extensive oxidative stress in cells and peroxidation of intracellular macromolecules, resulting in the overproduction of ROS; meanwhile, the concentration of calcium ions increases under the induction of radiation and aggravate calcium iron overload, both of which activate and promote the MPT-driven necrosis (Galluzzi et al. 2014).

Necroptosis. Necroptosis is a form of cell death that is triggered by perturbations of extracellular or intracellular homeostasis, and it is heavily dependent on the activity of MLKL, RIPK3, and RIPK1 kinase. Under the monitor of specific receptors, including (but not limited to) FAS, TNFR1 and pathogen recognition receptors (PRRs: TLR3, TLR4, and Z-DNA binding protein 1/ZBP1), necroptosis is induced by the cellular detection of abnormalities. During necroptosis initiated by TNFR1, primarily (with intracellular caspases inhibited), RIPK3 is catalytically activated through the interaction of the RIP homotype interaction motif/(RHIM) domain with RIPK1 to form a necrosome. The process expounded above is the main pathway of RIPK activation; with lack of expression of RIPK1, RIPK3 can also be activated by interacting with other molecules containing RHIM domains, such as ZBP1 and TICAM1. This pathway also plays an important role in instances of necroptosis. Activated RIPK3 catalyzes the phosphorylation of mixed-lineage kinase domain-like pseudokinase (MLKL) and induces the formation

of MLKL oligomers (Das et al. 2016). Once located on the plasma membrane, MLKL activates the ADAM family proteases on cell surface, thereby promoting the shedding of plasma membrane-associated proteins or the formation of $Mg2+$ permeant channels, which subsequently triggers the permeability of the plasma membrane and is ended with the occurrence of necroptosis. Experimental results show that active caspase-8 induces cell apoptosis under low-dose radiation and inhibits necrosis by cleaving RIP; under high-dose radiation, however, decreased caspase-8 activity prompts the formation of intracellular RIP1/RIP3 complex to mediate necroptosis in tumor cells (Zhou et al. 2021).

Parthanatos. Parthanatos (PAPR1-dependent cell death) is driven by overactivation of ADP-ribose-polymerase-1 (PAPR-1), a specific component of the DNA damage response mechanism (DDR), that not only occurs after severe DNA alkylation damage but can also be induced by cellular stimuli such as oxidative stress and hypoxia. As a result, bioenergetic cessation and AIF, MIF-dependent DNA degradation emerge in the cells. PAPR1 mainly repairs damaged DNA through base-excision repair and non-homologous end joining pathways to ensure the normal function of genetic material. Nevertheless, once damage is beyond repair, enhanced and prolonged hyperactivation of PARP1 leads to depletion of NAD^+ and then inhibits mitochondrial ATP synthesis. Simultaneously, PAPR1 can catalyze the formation of poly-ADP ribose polymers, which can bind to AIFM1 (mitochondrial-related apoptosis inducing factors, especially AIF) to facilitate the release of AIF into the cytoplasm and its transfer to the nucleus, mediating large-scale DNA fragmentation and chromatin condensation. Moreover, reactive nitrogen, especially NO, is also a fundamental factor in hyperactivation of PAPR1. Parthanatos occurs with hyperactivation of

PAPR1 when radiation inflicts excessive DNA damage or provokes intracellular production of iNOS and NO in tumor cells (Zhou et al. 2021).

Autophagy-dependent cell death

Autophagy-dependent cell death is a type of death mode depending on the autophagy mechanism or its components. Autophagy is a process in which a cell engulfs its own macromolecules or organelles to coat them into vesicles and then fuses with lysosomes to form autophagic lysosomes where the constituents are degraded. The mechanism of autophagy is the adaptation of cells to harmful external stimuli during stress, which appears to facilitate cells' survival when onfronted with specific pathophysiological or strong stimuli (such as high-dose radiation exposure); however, excessive autophagy can trigger cell death (Chaurasia et al. 2016; Denton and Kumar 2019; Linder and Kogel 2019) (Fig. 3).

In mammalian cells, the initiation of the classical autophagy pathway is mainly accomplished by the interaction of the mammalian target of the rapamycin complex 1 (mTORC1) and the ULK 1 (Atg 1) complex. When stimuli, such as nutritional deficiencies, hypoxia, or cell stress, is detected, AMPK inhibits the activity of mTOCR 1 complex to release suppression of autophagy. The mTOCR1 then activates ULK 1 through dephosphorylation and facilitates the formation of the UKL1 complex with FIP200 and mAtg13, contributing to the occurrence of autophagosomes. The 6-key molecule initiating the formation of autophagosome vesicle membrane is a ClassIIIPI3K complex (class III phosphatidylinositol 3-kinase/PtdIns3K). A compound system that mainly relies on ubiquitination (E1 and E2) also exerts a vital effect: the binding with Atg12 and modification of Atg8/LC3 mediate the extension of vesicles. After autophagosomes form and encapsulate abnormal biological macromolecules or other cellular components, they urge lysosomes to combine, dissolve, and digest or recycle degradation products (Li W et al. 2019).

