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REVIEW ARTICLE

The DNA-damage response and nuclear events as regulators of nonapoptotic forms of cell death

Evgeniia A. Prokhorova[1,3] · Aleksandra Yu. Egorshina[1] · Boris Zhivotovsky[1,2] · Gelina S. Kopeina[1]

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Abstract

The maintenance of genome stability is essential for the cell as the integrity of genomic information guaranties reproduction of a whole organism. DNA damage occurring in response to different natural and nonnatural stimuli (errors in DNA replication, UV radiation, chemical agents, etc.) is normally detected by special cellular machinery that induces DNA repair. However, further accumulation of genetic lesions drives the activation of cell death to eliminate cells with defective genome. This particular feature is used for targeting fast-proliferating tumor cells during chemo-, radio-, and immunotherapy. Among different cell death modalities induced by DNA damage, apoptosis is the best studied. Nevertheless, nonapoptotic cell death and adaptive stress responses are also activated following genotoxic stress and play a crucial role in the outcome of anticancer therapy. Here, we provide an overview of nonapoptotic cell death pathways induced by DNA damage and discuss their interplay with cellular senescence, mitotic catastrophe, and autophagy.

Introduction

The first discrimination between apoptosis and necrosis was based on the changes in cellular morphology. Apoptosis was defined by cytoplasmic and nuclear shrinkage, chromatin condensation at the nuclear periphery, nuclear fragmentation and cell blebbing culminating in the formation of apoptotic bodies [1]. In contrast, necrotic cell death was characterized by cell swelling, mitochondrial dysfunction, oxidative stress, and early plasma membrane rupture resulting in the uncontrolled release of cellular contents. In 1976, the first biochemical feature of apoptosis, i.e., degradation of chromosomal DNA into oligonucleosomal-length fragments, was reported [2]. Over the following four decades, apoptosis research has been progressing rapidly, yielding a number of important practical therapeutic implications. In contrast, necrosis was regarded for many years as an unregulated mode of cell death, which occurs when the cell is challenged with stress beyond its threshold. Accordingly, necrosis, as a process that cannot be either prevented or modulated, was not considered as a target for pharmacological intervention, therefore, little attention was given to it by the scientific community.

The possibility that necrosis might also occur in a regulated fashion emerged in 1988, when tumor necrosis factor α (TNFα), a classical death receptor activation signal, was shown to promote necrosis in the absence of any cellular damage [3]. The discovery of necrostatin-1, an inhibitor of necrotic cell death, supported the view that necrotic cell death might be dependent on the cellular molecular machinery [4], and sparked interest in regulated non-apoptotic cell death modalities.

Since then, our knowledge of molecular mechanisms underlying apoptotic and necrotic cell death phenotypes has significantly improved. Nowadays, ‘necrosis’ is no longer the term for the uncontrolled cell death. Rather, it is clear that there are several modes of cell death characterised by necrotic morphology that include necroptosis, parthanatos,

These authors contributed equally: Evgeniia A. Prokhorova, Aleksandra Yu. Egorshina

✉ Boris Zhivotovsky
Boris.Zhivotovsky@ki.se

✉ Gelina S. Kopeina
lirroster@gmail.com

[1] Faculty of Fundamental Medicine, MV Lomonosov Moscow State University, 119991 Moscow, Russia

[2] Division of Toxicology, Institute of Environmental Medicine, Karolinska Institutet, Box 210, 17177 Stockholm, Sweden

[3] Present address: Sir William Dunn School of Pathology, University of Oxford, Oxford OX1 3RE, UK

mitochondrial permeability transition (MPT)-dependent regulated necrosis, and ferroptosis [5].

The diversity of the described cell death programs demands a well-established classification. According to the last recommendations of the Nomenclature Committee on Cell Death, all known types of cell death are currently categorized into 'accidental' (ACD) and "regulated" (RCD) [6]. In many ways, the notion of ACD corresponds to the previous meaning of the term "necrosis", as ACD reflects the unpreventable demolition of the cell exposed to extreme physicochemical or mechanical stimuli that does not involve specific molecular mechanisms. RCD relies on genetically encoded machinery, and, therefore, its course can be both averted and modulated. Concerning the types of RCD, they are now not limited to apoptosis and cell death modalities with a necrotic morphotype, but include, for example, autophagic cell death, cell cannibalism by entosis and netosis; and neutrophil cell death. In addition, as the cell usually attempts to restore normal homeostasis, RCD is often preceded by adaptive stress responses (e.g., autophagy) [7, 8] that could be critical for designing effective therapeutic strategies. Furthermore, inhibition of inflammatory or cytotoxic reactions caused by the release of damage-associated molecular patterns (DAMPs) during the propagation of some RCD modalities, as well as in the case of the execution of ACD, might provide additional therapeutic advances.

Undoubtedly, apoptosis is one of the most studied forms of RCD. However, multiple lines of evidence indicate that the contribution of other RCD modalities in both physiological and pathological processes should also be given credit. Importantly, the ability to control nonapoptotic cell death modalities might provide new avenues for improving current treatments of various disorders, in particular, cancer. While conventional cancer therapies are typically focused on triggering apoptosis and overcoming apoptosis resistance of tumor cells, most cancer cells retain the ability to succumb to other RCD types [9]. Moreover, if apoptosis is inhibited, the number of cancer cells undergoing nonapoptotic cell death generally increases [10] that can be used to enhance cancer therapy efficiency.

Therefore, in order to develop new therapeutic strategies, a comprehensive understanding of the molecular mechanisms implicated in nonapoptotic cell death is essential. Here, we provide detailed information about the events that initiate nonapoptotic cell death and occur over the course of its execution in mammalian cells in response to DNA damage induced by natural stress factors, as well as a large panel of anticancer therapeutic agents. We argue that as a number of the most common stimuli of cell death, including DNA damage, arise from the nucleus, and the most immunogenic and cytotoxic DAMPs are those of nuclear origin, dissection of the nuclear signaling might be especially important for the invention of novel therapeutic approaches. Our attention is focused on the activation of nonapoptotic mechanisms in response to DNA damage because they are still much less characterized than apoptotic pathway. The nuclear mechanisms that underlie apoptotic events have previously been described (see in [11]). Besides the description of nonapoptotic modes of cell death, we assert that their interplay with nonlethal processes such as cellular senescence, mitotic catastrophe, and autophagy that extremely influence the course of each other should not be neglected during cancer treatment.

DNA damage response (DDR)

DNA damage is one of the most common primary inducers of not only apoptotic but also nonapoptotic cell death. Errors during DNA replication and generation of reactive oxygen species (ROS) in the course of cellular metabolism constitute the two major physiological DNA lesion triggers. In addition, DNA is the main target of various genotoxic agents and stresses (e.g., ultraviolet light, ionizing radiation (IR), carcinogens, and cytotoxic drugs).

