Environmental Science and Pollution Research
https://doi.org/10.1007/s11356-020-09360-5

REVIEW ARTICLE

Mechanisms and pathogenesis underlying environmental chemical-induced necroptosis

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Received: 28 January 2020 / Accepted: 18 May 2020

Abstract

Necroptosis is a regulated cell death that is governed by mixed lineage kinase domain-like, receptor-interacting serine-threonine kinase 3 and commonly displays with necrosis morphological characteristics. This study examined the molecular mechanisms involved in the chemical-induced necroptosis where a systematic evaluation of experimental studies addressing this issue is missing. We strictly reviewed all scientific reports related to our search terms including "necroptosis" or "programmed necrosis", "environmental chemicals" or "air pollutants" or "pesticides" or "nanoparticles" and "Medicines" from 2009 to 2019. Manuscripts that met the objective of this study were included for further evaluations. Studies showed that several pathological contexts like cancer, neurodegenerative disorders, and inflammatory diseases were related to necroptosis. Furthermore, multiple chemical-induced cytotoxic effects, such as DNA damage, mitochondrial dysregulation, oxidative damage, lipid peroxidation, endoplasmic reticulum disruption, and inflammation are also associated with necroptosis. The main environmental exposures that are related to necroptosis are air pollutants (airborne particulate matter, cadmium, and hydrogen sulfide), nanoparticles (gold, silver, and silica), pesticides (endosulfan, cypermethrin, chlorpyrifos, and paraquat), and tobacco smoke. To sum up, air pollutants, pesticides, and nanoparticles could potentially affect human health via disruption of cell growth and induction of necroptosis. Understanding the exact molecular pathogenesis of these environmental chemicals needs further comprehensive research to provide innovative concepts for the prevention approaches and introduce novel targets for the amelioration of a range of human health problems.

Keywords Apoptosis · Cell death · Environmental chemicals · Nanoparticles · Necroptosis

Highlights
- Necroptosis can be triggered in response to the activation of multiple cell-surface receptors.
- Abnormal and extreme activation of necroptosis may be concerned with cellular/tissue damage and ultimately lead to pathological abnormalities.
- Air pollutants, pesticides, nanoparticles, and tobacco smoke could potentially mediate chemicals-induced necroptosis.
- Cell type, exposure duration, and does play an essential role in chemicals-induced necroptosis.

Responsible Editor: Lotfi Aleya

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Published online: 19 July 2020

Introduction

Necroptosis is defined as a novel cell death that has some distinguishing features in comparison with other cell death forms (Table 1). Necroptosis is known as "programmed necrosis" and it has the same morphological changes as we have in necrosis, including plasma membrane integrity loss, translucent cytosol, cell volume increase, and swollen organelles (Pasparakis and Vandenabeele 2015). Contrary to the necroptosis, these features did not occur in apoptosis and some features including blebbing of the plasma membrane, cell shrinkage, nuclear condensation, chromosomal DNA cleavage, and apoptotic bodies formation without plasma membrane rupture are posed as a distinguishing feature of apoptotic cell death (Fig. 1) (Huang et al. 2018). It has been demonstrated that toll-like receptors, death receptors, interferon, and some other intermediaries are involved in necroptosis. Necroptosis is occurring in the caspase-independent pathway moreover receptor-interacting protein kinase 1 and 3 (RIPK1 and RIPK3) and mixed lineage kinase domain-like (MLKL) indicate the primary governing components of this pathway, which could be inhibited by specific small-molecule blockers (Fig. 2) (Degterev et al. 2005; Galluzzi et al. 2017). A significant property of necrosis is the damage-associated molecular patterns (DAMPs) and the formation of cytokines/chemokines because of the plasma membrane permeabilization, which can consequently activate robust inflammation and an immune reaction (Kaczmarek et al. 2013; Zhang et al. 2010). Despite these distinct characteristics, the mechanisms of necroptosis are assumed to be strictly associated with other types of cell death (e.g., apoptosis and autophagy) (Lalaoui et al. 2015). The regulatory molecules and upstream signaling pathways are shared in apoptosis and necroptosis and it is crucial to decide whether the cells undergo apoptosis or necroptosis (Linkermann and Green 2014). Several factors, including stimuli, cell type, genetic background, and intracellular conditions, can influence the type of cell death. Apoptosis poses as the preferred cell death mechanism, and necroptosis acts as an alternative approach to eradicate stressed and infected cells that fail to undergo apoptosis (Mocarski et al. 2015).