Nuclear autophagy (caused by DNA damage, etc.) plays a key role in autophagy-dependent death. Radiation-induced DNA damage (especially DNA double-strand breaks) can induce autophagy. It has been reported that inhibition of the ULK1 interacting protein FIP200 can damage DDR, thereby triggering cell death under oxidative stress induced by ionizing radiation (Ying and Padanilam 2016). P53 and ATM function are the linking proteins between radiation-induced DDR and autophagy. After DNA damage, P53 induces autophagy through transcriptional induction of several genes, including damage-regulated autophagy modulator (DRAM), ULK1/2, sestrin1/2, and bnip3c (Galluzzi et al. 2014); when radiation-induced DNA damage depletes NAD + and consequently ATP, polyadenylation polymerase 1 (PAPR 1) is overactivated. This energy imbalance can activate autophagy via the AMPK pathway (Roshani-Asl et al. 2020).

Besides DNA damage, protein folding errors, mitochondrial dysfunction, and ER stress induced by radiation can also provoke autophagy (Chaurasia et al. 2016.)

Mitochondrial autophagy (Mitophagy) is an atypical cell autophagy, whose pathway is dependent or independent of the interaction of PINK1 (a mitochondrial-specific kinase), PARKIN, and E3 ubiquitin ligase. Studies have shown the relation between radiation-induced mitochondrial dysfunction or biogenesis and mitophagy. Moreover, mitophagy has a strong correlation with metabolic reprogramming of cancer cells after irradiation. Many glycolysis regulatory
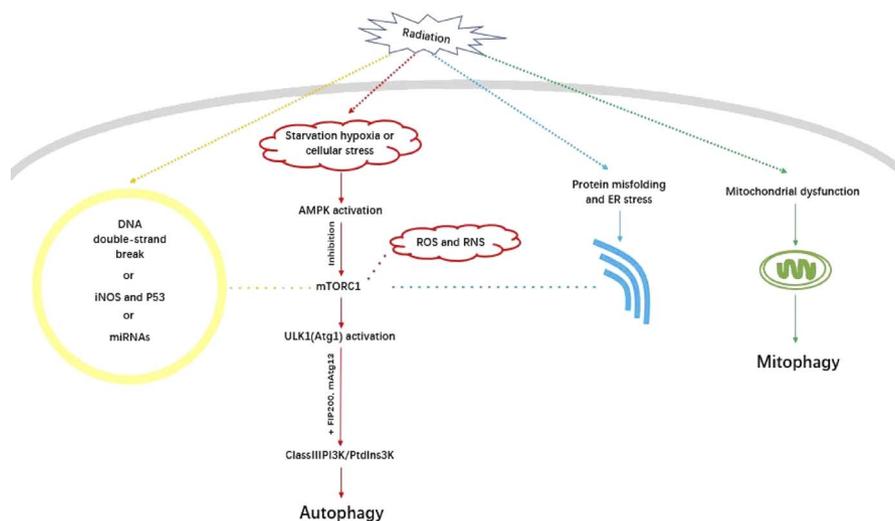
Fig. 3. Signaling pathways involved in radiation-induced autophagy-dependent cell death. The initiation of classical autophagy pathway is mainly accomplished by the interaction of mammalian target of rapamycin complex 1(mTORC1) and ULK 1 (Atg 1) complex. Moreover, there is an atypical cell autophagy called Mitochondrial autophagy (Mitophagy), whose pathway is mainly dependent or independent of the interaction of PINK1 (a mitochondrial-specific kinase), PARKIN and E3 ubiquitin ligase.

genes and specific markers of mitophagy are upregulated in irradiated cells, thus providing a survival advantage for cells. This also exploits a new direction for radiotherapy research in the future (Ney 2015).

The endoplasmic reticulum can function through the following mechanisms under radiation induction: (1) endoplasmic reticulum stress induces autophagy by downregulating the activity level of the Akt/TSC/MTOR pathway; (2) under exposure of radiation, the dominant Perk and IRE1 pathways cause ER stress through activation of Perk-eif2a, ultimately leading to autophagy [20]; or (3) as a result of the damage caused by radiation-induced reactive oxygen species, a process collectively known as unfolded protein response (UPR) is induced in the ER and triggers an active signal to increase the cytosolic calcium load released from the ER. Briefly speaking, production of ROS results in the activation of ER stress mediated by UPR. These couplings indicate that there is presumably a correlation between ROS, ER stress, [Ca2+]i and autophagy (Kim et al. 2010).

There are other important pathways between radiation and autophagy:

(1) Among the key molecules induced by radiation, inducible nitric oxide synthase (iNOS) and nitric oxide (NO) have been confirmed to be involved in radiation-induced cellular autophagy. The promoter region of iNOS gene contains various sequences of related transcription factors, such as nuclear factor κB (NF-κB) and Kruppel-like factor 6 (KLF6), whose transcription leads to increase NO and thus induces caspase-mediated apoptosis and protein nitration-mediated autophagy (Kiang et al. 2009; Gorbunov and Kiang 2009);
(2) The regulatory effect of radiation-induced microRNAs in cells has also been confirmed, providing new possibilities in improving tumor radiotherapy (recent researches have shown that miR-199a-5p plays a role in the regulation of autophagy after irradiation) (Yi et al. 2013; Chaudhry 2014); and
(3) Relevant to the maintenance of genome stability, chaperone-mediated autophagy exerts crucial influences on the degradation of CHK1 after exposure to DNA damaging agents (etoposide and gamma radiation). What is more, chaperone-mediated inactivation of autophagy gives rise to accumulation of DNA damage in specially cultured mouse fibroblasts (Park et al. 2015).