DNA damage can involve either one or both DNA strands. The central role in detection and repair of double strand breaks (DSBs) belongs to MRE11–RAD50–NBS1 (MRN) protein complex that induces ATM (Ataxia-Telangiectasia Mutated) activation [12]. Single-strand DNA breaks lead to ATR (Ataxia-Telangiectasia and Rad3-related) activation that can also be promoted by the MRN protein complex [13, 14]. Once activated ATM, ATR, and DNA-PK phosphorylate checkpoint kinases Chk1 and/or Chk2. Both proteins block activity of Cdc25, a positive regulator of the cell cycle progression (Fig. 1). In addition, ATM and ATR activate the p38MAPK/MK2 complex via TAOs (thousand and one amino acid kinases) that also controls the G_1/S, intra-S and G_2/M checkpoints and causes cell cycle arrest [15] (Fig. 1). Then, if genomic integrity is reestablished, the cell reenters cell cycle. In the case of its failure, the mechanisms that protect the cell from damage accumulation and malignant transformation are engaged. Consequently, p53 [16] and/or other transcription factors, mainly p63 and p73 [17], are activated and promote synthesis of different proteins, as well as expression of microRNAs [18], involved in the cell cycle arrest, apoptotic, and nonapoptotic cell death; cellular senescence and stress adaptive responses, namely, autophagy and inducible DNA repair processes. Genes responsible for base and nucleotide excision DNA repair are induced following genotoxic stress through p53 and AP-1 [19]. Phosphorylation of different amino acids of p53 regulates a balance between survival and lethal programs. Thus, p53 Ser15 phosphorylation triggers prosurvival response [20], while p53 Ser46 phosphorylation is associated with nonrepairable

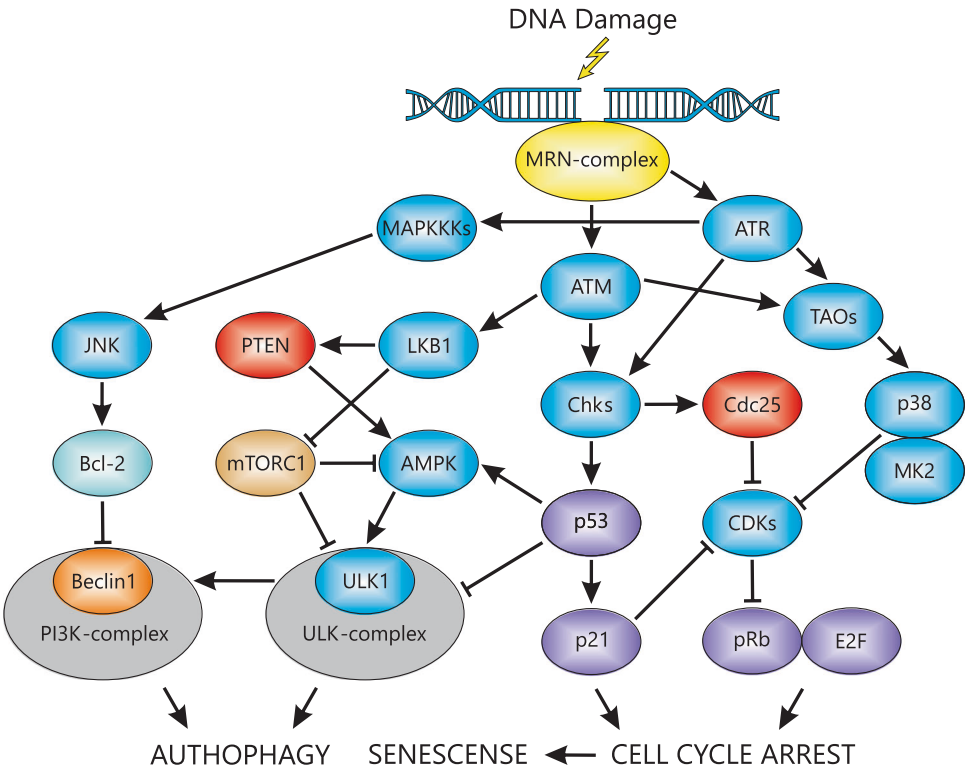

Fig. 1 Nonlethal forms of cellular response to DNA damage. Arrows indicate positive regulation; the block sign—inhibition. The abbreviations and explanations are listed in the text. Blue color denotes kinases, yellow—MRN-complex, red—phosphatases, orange—autophagy-related proteins, and lilac—proteins regulating cell cycle

DNA damage and prodeath response [21]. Apart from DNA damage, stimuli such as alterations in chromosomal distribution or mitotic spindle defects may also result in the activation of cell death machinery. In such a case, mitosis is arrested and cellular senescence or mitotic catastrophe, that subsequently operates through apoptosis or necrosis, are engaged [22].

Mitotic catastrophe and cellular senescence, tumor-suppressive counterparts

According to the recommendations of the Nomenclature Committee on Cell Death, senescence and mitotic catastrophe are not considered as forms of RCD. Nevertheless, molecular machinery involved in RCD is used for the manifestation of these processes. Cellular senescence is an irreversible cell cycle arrest that is characterized by complex phenotypic changes in cells. The main senescence phenotypic changes that distinguish it from other types of irreversible cell cycle arrest comprise a flat cell phenotype, expression of senescence-associated β-galactosidase along with the cyclin D-dependent kinase inhibitor $p16^{Ink4A}$; senescence-associated heterochromatin foci and senescence-associated secretory phenotype (SASP). Thus, IL-8 (CXCL-8) is often used as SASP biomarker [23, 24]. Several types of senescence are usually distinguished, and here we discuss the types that can be induced by DNA damage and play a tumour suppression function.

Replicative senescence has been observed in normal human fibroblasts that have lost their growth potential during long-term cultivation [25, 26]. This phenomenon is associated with telomere dysfunction resulting from the shortening of telomeres during rounds of DNA replication [27–29]. Critically shortened telomeres and destroyed telomere organization result in DDR induction [30]. Thus, telomere ends could be recognized as DSBs that initiate the activation of DNA damage checkpoints. Normally, a telomere is organized as a lasso-like structure through interaction with telomere-binding proteins that prevent DDR [31]. In addition, telomere-binding proteins, such as telomeric repeat-binding factor 2 (TRF2) and protection of telomeres 1 (POT1) suppress the checkpoint activity of ATM and ATR [32, 33]. During DNA replication, the number of telomere repeats is reduced, resulting in the loss of telomere-bound inhibitors of ATM and ATR. If telomeres are shortened below the threshold, chromosome ends are recognized as DNA breaks, triggering DDR and replicative senescence via activation of p53-p21 and/or retinoblastoma (pRB)-$p16^{Ink4A}$ pathways.