The relation of environmental pollution and human health is affected by a vicious series of events: chemicals can induce stress, and prolong stress could exacerbate the effects of the chemicals. Therefore, human health could potentially be influenced by various internal and external stressors (Askari et al. 2018; Keshavarz-Bahaghighat et al. 2018; Sanadgol et al. 2018). It is well established that necroptosis induction is one of the critical effects of environmental pollutants, and it seems that necroptosis inhibition can reduce the side effects of chemicals. Here we introduce mechanism and pathogenesis of necroptosis as an emerging molecular pathway, explore how it can be affected by different environmental chemicals, and also support the possible intervention approaches in order to improve human health.

Necroptosis

Physiological role of necroptosis

As aforementioned, necroptosis is initially considered as a secondary cell death pathway after apoptosis where caspases are not principal regulators. At present, it is hypothesized that necroptosis may be triggered to evoke physiological and pathological consequences to diverse stimuli, although its exact mechanism of action remains unknown (Cho and Park 2017). From physiopathological aspects, its activation may be both beneficial or harmful for cells depending on the stimulus context, cell-specific responses, and final consequences. Like apoptosis, necroptosis plays a critical role in eliminating

Table 1 Key differences between necroptosis, apoptosis, and autophagy processes

	Necroptosis	Apoptosis	Autophagy
Cell death mode	Programmed	Programmed	Programmed
Initiators	TNF-α, FasL, or TRAIL, microbial pathogens, ischemic damage	TNF-α, FasL, or TRAIL, infectious pathogens	Nutrient deprivation, HDAC inhibitors, hypoxia, infectious pathogens
Signaling pathway	RIP1/RIP3/MLKL/PGAM5	Intrinsic and extrinsic pathways	Caspase-independent autophagosome formation, lysosomal protease
Cell and organelles morphology	Swelling	Shrinkage	Double-membraned autophagic vacuoles accumulation
Membrane integrity	Plasma membrane rupture	Plasma membrane blebbing	Without change
Biological markers	Lack of caspase activation, ATP levels decrease, activation of RIP1, RIP3, and MLKL; DAMPs release (e.g., HMGB1)	Caspase, Poly (ADP-ribose) polymerase	LC3-I to LC3-II conversion substrate (e.g., p62) degradation
Physiological significance	Inflammation and innate immunity	Clearance of dead cells	Intracellular quality control
Inhibitors	Necrostatins (e.g., Nec-1) Necrosulfonamide	Caspase inhibitors	Autophagy inhibitors (e.g., 3-MA, wortmannin)

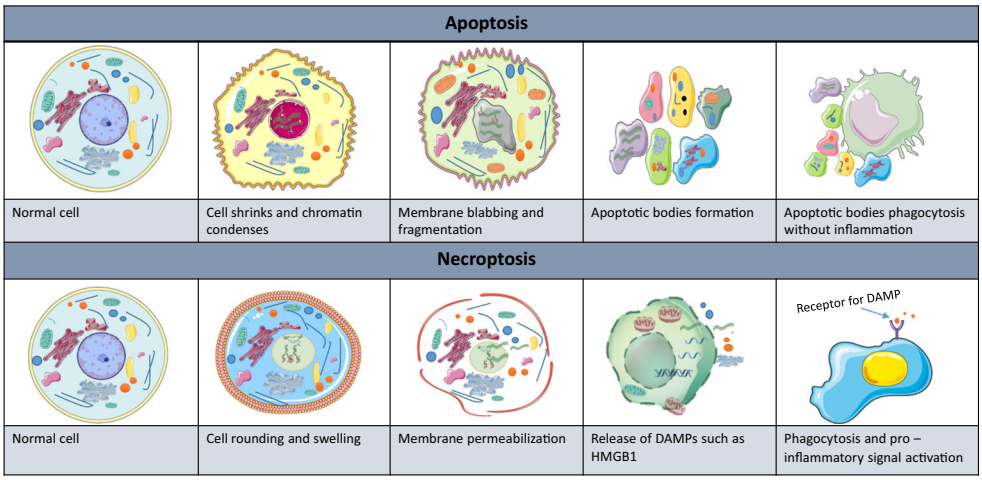

Fig. 1 Hallmarks of apoptosis and necroptosis

cells during normal development, differentiation, and pathophysiological conditions. Growing evidence suggests that necroptosis is mediated via various specialized molecular pathways that have a cell-specific manner (Fulda 2016).