Pyroptosis

Pyroptosis is a form of cell death that is heavily dependent on members of the Gasdermin protein family and mainly activated by inflammatory caspase-1 and caspase-11 (Galluzzi et al. 2018). Gasdermin protein family members can be activated and cleaved by caspase1/11 through classical and non-classical pathways, thereby forming plasma membrane pores and causing cell swelling and death. Originally considered to occur merely in cells of the monocyte system and rely on the activation of inflammatory caspase-1, pyroptosis was later found to occur in other cell lineages induced by other caspases (such as caspase-3) and participate in innate immunity to intracellular pathogens as well (Shi et al. 2017) (Fig. 4).

At the molecular level, depending on diverse initial stimuli, pyroptosis usually depends on the activation of one or more caspases, including caspase-1, caspase-3, mouse caspase-11, and its homologous human caspase-4/5. There is a wealth of evidence verifying that lipopolysaccharide/LPS of gram-negative bacteria acting on PRRs is the main cause of pyroptosis, which next activates downstream molecules-Gasdermin family proteins, with similar N-terminal domains (mainly GSDMD); in addition, activated caspase-1 can also
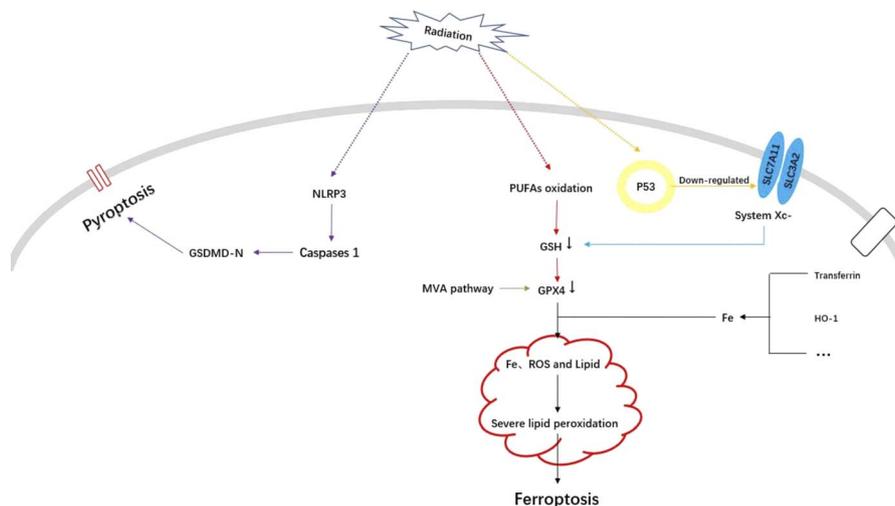
Fig. 4. Signaling pathways involved in radiation-induced pyroptosis and ferroptosis. Various pathways induce ferroptosis directly or indirectly by affecting the activity of glutathione peroxidase(GPXs). These pathways include system Xc-, P53, GPX4, transportation of voltage-dependent anion channels/VDACs, methionine sulfur transfer pathway, heme oxygenase 1/HO-1, and the internal iron source of transferrin.

cleave GSDMD and trigger pyroptosis. The occurrence of pyroptosis is associated with the secretion of IL-1 beta and IL-18, thus mediating a strong pro-inflammatory effect (Shi et al. 2017).

Studies have observed the increased caspase-1 activity and proportion of pyroptosis under 10 and 20 Gy irradiation in bone marrow-derived macrophages (BMDM) (Liu et al. 2017); analogously, the activation of NLRP3 inflammasomes cannot only mediate radiation-induced pyroptosis of BMDM but also induce the pyroptosis of damaged lung tissue cells in mice under radiation (Han et al. 2017). Moreover, under 10 Gy x-ray irradiation, pyroptosis of human umbilical vein endothelial cells (HUVECs) is induced, and the expression of Cx43 is decreased. Overexpression of Cx43 can significantly attenuate pyroptosis as it decreases the level of active caspase-1 (Li et al., 2019a). These studies suggest that pyroptosis serves as an important form of ionizing radiation-induced death as well, although which cells are more inducible remains indistinct.

Ferroptosis

Ferroptosis is a novel mode of death that can be controlled by its own GPX4, triggered by oxidative stress and can be inhibited by iron chelators and lipophilic antioxidants (Galluzzi et al. 2018). It has recently been recognized as a significant mechanism of tumor suppression. Essentially, ferroptosis is iron toxicity death caused by accumulation of severe lipid peroxidation, which depends on the generation of ROS and the presence of iron. The process of ferroptosis is independent of the mechanisms of caspases, necrosome components, CYPD, and manifests as necrotic morphology: mainly mitochondrial changes, including shrinkage, ultrastructure with high electron density, reduction/disappearance of cristae, and OMM rupture.