Two other types of cellular senescence—stress-induced premature senescence (SIPS) and oncogene-induced senescence (OIS)—are phenotypically similar to replicative senescence but are not associated with the shortening of telomeres. SIPS is triggered in response to subcytotoxic stresses leading to accumulation of DNA damage in various types of human proliferative cells [34]. For example, low

subcytotoxic doses of IR induce SISP both in normal and tumor cells. The latter express telomerase and do not undergo telomere-dependent replicative senescence. In this case, IR-induced SIPS stops proliferation of tumor cells and, therefore, could play an important role in tumor suppression after radiotherapy. The second type—OIS—could also be considered a result of DDR induced by oncogene-mediated DNA damage in normal cells [35, 36]. For example, the activation of oncogene H-RasV12 leads to an increase of mitochondrial ROS [37] and genomic DNA hyperreplication [38], resulting in DNA damage. In addition, DNA damage partially originates from nucleotide deficiency caused by H-RasV12-mediated downregulation of de novo deoxyribonucleotide biosynthesis [39]. Taken together, SIPS and OIS represent additional tumor suppression mechanisms and restrain cell proliferation and transformation induced by sublethal genotoxic stress or oncogene activation.

The main role in senescence propagation belongs to p53-p21 and $p16^{Ink4A}$-pRB signaling pathways. Activated in response to DNA damage, p53 upregulates transcription of a number of genes, such as p21 [40], promyelocytic leukemia protein (PML) [41], plasminogen activator inhibitor (PAI-1) [42], and DEC1 [43]. All of these proteins are described as senescence markers and are directly involved in senescence induction [44]. Thus, p21 promotes G1 cell cycle arrest via the inhibition of the activity of cyclin-CDK2/4 and PCNA [45]. At the same time, PML accumulated in PML nuclear bodies (PML-NBs) is able to recruit $p16^{Ink4A}$, p53, and the pRb/E2F complex to the PML-NBs and regulate the expression of their target genes, leading to senescence manifestation [46, 47].

Another pathway that can determine the fate of cells exposed to DNA damage is mitotic catastrophe. While mitotic catastrophe is a nonlethal process, it constitutes a crossroad that could drive cells into apoptosis, regulated necrosis or cellular senescence [22, 48, 49]. It is initiated if cells cannot complete mitosis, most often owing to gross chromosomal aberrations or mitotic spindle defects. Such perturbations of the mitotic apparatus are monitored over the course of mitosis by the specific spindle-assembly checkpoint. If danger is sensed during the M phase, the cell cycle is arrested, leading to mitotic catastrophe. Given the fact that mitotic catastrophe helps to avoid the amplification of cells with increased chromosome instability, it can be regarded as an additional tumor suppressive mechanism. Morphologically, mitotic catastrophe is different from other types of cell death in that it is characterized by chromosomal breaks, micronucleation, and multinucleation resulting from deficient karyokinesis [50]. The most prominent biochemical characteristic of mitotic catastrophe is mitotic arrest (Fig. 2), while other features of this phenomenon are rather unknown. Activation of such proteins with tumor suppressor functions as p53 [51, 52] (Fig. 2), p73 [53, 54], and caspase-2 [55–59] was shown to contribute to the process in some cases but its general significance needs further investigation.

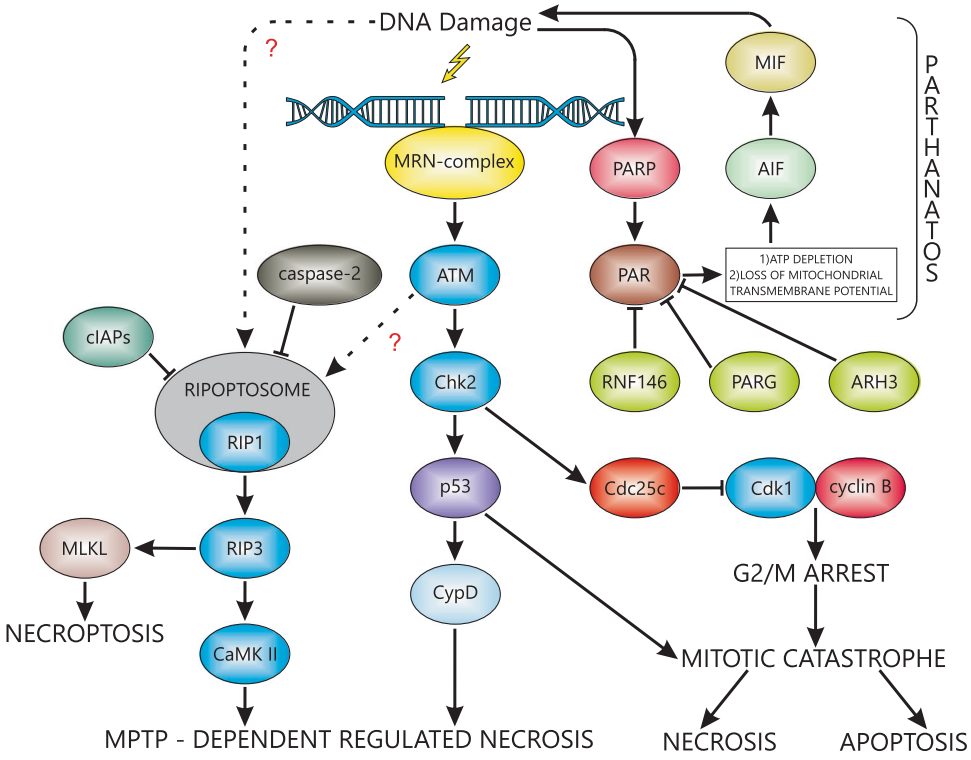

Fig. 2 Nonapoptotic forms of cell death induced in response to DNA damage. Arrows indicate positive regulation, dotted arrows with question marks—unknown signaling pathway(s), the block sign—inhibition. The abbreviations and explanations are listed in the text. Blue color denotes kinases, yellow—MRN-complex, red—phosphatases, lilac—proteins regulating cell cycle, dark gray—caspases, light green—hydrolases, and raspberry—cyclins

ATR inhibition in the absence of ATM and p53 is known to promote mitotic catastrophe [60]. Blocking ATR leads to replication fork collapse and generation of DSBs in replicated sister chromatids. In the absence of ATM and p53 double strand ends of two independently generated partially replicated sister chromatids can be ligated, resulting in deletions and aberrant chromosomal translocations. Moreover, chemical inhibition of the Hedgehog pathway also induces DNA damage through the ATR/Chk1 axis that triggers an aberrant mitotic checkpoint response and mitotic catastrophe [61]. Inhibitors of poly (ADP-ribose)polymerase 1 (PARP1) and Wee1 alone or in combination also lead to checkpoint defects, dysregulation of mitotic entry and subsequent mitotic catastrophe [62–64]. Taken together, the propagation of mitotic catastrophe requires the blocking of at least two molecular pathways regulating the cell cycle arrest and DNA repair.