Moreover, extrinsic apoptosis and necroptosis contribute to the host defense mechanism against microbial infection. Viruses such as adenoviruses, poxviruses, and herpes viruses interrupted cell regulatory mechanisms, and easily replicates and spread at their host cells (Ramroodi et al. 2013; Saravani et al. 2014). For instance, vaccinia viruses encode a caspase 8 inhibitor peptide to block apoptotic cell death during infection. Under this caspase-compromised condition, cells are committed to alternative necroptosis (Cho et al. 2009). The successful necroptosis is vital to provoke an innate immune response by killing infected cells and releasing danger signals from host cells into the external milieu. Furthermore, necroptosis in T cells regulates antigen-activated T-cell proliferation and survival. Caspase-8 negatively regulates

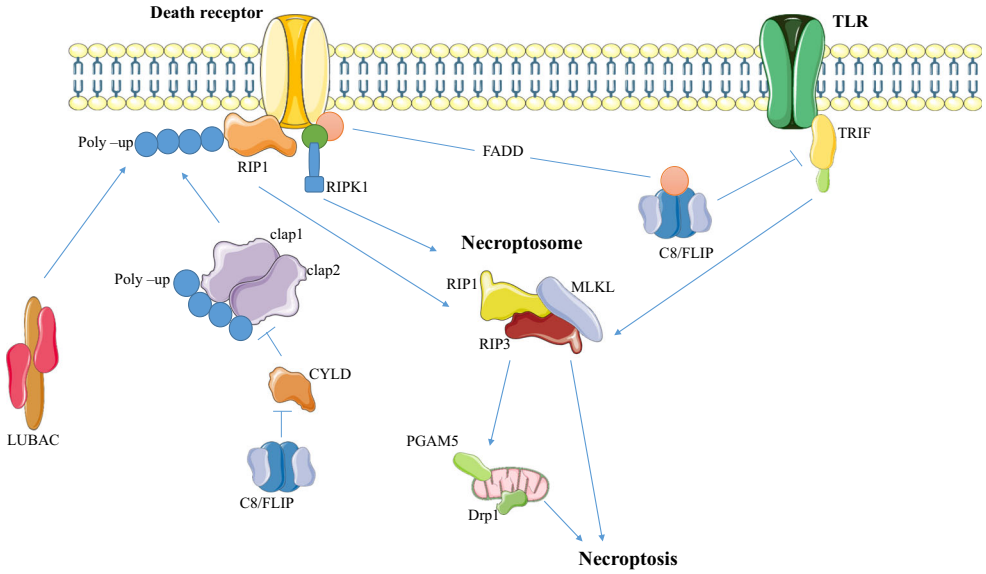

Fig. 2 Molecular mechanism of necroptosis cell death. During necroptosis, TNF (tumor necrosis factor) family cytokines, including TNFα, Fas/CD95, and TNF-related apoptosis-inducing ligand (TRAIL) bind to relevant receptors and promote intracellular receptor interacting protein kinases (RIPK). After binding of TNF-α to the TNF receptor (such as TNFR1), tumor necrosis factor receptor 1 (TNFR1) recruiting receptor interacting protein 1 (RIP1), TNFR-associated factor 2 (TRAF2), cellular inhibitor of apoptosis protein 1 (cIAP1), and make a tumor necrosis factor receptor 1 (TNFR1) signal complex I. The complex recruits the transforming growth factor β-activated kinase 1 (TAK1) and IκB kinase (IKK) complex to activate the nuclear factor kappa B (NF-κB) signaling pathway and the mitogen-activated protein kinase (MAPK) cascade makes a pro-inflammatory signal and inhibits cell death. Activation of toll-like receptor (TLR) increases the formation of complex IIb consisting of RIP1, RIP3, Fas-associated protein with a death domain (FADD), and pro-caspase-8. Next, activated RIP3 recruits mixed lineage kinase domain like pseudokinase (MLKL) to activate the necrotic pathway. In caspase inhibition state, Toll-like receptor (TLR) forms an endosomal platform to recruit RIP1 and RIP3 and stimulates necroptosis in the RIP1-independent way. RIP3 is activated subsequent phosphorylation, binds to the MLKL through its kinase domain, and phosphorylates the MLKL. Oligomerization occurs subsequent MLKL monomer phosphorylation, which can be moved from cytoplasm to plasma membrane and activate necroptosis

necroptosis, promoting the survival of activated T cells under physiological conditions. It has been demonstrated that in mice lacking caspase-8, T cells fail to show immune response when infected with murine hepatitis virus (Lu et al. 2011).