Directly or indirectly, the different pathways to induce ferroptosis ultimately derive from affecting the activity of glutathione peroxidase (GPXs) (Hirschhorn and Stockwell 2019). These are:

(1) Inhibition of system Xc-: Ferroptosis activators, such as Erastin RSL3, etc. can induce ferroptosis by inhibiting the cystine glutamate transport receptor (system Xc-) and thus block the absorption of glutathione, which is a necessary cofactor for GPXs to function. With declined activity of GPXs, the antioxidative capacity of cells is decreased, and lipid reactive oxygen species are accumulated, thereby causing oxidative death;
(2) p53-mediated ferroptosis: experiments by Jiang et al. have verified that P53 gene activation significantly reduces the antioxidant capacity of cells (Jiang L et al. 2015). The absorption of cystine by system XC can be inhibited by P53 through downregulating the expression of SLC7A11 (one of the heterodimeric system Xc-compositions), which decreases in the activity of cystine-dependent glutathione peroxidase and leads to ferroptosis;

(3)Direct inhibition of GPX4: GPX4 in the GPXs family, the target protein of RSL3 (Ras-selective-lethal compound3), plays the most significant role in ferroptosis. RSL3 and others can directly act on GPX4 and inhibit its activity, which leads to the reduction of antioxidant capacity of cells, increase of the lipid reactive oxygen species, and ultimately ferroptosis. In addition, the mevalonate or MVA pathway can act on GPX4 by regulating the maturation of selenocysteine (one of the amino acids in the active center of GPX4) tRNA and provoke ferroptosis; and
(4)Transportation of voltage-dependent anion channels or VDACs, methionine sulfur transfer pathway, heme oxygenase 1 or HO-1 and the internal iron source of transferrin can all play a part in ferroptosis (Fig. 4).

GSH is an important antioxidant. GPX4 can limit lipid peroxidation by catalyzing the reduction of GSH-dependent lipids, becoming a major endogenous inhibitor of ferroptosis. Recent evidence suggests that ferroptosis involves the preferential oxidation of specific phosphatidylethanolamines containing polyunsaturated fatty acids (PUFAs), such as arachidonic acid and epinephrine. Lipid peroxides can be formed via self-oxidation or via enzymatic reactions catalyzed by lipoxygenases (LOXs) and cyclooxygenases (COXs). Therefore, in the process of cell death, the peroxidation of PUFAs is mainly regulated by the antagonistic activity of LOXs (direct catalytic lipid peroxidation) and GPX4 (indirect inhibition).

Radiation-induced ferroptosis has been reported in a model of radiation-induced acute lung injury. Ferroptotic characteristic changes of mitochondria were observed by transmission electron microscopy (TEM), and treatment with ferroptosis inhibitor significantly alleviated radiation-induced histopathological changes in mice lungs and decreased the levels of ROS in lungs and the inflammatory cytokine levels (TNF-α, IL-6, IL-10, and TGF-β1) (Li X et al. 2019a). Ferroptosis inhibitor lipoxstatin-1 alleviates radiation-induced lung injury by activating the Nrf2 pathway and down-regulates TGF-β1, providing a new target for lung injury treatment (Li et al., 2019c). Furthermore, ferroptosis is also a part of radiation-induced cancer cell death. Radiation induces not only reactive oxygen species (ROS) but also the expression of AcSL4 (lipid metabolizing enzyme required for ferroptosis), which leads to lipid peroxidation and ferroptosis in tumor cells (Ye et al. 2020).

Immunogenic cell death

Immunogenic cell death (ICD) is a functionally specific mode of death that can activate adaptive immune responses to endogenous (cellular) or exogenous (viral) specific antigens expressed by dead cells (Galluzzi et al. 2018); that is, to activate the adaptive immune response of itself or the host. Due to the requirement for the involvement of

the immune system, this type of radiation-induced cell death is mainly carried out in the human (or animal) body. In radiotherapy, ICD plays an important role (Galluzzi et al. 2016). Initially, ICD was only thought to occur in the death of tumor cells in the radiation area. Later, it was discovered that radiotherapy could attack the remaining tumor cells using the host's immune system. Additionally, radiation-induced immune-mediated tumor rejection can be considered as an alternative way of radiosensitization, known as the fifth principle of radiobiology (Golden and Apetoh 2015).

In vivo and clinically, the original pro-immunogenic effects of radiotherapy tend to be masked by overwhelming immunosuppressive microenvironment. Nevertheless, when some established immunosuppressive barriers are removed, for example, by adding immune checkpoint inhibitors (such as anti-CTLA4 or anti-PD-1) to local radiotherapy, the immunogenic effects of radiotherapy can induce immune-mediated tumor rejection (Golden et al. 2013). It has also recently been demonstrated that low-dose radiotherapy can reprogram macrophages to the iNOS+ or M1 phenotype, enabling them to recruit tumor-specific T cells and promote tumor rejection (Klug et al., 2013). Furthermore, repeated irradiation with a dose insufficient to induce Trex1 amplifies the production of interferon beta(IFN-κB), which leads to the recruitment of BATF3-dependent dendritic cells and activation (among various tumor cells, radiation doses exceeding 12–18 Gy induce the DNA exonuclease Trex1 and weaken its immunogenicity by degrading the DNA accumulated in the cytosol after radiation (Vanpouille-Box et al. 2017).