In mitotic catastrophe, cell death can occur within hours or days after mitotic exit, for example, after radiotherapy [65, 66]. Low doses of DNA-damaging chemotherapeutic agents can also induce mitotic catastrophe followed by cell death, e.g., 50 ng/ml doxorubicin and 0.1 nM lidamycin induce a senescence-like phenotype and mitotic catastrophe in human hepatoma cell lines [67, 68]. Moreover, doxorubicin-induced mitotic catastrophe leads to enhanced autophagy and subsequent apoptosis that is regulated by Mcl-1 and Bcl-xL [69]. Importantly, cancer cells are marked by dysregulation of the cell cycle and resistance to apoptotic cell death. Considering this, low doses of DNA-damaging agents and activation of DDR following mitotic catastrophe might help to overcome resistance of cancer cells to therapy.

Interestingly, cellular senescence and mitotic catastrophe could be triggered simultaneously or consistently. For example, overexpression of Mad2-interacting protein $p31^{comet}$ induced senescence that was accompanied by mitotic catastrophe with massive nuclear and chromosomal abnormalities [70]. However, in some cases the induction of cellular senescence and mitotic catastrophe is mutually exclusive. Thus, phosphatase and tensin homolog (PTEN) activation and inhibition of mitotic spindle disassembly lead to strong mitotic catastrophe and subsequent apoptosis [71], while PTEN loss induces senescence [72].

Notably, since most tumor cells display highly heterogeneous chromosomal content, specifically, aneuploidy or polyploidy, they are intrinsically more susceptible to cell death following mitotic abnormalities, and thus, to the induction of mitotic catastrophe or cellular senescence [73]. Moreover, much lower drug concentrations are sufficient to drive cancer cells into mitotic catastrophe or senescence than those needed to trigger apoptosis or necrosis [68, 74–76]. Correspondingly, the induction of mitotic catastrophe or senescence would significantly limit side effects that is a very attractive point for anticancer therapy. However, it is essential to remember that prosenescence therapy may also increase the risk of cancer relapse. Senescent cells secrete SASP that could stimulate tumor cell proliferation [77]. In this case, the inhibition of SASP production can be recommended to prevent cancer recurrence.

Autophagy and the DNA damage response link

The terms “autophagy” and “autophagic cell death”, although describing processes involving the same cellular molecules, significantly differ in their essences. While the first notion relates to a type of cellular adaptation to stress, the latter designates a cell death modality. By the definition, autophagic cell death does not involve apoptotic or necrotic effectors, and does not occur during mitosis, but relies on the autophagy machinery and, as well as autophagy, is associated with the massive formation of autophagosomes and autolysosomes [50]. Unless it is proven that autophagy mechanistically mediates the switch to cell death, the term “autophagy-dependent cell death” is preferred [78]. Although autophagy is a well-known cytoprotective mechanism essential for cellular metabolism, the significance of autophagic cell death in mammalian cells is still elusive, as there are only few examples [79] and no compelling evidence. Generally, autophagic cell death is often revealed only when apoptosis is inhibited, thus acting as a backup mechanism to execute the death process [79].

DNA damage can trigger autophagy, but the underlying mechanisms remain largely unknown. Moreover, autophagy can act as a protecting mechanism against cell death induced by DNA damaging agents. Thus, treatment of melanoma cells with an anthracene-based ligand, an agent that stabilizes telomeric G-quadruplexes and triggers DNA damage, induced autophagy that diminished the cytotoxic effect of the agent [80]. Temozolomide treatment of glioblastoma cells triggered autophagy stimulating senescence rather than apoptosis [81]. The inhibition of autophagy was demonstrated to improve its cytotoxic activity and increase drug-mediated apoptosis.

Again, p53 is crucial in determining the cell’s fate. According to the conventional view, pSer15-p53 can induce the expression of autophagic and antiapoptotic genes in response to mild DNA damage, whereas, following severe genotoxic stress, pSer46-p53 favors the upregulation of genes associated with apoptotic cell death [21]. However, nowadays it is becoming increasingly clear that autophagic response usually accompanies the induction of cell death mechanisms. DNA repair systems like homologous recombination, base excision repair, and nucleotide excision repair are activated along with a relatively nonselective autophagic response and such reaction is required for cells to withstand DNA damage [19].

Among the proteins activated upon genotoxic stress, ATM seems to be crucial for autophagy initiation. This protein can activate LKB1 that promotes inhibition of mTORC1 [82] and directly phosphorylates PTEN that results in its nuclear accumulation and activation of AMP-activated protein kinase (AMPK) [83]. Active AMPK can directly phosphorylate ULK, promoting autophagy [84] (Fig. 1). In addition, not only ATM is involved in DNA damage-mediated autophagy, ATR/Chk1 signaling also regulates autophagy via lysosomal translocation of TSC2 after DNA damage [85].

At the same time, ATM, as well as other kinases activated following DNA damage, facilitates p53 stabilization and its subsequent accumulation in the nucleus. When in the cytosol, p53 inhibits autophagosome formation as it binds to FIP200 and represses its interaction with ULK1, autophagy-related protein 13 and ATG101 [86] (Fig. 1). After p53 translocation into the nucleus, autophagy is generally promoted, not only owing to the fact that autophagosome formation becomes possible, but also because p53 upregulates a range of proautophagic genes. Thus, AMPK, DRAM1, sestrins-1, -2; and PTEN are upregulated, while expression of proteins involved in autophagy inhibition, such as Bcl-2 and a number of growth factor receptors, is repressed [87]. In addition, Bcl-2 can be phosphorylated by JNK—another kinase that plays an important role in DDR [88]. Phosphorylated Bcl-2 dissociates from the Bcl-2-Beclin 1 complex that leads to release of Beclin 1 and autophagy activation (Fig. 1).

It is not only kinases that control the induction of autophagy in DDR. PARP1 has also been mechanistically involved in adaptive autophagic processes. Its hyperactivation leads to the depletion of cellular NAD^+ that, in turn, provokes a drop in the intracellular ATP level generally followed by AMPK activation and autophagy promotion [89, 90]. Moreover, NAD^+ is also consumed by the deacetylase sirtuin 1 that stimulates autophagy directly via the upregulation of the forkhead box O transcription factors [91, 92].

Furthermore, in budding yeast DNA damage can induce noncanonical autophagy that was termed as genotoxin-induced targeted autophagy (GTA). Controlling GTA genes does not significantly affect rapamycin-induced autophagy. GTA depends on Mec1/ATR and Rad53/Chk2 checkpoint kinases [93]. It is conceivable that in mammalian cells there is a specific autophagy pathway activated exclusively in response to DNA damage.