Mitotic catastrophe

Mitotic catastrophe describes a series of events that lead to premature or inappropriate entry into the division phase due to physical and chemical factors, which play a specific role in radiation-induced cell death. Factors accounting for the failure of this mitotic failure include extensive DNA damage, dysfunction of the mitotic mechanism, abnormal stability of microtubules, and cycle checkpoint defects, etc. There are two main ways to induce lethiferous mitotic catastrophe (Vitale et al. 2011): (1) downregulation of P53 leads to the suppression of G2 or M phase checkpoints, rendering DNA damage beyond repair, and (2) centrosome hyper-amplification (Li et al., 2019c; Ye et al. 2020), where over-expanded centrosomes result in multipolar division, abnormal chromosome separation, and cells with abnormal nuclei (megakaryon, binuclear, or multinuclear, etc.). These two approaches may be interrelated because the key molecule for initiating centrosome amplification is the CDK2-cyclinA or E complex, which is also regulated by P53 (Bourke et al. 2007). In addition, P21 could not be effectively upregulated after irradiation in the absence of P53, resulting in activation of the CDK2 or cyclin A/E or a complex (Dodson et al. 2007).

In experiments with radiotherapy or radioimmunotherapy, cell death due to mitotic catastrophe can be observed (Roninson et al. 2001; Eriksson et al. 2003; Eriksson et al. 2007). When irradiated, cells experience a short G2 arrest and then advance into mitosis followed by activation of the mitotic checkpoint (also known as the spindle assembly checkpoint) to prevent mitosis (Eriksson and Stigbrand 2010). Evidence suggests that in some cells, the delayed apoptotic pathway is activated during the cessation of mitosis, which occurs in the mid-term and triggers activation of caspases and subsequent mitochondrial damage; it can also alternatively enter abnormal mitosis and ultimate death via necrosis and senescence. There is a delay in mitotic disorder, which usually occurs 2–6 d after radiation (Ruth and Roninson 2000).

Cell senescence

At the onset of senescence, although metabolism is still ongoing, cells will permanently lose their ability to proliferate, be irreversibly blocked in the state of G1 phase, and eventually die (Regulski 2017). Senescence usually occurs in normal cells that reach the limit of proliferation due to shortened telomeres. Radiation-induced senescence is a form of proliferation cell death triggered by radiation. Low-dose radiation can induce DNA damage response (DDR), which senses DNA damage and sends a signal amplification cascade to activate transient cell cycle arrest; severe DNA failure beyond repair may activate cell senescence (Rodier et al. 2009). Radiation-induced senescence does not depend on the erosion and shortened erosion of chromosomal telomeres; it needs additional discussion due to a number of publications that demonstrate changes in telomere regulation by TERT and other genes.

After irradiation, the activation of P53 facilitates cell survival through growth arrest and DNA damage repair. According to the extent and type of damage, however, P53 promotes the senescence of tumor cells after radiotherapy, often accompanied by P21 expression. When P53 signaling is impaired, radiation-induced senescence seems to be diminished. Nevertheless, accelerated senescence has also been reported in the absence of P53 or P21 and P16, suggesting that other genes may be involved in the regulation of this process (Ou and Schumacher 2018).

CONCLUSION

From the reviews above, the main characteristics of ionizing radiation-induced cell death are summarized as follows:

1. Once the dose is high enough, radiation effects mostly appear as destructiveness similar to hitting with a "heavy punch," which breaks up or even shatters cells, making it difficult to find responses of the cell itself;

Table 1. List of death patterns induced by various radiation effects and its corresponding characteristics.

Radiation effect	Death pattern	Characteristics
directly and largely destroy intracellular components such as macromolecule, DNA and organelles	necrosis	passive death induced by MPT, RIP complex and overactivation of PARP1; Cause inflammation
act on apoptosis-related receptors or cause perturbation of intracellular microenvironment	apoptosis	active death depending on caspases and Bcl-2 family; formation of apoptotic bodies; Without inflammation
extensive damage of intracellular components	autophagy	an important cell mechanism to ensure itself by digesting damaged components; in severe cases, autophagy-dependent cell death occurs
severe accumulation of peroxidation	ferroptosis	necrotic-like death in the presence of iron and ROS
activate surface antigens or immune cells	immunogenic cell death	depends on the effect (inhibit or kill) of the immune system
stimulate intracellular inflammatory effects	pyroptosis	the Gasdermin family forms a pore in the plasma membrane, causing cell swelling; inflammation caused by IL-18 and IL-1β
damage to cycle-related genes or chromosomes and essential components of division	mitotic catastrophe	irreversible cell cycle arrest; non-fatal death

2. Radiosensitivity varies from cell phenotypes and phases of the cell cycle, and it leads to different cell deaths because of irradiation exposure;

3. There is also rigorous and specific dose-dependence on even the identical cells, indicating that radiation with different doses corresponds to different death modes;

4. Due to the extensive effect of radiation, various responses seem to appear in various cellular subregions within one cell; in other words, there is no specific division in cell deaths; and

5. It is the existence of common initial activation and signaling molecules among all kinds of cell deaths, as well as sophisticated crossways in cellular molecules, that makes it more laborious to distinguish and classify various cell deaths (Table 1).