Intriguingly, not only DNA damage triggers autophagy but there is reciprocal coupling between these processes indicating that autophagy can influence DNA damage repair. Thus, absence of FIP200 and subsequent suppression of autophagy enhance apoptosis and decrease cell survival, sensitizing mouse embryonic fibroblasts to ionizing radiation [94]. Autophagy inhibition also leads to accumulation of p62/SQSTM1 that interacts and blocks nuclear E3 ligase RNF168 [95]. This protein ubiquitinates histone H2A and plays an important role in the detection of DNA breaks. p62-mediated inhibition of RNF168 results in blockage of BRCA1, RAP80, and Rad51 recruitment to the sites of DSBs, affecting HR/NHEJ DNA repair [96].

Taken together, the main DNA damage-activated kinases —ATM, ATR, and JNK—play a key role in the promotion of autophagy via AMPK, mTOR, and Bcl-2 activation. Further, similar to starvation, DNA damage induces canonical autophagy molecular pathways. However, existence of special noncanonical genotoxin-induced autophagy suggests the existence of new specific autophagic processes in response to DNA damage. Stimulation of autophagy upon genotoxic stress gives the cell a chance to recover from damage and, unsurprisingly, DNA damage repair directly depends on autophagy on molecular level.

Necroptotic signaling in response to DNA damage

In response to DNA damage induced by chemotherapeutic agents at least two types of programmed necrosis have been observed—necroptosis and mitochondrial permeability transition pore (MPTP)-dependent regulated necrosis [97]. Necroptosis is defined as a mode of regulated necrosis that encompasses sequential activation of the receptor-interacting protein kinase 1 (RIPK1), RIPK3, and mixed lineage kinase domain-like (MLKL) protein [50]. The useful morphological features for necroptosis detection are nuclear shape (round and regular) and increased volume (swelling) [98, 99]. Despite its dilatation, the nuclear envelope of necrotic cells is usually intact, with no changes in its topology and structure. At the same time, no DNA fragmentation is detected and chromatin condensation into compact patches can be observed [99].

Various stimuli, such as DNA damage, engagement of T-cell receptors, TLR or TNF receptors (TNFR), or viral infection, can lead to RIPK1/3 activation and formation of their complex, the necrosome. The assembly of the necrosome relies on the interaction between RIP homotypic interaction motif domains of RIPK1/3. Following RIPK1- and then RIPK3-mediated phosphorylation events, MLKL is recruited and forms oligomers that translocate to cellular membranes, including the plasma membrane, and cause its lysis via incompletely understood mechanisms [100–102]. Importantly, the induction of necroptosis is possible only when caspase-8 is inhibited by chemical caspase inhibitors or virally expressed proteins (Fig. 2). Otherwise, active caspase-8 is able to cleave RIPK1/3 and inhibit necroptosis [5, 103]. Moreover, upon genotoxic stress initiator caspase-2 has also been found to negatively regulate RIPK1-mediated necroptosis in a necrosome-independent manner [104] (Fig. 2).

The main multiprotein complex that plays a key role in necroptosis induction in DDR is called the Ripoptosome and includes RIPK1, FADD, caspase-8, and caspase inhibitor cFLIP isoforms [105]. cFLIP-L inhibits Ripoptosome assembly, conversely, cFLIP-S promotes Ripoptosome formation [106]. The Ripoptosome requires RIPK1 kinase activity and is able to promote caspase-8-mediated apoptosis or caspase-independent necroptosis. It is negatively regulated by cIAP1, cIAP2, and XIAP that target complex components for ubiquitination and degradation. Interestingly, the phosphorylation status of caspase-8 also regulates necroptosis [106]. Interaction between RIPK1/3 has been demonstrated to depend on c-Src-mediated phosphorylation of caspase-8 upon paclitaxel-induced mitotic and genotoxic stresses. On the other hand, RIPK3-dependent phosphorylation of MLKL, its oligomerization, and plasma membrane translocation can be regulated by phosphatidylinositol transfer protein alpha (PITPα) that facilitates MLKL oligomerization via interaction of PITPα with the N–terminal part of MLKL [107].

Interestingly, a recent study has shown that during necroptosis MLKL, RIPK1, and RIPK3 translocate to the nucleus before MLKL redistribution to the plasma membrane [108]. However, as it is the first report demonstrating their nuclear translocation upon necroptosis induction, further studies are essential to confirm the event and elucidate the exact nuclear functions of these proteins. Considering the fact that RIPK1 plays a crucial role in the determination of the cell's fate after extensive DNA damage [109], translocation of all necroptotic key components might be critical in the regulation of the necroptotic pathway.

The second type of programmed necrosis activated upon DDR, MPTP-dependent regulated necrosis, does not depend on caspase activity and is regulated by cyclophilin-D (CypD) and p53. p53 is able to translocate to mitochondria and directly interact with CypD, leading to pore formation, mitochondrial swelling, and necroptosis induction [110, 111] (Fig. 2). CypD-mediated MPTP is followed by the release of apoptosis inducible factor (AIF) from the mitochondria and its nuclear translocation followed by chromatinolysis [112]. It is of note that the mechanisms of chromatin fragmentation during MPTP-dependent regulated necrosis remain obscure. It would be interesting to see whether migration inhibitory factor (MIF) that has been recently identified as an essential player in parthanatos (see below) is involved in this cell death type. In addition, the dissipation of the mitochondrial transmembrane potential causes ATP hydrolysis in order to restore the mitochondrial potential, while NAD^+ pools are depleted by NAD^+ glycohydrolases that further promote regulated necrosis.

MPTP-dependent regulated necrosis does not depend on RIPK1/3 or MLKL, but can be accompanied by RIPK1/3-mediated necroptosis due to autocrine production of TNFα [97, 113]. There are little data elucidating whether there is one common pathway, in which CypD and RIPK1/3 interfere or whether two independent necroptotic pathways exist. On the one hand, using ischemia-reperfusion injury mice model, cisplatin has been found to induce two distinct pathways, CypD-dependent MPTP-necrosis and RIPK1/3-mediated necroptosis [114]. On the other hand, RIPK3 could be involved in myocardial necrosis through phosphorylation of CaMKII and subsequent MPTP opening [115] (Fig. 2). Intriguingly, RIPK3 activity does not depend on RIPK1 and MLKL, so this mechanism could be considered as mixed RIP3-CaMKII-CypD myocardial necrotic pathway induced by ischemia-reperfusion or doxorubicin treatment. Therefore, CypD- and RIPK1/3-mediated necrotic pathways function independently but, in some tissues, at least RIPK3 might be involved in the MPT-induced programmed necrosis.