As can be seen from this summary, at odds with cell death targeted by specific ligands (such as Fas combined with FasL), the mechanism of radiation-induced occurrence is extremely complex, and its pathways are diverse, thus resulting in various cell deaths. The reason is probably that the targets of ionizing radiation are too complicated and vary with the changes of the radiation dose and the environment. This is also where the nodus in studies of the mechanism of cell death in radiobiology lies. The author suggests that ionizing radiation, as a strong external stimulus, requires researchers to continuously explore the key "connecting points" for its effect and draw conclusions to make a difference in radiation protection and radiotherapy, which is essential to inhibiting ionizing radiation-induced cell death.

REFERENCES

Akpolat M, Oz ZS, Gulle K, Hamamcioglu AC, Bakkal BH, Kececi M. X irradiation induced colonic mucosal injury and the detection of apoptosis through PARP-1/p53 regulatory pathway. Biomed Pharmacother 127:110134; 2020.

Bourke E, Dodson H, Merdes A, Cuffe L, Zachos G, Walker M, Gillespie D, Morrison CG. DNA damage induces Chk1-dependent centrosome amplification. EMBO Rep 8:603–609; 2007.

Chaudhry MA. Radiation-induced microRNA: discovery, functional analysis, and cancer radiotherapy. J Cell Biochem 115:436–449; 2014.

Chaurasia M, Bhatt AN, Das A, Dwarakanath BS, Sharma K. Radiation-induced autophagy: mechanisms and consequences. Free Radic Res 50:273–290; 2016.

Contassot E, Gaide O, French LE. Death receptors and apoptosis. Dermatol Clin 25:487–501; 2007.

Das A, McDonald DG, Dixon-Mah YN, Jacqmin DJ, Samant VN, Vandergrift WA III, Lindhorst SM, Cachia D, Varma AK, Vanek KN, Banik NL, Jenrette JM III, Raizer JJ, Giglio P, Patel SJ. RIP1 and RIP3 complex regulates radiation-induced programmed necrosis in glioblastoma. Tumour Biol 37:7525–7534; 2016.

Denton D, Kumar S. Autophagy-dependent cell death. Cell Death Differ 26:605–616; 2019.

Dodson H, Wheatley SP, Morrison CG. Involvement of centrosome amplification in radiation-induced mitotic catastrophe. Cell Cycle 6:364–370; 2007.

Elmore S. Apoptosis: a review of programmed cell death. Toxicol Pathol 35:495–516; 2007.

Eriksson D, Joniani HM, Sheikholvaezin A, Löfroth PO, Johansson L, Riklund Ahlström K, Stigbrand T. Combined low dose radio- and radioimmunotherapy of experimental HeLa Hep 2 tumours. Eur J Nucl Med Mol Imag 30:895–906; 2003.

Eriksson D, Löfroth PO, Johansson L, Riklund KA, Stigbrand T. Cell cycle disturbances and mitotic catastrophes in HeLa Hep2 cells following 2.5 to 10 Gy of ionizing radiation. Clin Cancer Res 13(18 Pt 2):5501s–5508s; 2007.

Eriksson D, Stigbrand T. Radiation-induced cell death mechanisms. Tumour Biol 31:363–372; 2010.

Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, Alnemri ES, Altucci L, Amelio I, Andrews DW, Annicchiarico-Petruzzelli M, Antonov AV, Arama E, Baehrecke EH, Barlev NA, Bazan NG, Bernassola F, Bertrand MJM, Bianchi K, Blagosklonny MV, Blomgren K, Borner C, Boya P, Brenner C, Campanella M, Candi E, Carmona-Gutierrez D, Cecconi F, Chan FK, Chandel NS, Cheng EH, Chipuk JE, Cidlowski JA, Ciechanover A, Cohen GM, Conrad M, Cubillos-Ruiz JR, Czabotar PE, DAngiolella V, Dawson TM, Dawson VL, De Laurenzi V, De Maria R, Debatin KM, DeBerardinis RJ, Deshmukh M, Di Daniele N, Di Virgilio F, Dixit VM, Dixon SJ, Duckett CS, Dynlacht BD, El-Deiry WS, Elrod JW, Fimia GM, Fulda S, García-Sáez AJ, Garg AD, Garrido C, Gavathiotis E, Golstein P, Gottlieb E, Green DR, Greene LA, Gronemeyer H, Gross A, Hajnoczky G, Hardwick JM, Harris IS, Hengartner MO, Hetz C, Ichijo H, Jäättelä M, Joseph B, Jost PJ, Juin PP, Kaiser WJ, Karin M, Kaufmann T, Kepp O, Kimchi A, Kitsis RN, Klionsky DJ, Knight RA, Kumar S, Lee SW, Lemasters JJ, Levine B, Linkermann A, Lipton SA, Lockshin RA, Lopez-Otin C, Lowe SW, Luedde T, Lugli E, MacFarlane M, Madeo F, Malewicz M, Malorni W, Manic G, Marine JC, Martin SJ, Martinou JC, Medema JP, Mehlen P, Meier P, Melino S, Miao EA, Molkentin JD, Moll UM, Munoz-Pinedo C, Nagata S, Nuñez G, Oberst A, Oren M, Overholtzer M, Pagano M, Panaretakis T, Pasparakis M, Penninger JM, Pereira DM, Pervaiz S, Peter ME, Piacentini M, Pinton P, Prehn JHM, Puthalakath H, Rabinovich GA, Rehm M, Rizzuto R, Rodrigues CMP, Rubinsztein DC, Rudel T, Ryan KM, Sayan E, Scorrano L, Shao F, Shi Y, Silke J, Simon HU, Sistigu A, Stockwell BR, Strasser A, Szabadkai G, Tait SWG, Tang D, Tavernarakis N, Thorburn A, Tsujimoto Y, Turk B, Vanden Berghe T, Vandenabeele P, Vander Heiden MG, Villunger A, Virgin HW, Vousden KH, Vucic D, Wagner EF, Walczak H, Wallach D, Wang Y, Wells JA, Wood W, Yuan J, Zakeri Z, Zhivotovsky B, Zitvogel L, Melino G, Kroemer G. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death Differ 25:486–541; 2018.

Galluzzi L, Kepp O, Krautwald S, Kroemer G, Linkermann A. Molecular mechanisms of regulated necrosis. Seminars Cell Development Biol 35:24–32; 2014.

Galluzzi L, Zitvogel L, Kroemer G. Immunological mechanisms underneath the efficacy of cancer therapy. Cancer Immunol Res 4:895–902; 2016.

Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer Immunol Res 1:365–372; 2013.

Golden EB, Apetoh L. Radiotherapy and immunogenic cell death. Semin Radiat Oncol 25:11–17; 2015.

Gorbunov NV, Kiang JG. Up-regulation of autophagy in small intestine Paneth cells in response to total-body gamma-irradiation. J Pathol 219:242–252; 2009.

Han R, Wu D, Deng S, Liu T, Zhang T, Xu Y. NLRP3 inflammasome induces pyroptosis in lung tissues of radiation-induced lung injury in mice. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 33:1206–1211; 2017.

Hirschhorn T, Stockwell BR. The development of the concept of ferroptosis. Free Radic Biol Med 133:130–143; 2019.

Jiang L, Hickman JH, Wang SJ, Gu W. Dynamic roles of p53-mediated metabolic activities in ROS-induced stress responses. Cell Cycle 14(18):2881–2885; 2015.

Kang R, Li R, Dai P, Li Z, Li Y, Li C. Deoxynivalenol induced apoptosis and inflammation of IPEC-J2 cells by promoting ROS production. Environ Pollut 251:689–698; 2019.

Kerr JF, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 26:239–257; 1972.

Kiang JG, Smith JT, Agravante NG. Geldanamycin analog 17-DMAG inhibits iNOS and caspases in gamma-irradiated human T cells. Radiat Res 172:321–330; 2009.

Kim KW, Moretti L, Mitchell LR, Jung DK, Lu B. Endoplasmic reticulum stress mediates radiation-induced autophagy by perk-eIF2alpha in caspase-3/7-deficient cells. Oncogene 29(22):3241–3251. 2010.

Klug F, Prakash H, Huber PE, Seibel T, Bender N, Halama N, Pfirschke C, Voss RH, Timke C, Umansky L, Klapproth K, Schakel K, Garbi N, Jager D, Weitz J, Schmitz-Winnenthal H, Hammerling GJ, Beckhove P. Low-dose irradiation programs macrophage differentiation to an iNOS$^+$/M1 phenotype that orchestrates effective T cell immunotherapy. Cancer Cell 24(5):589–602; 2013.

Kondo T. Radiation-induced cell death. Nihon Rinsho 70:389–393; 2012.

Laubach V, Kaufmann R, Bernd A, Kippenberger S, Zoller N. Extrinsic or intrinsic apoptosis by curcumin and light: still a mystery. Int J Mol Sci 20(4):905; 2019.

Le J, Hickman JH, Wang SJ, Gu W. Dynamic roles of p53-mediated metabolic activities in ROS induced stress responses. Cell Cycle 14:2881–2885; 2015.

Li C, Tian M, Gou Q, Jia YR, Su X. Connexin43 modulates x-ray-induced pyroptosis in human umbilical vein endothelial cells. Biomed Environ Sci 32:177–188; 2019.

Li W, Zhang L. Regulation of ATG and autophagy initiation. Adv Exp Med Biol 1206:41–65; 2019.