Parthanatos: the deadly interplay of PARP1, AIF, and MIF

One important sensor of DNA damage is the abundant nuclear enzyme PARP1. This protein is recruited to the sites of DNA breaks and promotes the NAD^+-dependent covalent attachment of PAR polymers (PARylation) to its acceptor proteins, including PARP1 itself, histones, various DNA repair proteins, and transcription-related factors [13]. If DNA damage is nonrepairable, PARP1 hyperactivation leads to the induction of parthanatos, PARP1-dependent mode of regulated necrotic cell death [116]. The most well-known genotoxic drugs that trigger parthanatos are DNA-alkylating agents, e.g., N-methyl-N′-nitro-N-nitrosoguanidine that is often used in cell death studies as the gold standard for parthanatos induction. UV- and ROS-induced DNA damage also leads to parthanatos in some experimental settings [117].

Accumulation of PAR polymers at the sites of damaged DNA as a result of PARP1 prolonged activation is followed by the release of PAR from the nucleus into the cytoplasm. Once in the cytoplasm, PAR stimulates the release of mitochondrial AIF [118, 119] (Fig. 2), which translocates to the nucleus and leads to large-scale DNA fragmentation. The consequences of PARP1 hyperactivation, such as NAD^+ and ATP depletion, additionally favor AIF release and the loss of mitochondrial transmembrane potential, ultimately leading to necrotic cell death [120]. DNA fragmentation further stimulates PARP1 to initiate a vicious cycle.

Whereas PARP1 activation, accumulation of PAR, mitochondrial depolarization, and AIF nuclear translocation comprise the main biochemical features of parthanatos, on the morphological level it is characterized by early plasma membrane rupture, absence of membrane blebbing, and nuclear fragmentation. Molecular mechanisms involved in

parthanatos are just beginning to emerge, but more and more questions are arising. For instance, while the importance of PAR formation for parthanatos induction is generally accepted [120], it is still unclear how PAR polymers are released from the nucleus into the cytoplasm at the initial stage of cell death. It is very likely that PAR-cleaving enzymes play an important role in the initiation of this process. PAR glycohydrolase (PARG) is the main enzyme that counteracts PARP activity, normally ensuring a rapid turnover of PAR and preventing its accumulation and unwanted cell death. Whereas PARG knockout causes embryonic lethality in mice and decreased activity of PARG delays DNA repair and sensitizes cells to DNA damage [121], its overexpression blocks AIF nuclear translocation during parthanatos [120, 122]. ADP-ribosyl hydrolase 3 (ARH3) is another enzyme capable of cleaving PAR polymers, however ARH3 does not rescue PARG knockout mice [121] (Fig. 2).

The released PAR polymers may be either subjected to further proteolysis or serve as scaffolds for PAR-binding proteins. In fact, it is unclear how the released PAR chains can be spared from complete digestion. One possibility is that certain PAR-binding proteins might function as chaperones protecting it from cleavage as well as promoting its translocation out of the nucleus. Thus, several members of the histone family that are PARylated were found to localize to the mitochondria following DNA damage [123]. At the same time, it is possible that protein-attached PAR chains do not have to be released for parthanatos induction. In fact, both free and protein-conjugated PAR chains can promote parthanatos [120], although it is still unclear which ones are usually responsible for its initiation. Moreover, there might be proteins binding to PAR polymers and acting as a buffer against unwanted induction of parthanatos. For instance, PAR-dependent E3 ubiquitin ligase (Iduna or RNF146) was shown to bind to cytosolic PAR chains and prevent PARP1-induced AIF release and cell death [124] (Fig. 2). Taken together, PAR-binding proteins might be both positive and negative regulators of PAR signaling. In silico analysis suggested that more than 800 proteins contain the basic PAR-binding motif and are able to directly interact with PAR [125]. Characterization of the functions of these proteins, as well as of the proteins containing PAR-binding domains, will certainly further clarify our understanding of the role of different PAR binders in the regulation of various cellular processes, including cell death.

Whereas AIF was described as a protein that contains a PAR-binding motif and directly interacts with PAR [119, 125], it is unclear in what cell compartment the interaction takes place. Although PARP1 is predominantly localized to the nucleus, several studies demonstrated that it might also be present in the mitochondria and play an important role in the regulation of cellular bioenergetics [126]. Accordingly, PARylation events and PAR-AIF physical association were detected within the mitochondria [127–130]. Yet, whether mitochondrial PARP1 or another enzyme(s) is/are the major protein(s) responsible for PAR synthesis within the mitochondria remains unknown.

As mentioned above, PAR-dependent AIF release is followed by AIF translocation to the nucleus, where AIF promotes DNA fragmentation (into ~50 kb fragments). However, AIF itself does not have nuclease activity. For a long time, it was thought that it functions as activator of an unknown nuclease. Recently, this nuclease, MIF, has been identified [131]. AIF has been shown to bind and transport MIF to the nucleus where it cleaves genomic DNA (Fig. 2). Notably, the disruption of AIF and MIF interaction, depletion of MIF or blocking MIF nuclease activity inhibits chromatolysis and parthanatos. Thus, AIF-mediated nuclear translocation of MIF could be considered as another biochemical feature of parthanatos. Yet, there are also reports on AIF-independent PARP1-mediated necrotic cell death [132–135], implying that AIF function might be flexible and dependent on a cellular context. Whether MIF is also a context-specific component or an absolutely essential player in parthanatos remains to be elucidated.

Another important question is how PARP1 hyperactivation affects cellular metabolism, in particular, glycolysis and mitochondrial function. Several lines of data demonstrated that PARP1-mediated reduction of NAD^+ cellular level, a key cofactor in glycolysis and the TCA cycle, leads to a decrease in the glycolytic flux [136–139]. However, two recent studies suggested that glycolysis and bioenergetic reductions observed during parthanatos result not from NAD^+ depletion but from the PAR-dependent inhibition of hexokinase 1 (HK1), a key glycolytic enzyme [140, 141]. Thus, PAR binding to HK1 was shown to directly inhibit HK1 activity, leading to glycolytic defects, a decrease of NAD^+ level, and bioenergetic collapse [140, 141]. In addition, because AIF and HK1 were shown to interact [142, 143], PAR-induced release of AIF was hypothesized to contribute to the PARP1-mediated decrease of HK1 activity via the loss of AIF–HK1 interaction [140]. In fact, other enzymes playing important roles in cellular energy production might also be inhibited by prolonged activation of PARP1. For instance, a number of mitochondrial proteins, including several TCA cycle enzymes, are subjected to PARylation [126]. Thus, PARP1 hyperactivation might be linked not only to the inhibition of glycolysis but also to the TCA cycle enzymes. Further aspects of PAR-mediated inhibition of these enzymes, along with the consequences of other mitochondrial PARylation reactions, remain to be explored.