Li X, Duan L, Yuan S, He J. Ferroptosis inhibitor alleviates radiation-induced lung fibrosis (RILF) via down-regulation of TGF-beta1. J Inflamm (Lond) 16:11; 2019a.

Li X, Zhuang X, Qiao T. Role of ferroptosis in the process of acute radiation-induced lung injury in mice. Biochem Biophys Res Commun 519:240–245; 2019b.

Linder B, Kogel D. Autophagy in cancer cell death. Biology (Basel) 8(4):82; 2019.

Liu YG, Chen JK, Zhang ZT, Ma XJ, Lu GC. NLRP3 inflammasome activation mediates radiation-induced pyroptosis in bone marrow-derived macrophages. Cell Death Dis 8:e2579; 2017.

Luo X, Budihardjo I, Zou H, Slaughter C, Wang X. Bid, a Bcl2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors. Cell 94:481–490; 1998.

Ney PA. Mitochondrial autophagy: origins, significance, and role of BNIP3 and NIX. Biochim Biophys Acta 1853(10 Pt B):2775–2783; 2015.

Ou HL, Schumacher B. DNA damage responses and p53 in the aging process. Blood 131:488–495; 2018.

Park C, Suh Y, Cuervo AM. Regulated degradation of Chk1 by chaperone-mediated autophagy in response to DNA damage. Nat Commun 6:6823; 2015.

Proskuryakov SY, Gabai VL, Konoplyannikov AG. Necrosis is an active and controlled form of programmed cell death. Biochem (Mosc) 67:387–408; 2002.

Przybyszewski WM, Wideł M, Szurko A, Maniakowski Z. Dose rate-dependent cellular and molecular effects of ionizing radiation. Postepy Hig Med Dosw 11:468–477; 2008.

Regulski MJ. Cellular senescence: what, why, and how. Wounds 29:168–174; 2017.

Rodier F, Coppé JP, Patil CK, Hoeijmakers WA, Muñoz DP, Raza SR, Freund A, Campeau E, Davalos AR, Campisi J. Persistent DNA damage signaling triggers senescence-associated inflammatory cytokine secretion. Nat Cell Biol 11:973–979; 2009.

Roninson IB, Broude EV, Chang BD. If not apoptosis, then what? Treatment-induced senescence and mitotic catastrophe in tumor cells. Drug Resist Update 4:303–313; 2001.

Roshani-Asl E, Mansori B, Mohammadi A, Najafi S, Danesh-Pouya F, Rasmi Y. Interaction between DNA damage response and autophagy in colorectal cancer. Gene 730:144323; 2020.

Ruiter GA, Zerp SF, Bartelink H, van Blitterswijk WJ, Verheij M. Alkyl-lysophospholipids activate the SAPK/JNK pathway and enhance radiation-induced apoptosis. Cancer Res 59:2457–2463; 1999.

Ruth AC, Roninson IB. Effects of the multidrug transporter P-glycoprotein on cellular responses to ionizing radiation. Cancer Res 60:2576–2578; 2000.

Shi J, Gao W, Shao F. Pyroptosis: gasdermin-mediated programmed necrotic cell death. Trends Biochem Sci 42:245–254; 2017.

Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ, Inghirami G, Coleman CN, Formenti SC, Demaria S. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Comm 8:15618; 2017.

Vitale I, Galluzzi L, Castedo M, Kroemer G. Mitotic catastrophe: a mechanism for avoiding genomic instability. Nat Rev Mol Cell Biol 12:385–392; 2011.

Wang S, El-Deiry WS. TRAIL and apoptosis induction by TNF-family death receptors. Oncogene 22:8628–8633; 2003.

Yang S, Huang J, Liu P, Li J, Zhao S. Apoptosis-inducing factor (AIF) nuclear translocation mediated caspase-independent mechanism involves in x-ray-induced MCF-7 cell death. Int J Radiat Biol 93:270–278; 2017.

Ye LF, Chaudhary KR, Zandkarimi F, Harken AD, Kinslow CJ, Upadhyayula PS, Dovas A, Higgins DM, Tan H, Zhang Y, Buonanno M, Wang TJC, Hei TK, Bruce JN, Canoll PD, Cheng SK, Stockwell BR. Radiation-induced lipid peroxidation triggers ferroptosis and synergizes with ferroptosis inducers. ACS Chem Biol 15:469–484; 2020.

Yi H, Liang B, Jia J, Liang N, Xu H, Ju G, Ma S, Liu X. Differential roles of miR-199a-5p in radiation-induced autophagy in breast cancer cells. FEBS Lett 587:436–443; 2013.

Ying Y, Padanilam BJ. Regulation of necrotic cell death: p53, PARP1 and cyclophilin D—overlapping pathways of regulated necrosis? Cell Mol Life Sci 73:2309–2324; 2016.

Zhou Y, Liu L, Tao S, Yao Y, Wang Y, Wei Q, Shao A, Deng Y. Parthanatos and its associated components: promising therapeutic targets for cancer. Pharmacol Res 163:105299; 2021.

■ ■