Although PARP1 is the major PARP family member responsible for about 90% of the total cellular PAR synthesis and its deletion prevents the induction of parthanatos

upon DNA damage [116], other PAR-synthesizing enzymes, foremost, PARP2 that is also involved in DNA repair, might play an important role in parthanatic cell death. Whereas PARP1-null mice are viable and develop normally, PARP1 and PARP2 double knockout is embryonically lethal [144]. The functions of other PARP family members remain less characterized but future studies might also unravel their significance in parthanatos.

Other emerging ways for cells to die in a nonapoptotic fashion

Other types of regulated necrosis besides necroptosis and parthanatos include ferroptosis, autosis, netosis, and pyroptosis. Although they are triggered by distinct stimuli and proceed via different molecular mechanisms, they also share necrotic features [145].

Ferroptosis is an iron-dependent type of necrotic RCD induced by the inactivation of glutathione peroxidase 4 (GPX4) that is followed by the elevated production of lipid peroxides [6]. Morphologically, ferroptosis is characterized by smaller mitochondria but not by chromatin condensation, cell swelling, plasma membrane collapse or cytoplasmic vacuolation [146]. Biochemically, ferroptosis is accompanied by lipid peroxidation and not by mitochondrial ROS generation. It is not affected by caspase or cathepsin inhibitors but is inhibited by iron chelators and antioxidants [146].

Recently, ferroptosis has emerged as an additional mechanism through which p53 functions as an oncosuppressor. In this scenario, stress-activated p53 downregulates SLC7A11, a key component of the cysteine/glutamate antiporter, that inhibits cysteine uptake and increases the susceptibility of cells to ferroptosis [147]. Interestingly, while an acetylation-defective mutant $p53^{3KR}$ is not capable of arresting the cell cycle [148], it is fully capable of ferroptosis induction upon ROS-induced stress [147]. Such unexpected p53 role may explain mice lethality upon the loss of Mdm2, a critical negative regulator of p53, as well as contribute to its oncosuppressive functions. Indeed, while p53-mediated suppression of SLC7A11 precedes ROS-induced ferroptosis, SLC7A11 hyperexpression prevents this type of cell death in several tumors [149–151]. Undoubtedly, the elucidation of the precise mechanism through which p53 promotes ferroptosis induction might point out novel targets for the development of tumor-suppressive interventions.

Pyroptosis is typically initiated by the ligation of plasma membrane and endosome toll-like receptors and cytosolic NOD-like receptors (NLRs) to pathogen-associated molecular patterns (PAMPs)/DAMPs leading to formation of inflammasomes. For example, the NLRP3 inflammasome is comprised of NLRP3, adaptor protein ASC, and procaspase-1 [152]. NLRP3 inflammasome-mediated activation of caspase-1 ignites a panel of cellular responses, including maturation and secretion of proinflammatory cytokines IL-1β and IL-18. This is followed by osmotic cell lysis and release of intracellular proinflammatory molecules such as ATP and HMGB1. Morphologically, the formation of plasma membrane pores followed by membrane rupture is observed during pyroptosis, whilst nuclear and mitochondrial degenerations are kept to a minimum [153].

Currently, there are very few data describing the interplay between ferroptosis or pyroptosis and DDR, although several studies have confirmed the induction of these modes of cell death in response to DNA damage. For instance, cyclophosphamide-induced DNA damage has been shown to activate caspase-1 through NLRP3 complex formation leading to pyroptosis [154]. However, the mechanisms underlying these events are largely unknown and require further investigation.

DNA damage as a switch between different forms of nonapoptotic cell death

DNA damage triggers diverse molecular cascades that tightly regulate adaptive stress response and/or cell death depending on the degree of breakdown. The question of whether adaptation pathways and lethal mechanisms are induced simultaneously or consequently is open. For example, glioblastoma cells do not seem to have distinct thresholds for apoptosis, autophagy, or senescence induction after temozolomide treatment [155]. Nevertheless, more and more data suggest the existence of a switch between different nonapoptotic cell death modes upon genotoxic stress, for instance, the switch between autophagy and senescence that can inhibit and stimulate each other. The mechanisms of autophagy-dependent suppression of senescence underlay an interaction of proautophagic protein p62 and transcription factor GATA4 that was found to play an essential role in the promotion of senescence and SASP accumulation [156] (Fig. 3). In response to DNA damage, ATM and ATR regulate GATA4 activation stimulating senescence, whereas p62 mediates autophagy-dependent degradation of GATA4. Consequently, upon genotoxic stress, autophagy suppression promotes GATA4 stabilization and subsequent senescence [156]. It is possible that ATM and ATR directly phosphorylate GATA4 and/or p62, attenuating their interaction and suppressing GATA4 degradation [157] (Fig. 3). At the same time, there are several mechanisms by which autophagy is able to stimulate senescence. Firstly, upon DNA damage, ATM-dependent activation of AMPK leads to ULK1 phosphorylation and autophagy promotion that facilitates degradation of Cyclin E fragment (p18-CycE) [158]. In turn, in the cytoplasm p18-CycE interacts with Ku70 and

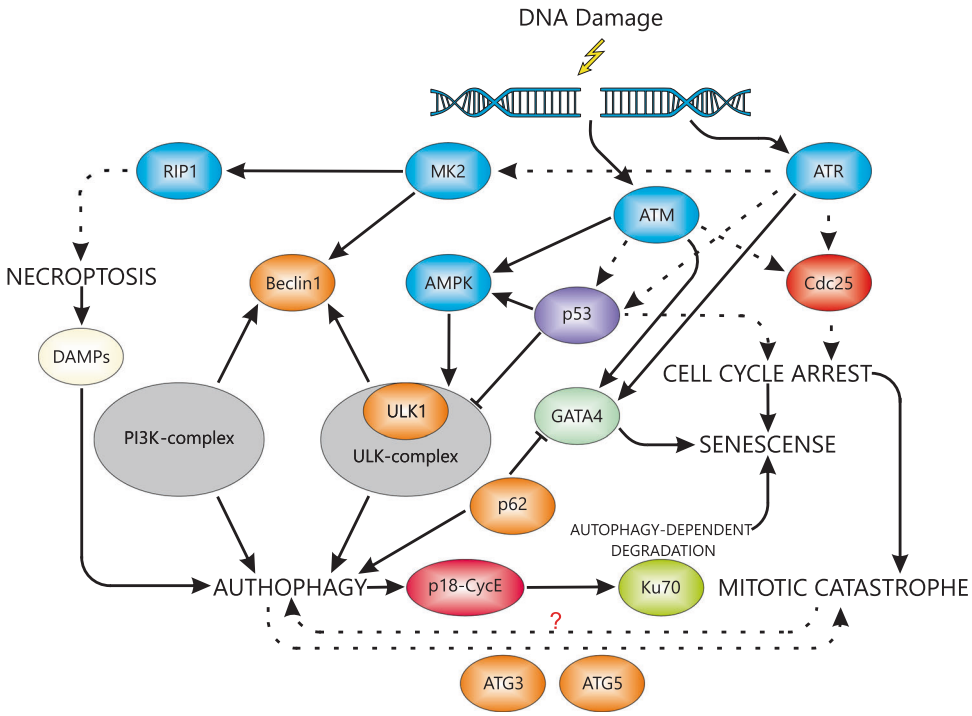

Fig. 3 Switch between nonapoptotic forms of DNA-damage response. Arrows indicate positive regulation, dotted arrows—depicted previously signaling pathways (Figs. 1, 2), dotted arrows with question marks—unknown signaling pathway(s), the block sign—inhibition. The abbreviations and explanations are listed in the text. Blue color denotes kinases, red—phosphatases, orange—autophagy-related proteins, lilac—proteins regulating cell cycle, and raspberry—cyclins

propels it into autophagy-dependent degradation that induces senescence [158] (Fig. 3). Secondly, autophagy generates a turnover of amino acids and other metabolites that are used for massive synthesis of the SASP factors, facilitating senescence. Thus, pharmacological or genetic inhibition of autophagy leads to an evasion of senescence and reduces senescence-associated secretion [159]. In addition, autophagy not only promotes senescence but also vice versa. For example, OIS has been found to be able to activate autophagy and upregulate proautophagic proteins, for example, ULK3 [160]. However, the question is open whether autophagy stimulation results from oncogene-mediated DNA damage via ATM–AMPK–ULK1 pathway or oncogenes function as drivers of proautophagic gene expression. It is likely that autophagy activation is needed for senescent cells to limit the damage and delay apoptotic cell death in order to recover normal cell function.

In addition to senescence, autophagy and mitotic catastrophe can also interfere. Several studies have reported that mitotic catastrophe is accompanied by autophagy induction in response to DNA damage [69, 161]. While the mechanisms of this interplay are largely unknown, putatively, cooperation of autophagy, and mitotic catastrophe is needed for positive, as well as negative regulation of cell death induced by genotoxic stress. Thus, the study of retinal pigment epithelial cells has revealed the cytoprotective role of autophagy in cells undergoing mitotic catastrophe [162]. At the same time, Sorokina et al. have demonstrated that in colorectal carcinoma cell lines autophagy is a necessary step for cell death induction after mitotic catastrophe provocation [69]. It cannot be excluded that an outcome of this interplay not only depends on the interconnection between the molecular machineries of these processes but is also regulated through autophagy-independent functions of autophagy-related proteins such as ATG3 and ATG5 (Fig. 3). Both of them have been shown to promote mitotic catastrophe in response to genotoxic stress; however, in this case pharmacological inhibition of autophagy did not rescue cells from mitotic catastrophe [163, 164]. Taken together, autophagy, senescence, and mitotic catastrophe are tightly bound on a molecular level and genotoxic stress does not induce only one of these processes but causes a complex of molecular events regulating all of them.

It is logical to assume that there is cooperation between autophagy and necroptosis. Necroptotic cell death is followed by the release of DAMPs that stimulates endocytosis and subsequent autophagy (Fig. 3), for example, in dendritic cells [165]. This observation is confirmed by data demonstrating that necroptotic phenotypes of caspase-8 knockout are accompanied by enhanced autophagy [166]. Whereas molecular mechanisms regulating a switch between necroptosis and autophagy under genotoxic stress have not yet been described, we can expect them to exist. For example, DDR promotes activation of p38MAPK-activated protein kinase 2 (MK2) that is able to control necroptosis via RIPK1 phosphorylation. At the same time, MK2 positively regulates starvation-induced autophagy through Beclin1 phosphorylation [167]. Consequently, MK2 might be the link through which DDR regulates the crosstalk between autophagy and necroptosis (Fig. 3).

Intriguingly, although there is no evidence suggesting direct interplay between necroptosis and senescence, its putative mechanism could be suggested. Thus, exposure of cells to DNA-damaging agents and radiation therapy leads to accumulation of DNA fragments in the cytosolic compartment [167]. Cytosolic DNA is sensed by different molecular mechanisms activating special stress response pathways that might be terminated by the induction of senescence and necroptotic cell death [162]. The key role controlling the switch between these processes belongs to transmembrane protein 173 (TMEM173; known as STING). In this case, cytosolic DNA stimulates STING dimerization in the endoplasmic reticulum (ER) and translocation to the ER-Golgi intermediate compartment that induces senescence through the TBK1–IRF3–IFNAR1 pathway as well as necroptosis via an unknown mechanism [162]. The described STING-mediated response can be regarded as another tumor suppressor mechanism and should be taken into account for the development of novel anticancer therapeutic strategies.

The mechanisms of the interplay between other types of cell death are poorly described. For instance, according to a common notion, mitotic catastrophe can cause two types of cell death—apoptosis or necrosis. However, there are few data about molecular pathways triggering necrosis under mitotic abnormalities. Taken together, DNA damage initializes a number of molecular cascades that switch on different nonapoptotic cell death modalities and cellular responses. In the first instance these processes help the cell to adapt to genotoxic stress, maintain cell viability, and recover normal cell function. However, further accumulation of DNA damage is sensed by the cell and in a certain time period the point of no return will be reached, triggering apoptotic and/or nonapoptotic cell death mechanisms.

Conclusion

DNA damage is a widespread stress factor that first triggers a temporary cell cycle arrest to allow the cell time to repair the DNA. If the damage is overwhelming and genomic integrity cannot be reestablished, the cell is able to activate a set of molecular pathways that will either "freeze" normal cell functions or result in cell death.

It is generally thought that in response to DNA damage, in particularly induced by chemo- and radiotherapy, cells undergo apoptotic cell death. However, genotoxic stress can also induce different modes of nonapoptotic cell death (necroptosis, MPTP-dependent regulated necrosis, or parthanatos) as well as nonlethal mechanisms (senescence, mitotic catastrophe, or autophagy) that could help the cell to escape or delay its death. The last three also possess significant tumor suppressive properties albeit they are not able to directly kill cancer cells. Taking into account that tumor cells are often inherently resistant to apoptosis-inducing therapies or acquire resistance during treatment, triggering nonapoptotic modes of cell death is a very attractive approach for anticancer therapy. However, the essential point to remember is that the DNA damage-mediated cell response could be accompanied by side effects that are not favorable for patients. Thus, the negative role of SASP in oncotherapy due to protumorigenic effects of secretory factors has been discussed [168]. Accordingly, inhibition of senescence by alternative nonapoptotic cell death pathways might be a promising strategy to avoid tumor recurrence.

Taken together, modulating stress adaptive responses and nonapoptotic cell death modes could help to increase treatment efficacy and minimize the side effects of chemo- and radiotherapy. Thus, developing our knowledge of these processes is not only of great academic significance, but will allow the development of the safest and the most effective therapeutic approaches targeting multiple molecular pathways.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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