To date, necroptosis has been reported in a variety of pathological conditions (Grootjans et al. 2017). It has been found that necroptosis widely occurs under pharmacological inhibition or genetic deletion of caspases, and acting as a supportive form of programmed cell death in cells unable to initiate apoptosis (Radogna et al. 2015). The occurrence of necroptosis through infection and inflammation has also been fully confirmed (Grootjans et al. 2017). Various stimuli contribute to the onset of necroptosis, such as activation of TNF, endoplasmic reticulum stress (Fan et al. 2015; Saveljeva et al. 2015), DNA damage (Matt and Hofmann 2016), anticancer drugs (Basit et al. 2013), viruses (Wang et al. 2014c), and bacteria (Li et al. 2018).

Pathophysiology and etiology

Pathologically evidence suggests that necroptotic cell death can cause various diseases such as ischemia-reperfusion injury and neurodegenerative diseases including Huntington's disease and retinal degeneration (Cho 2018). During the restoration of blood flow into tissues, tissue damage occurs with severe neutrophil infiltration and cytokine production. Furthermore, necroptosis is involved in traumatic brain and spinal cord injuries (Wang et al. 2012; Wang et al. 2014d). Receptor interacting protein 1 (RIP1) plays an essential and complex role in regulating necrotrophic cell death, from its activation to its inhibition, and this function depends on the cell type and its context (Gong et al. 2019). Exposure to specific RIP inhibitors such as necrostatin-1 (Nec-1) effectively protects cells from necroptosis. Nec-1 administration could protect hippocampal HT-22 cells against glutamate-induced oxytosis (Xu et al. 2007). Inhibition of RIPK1 or RIPK3 silencing significantly rescues necroptotic cell death (Zhu et al. 2011). Furthermore, Nec-1 reduces or delays necroptotic damage in transgenic mice expressing mutant Huntingtin protein, astrocytes from amyotrophic lateral sclerosis, and retinal pigment epithelium (Murakami et al. 2014). Updated references demonstrate that in chronic obstructive pulmonary disease (COPD) pathogenesis, one of the potential causes of necroptosis is by cigarette smoke damage to airway epithelial cells (Pouwels et al. 2015). On the other hand, an infection could promote necroptosis in the host cells, and especially the vaccinia virus diverts cell death to necroptosis in a RIP3-dependent pathway via expression of caspase-1 and caspase-8 inhibitors (Veyer et al. 2017).

Necroptosis has been demonstrated to be involved in various neurological disorders, including trauma, strokes, multiple sclerosis and, Huntington's disease (Liu et al. 2015). Furthermore, genetic or pharmacological interference with necroptosis signaling results in neuroprotection against ischemic heart or brain injury (Liu et al. 2015; Luedde et al. 2014; Yamanaka et al. 2011). RIP3 deficiency or administration of Nec-1 has been demonstrated to exhibit protective effects on necroptosis-based heart or brain damage (Luedde et al. 2014). Apart from RIP3, additional potent target proteins have been identified as regulators of necroptotic cell death, including RIP1, MLKL, PGAM5, and CYLD (Moquin et al. 2013), which comprise a cascade of signaling pathways for necroptosis (Fig. 2). Subsequently, a small number of inhibitors targeting RIP1 or MLKL have been developed to effectively protect against necroptotic cell death (Wang et al. 2014b).

Molecular mechanisms and regulatory pathways

When some triggers stimulate and activate the death domain of tumor necrosis factor (TNF) receptor superfamily (i.e., tumor necrosis factor 1 (TNFR1), Fas/CD95, and tumor necrosis factor-related apoptosis-inducing ligand-receptor (TRAIL-R)) and Toll-like receptors (TLRs), could result into necroptosis (Micheau and Tschopp 2003). A cellular membrane-embedded network named as Complex I generates after the stimulation of TNF/TNFR1, and consist of adaptor proteins such as TNFR1-associated death domain protein (TRADD), TNF receptor-associated factors 2 (TRAF2), cellular inhibitor of apoptosis protein-1 and 2 (cIAP1 and cIAP2), RIPK1, and the linear ubiquitin chain assembly complex (LUBAC) (Su et al. 2016). Ubiquitination of nuclear factor-κB (NF-kB) essential modulator (NEMO), RIPK1, and other adaptor proteins are enhanced by LUBAC, and at the same time, cIAP1 and cIAP2 promote ubiquitination of RIP1. The ubiquitin structure which is developed in Complex I is a significant control point for triggering of either NF-kB, apoptosis, and necroptosis (Dondelinger et al. 2015). This is constantly produced as a consequence of transforming growth factor β-activated kinase 1 (TAK1) and the IκB kinase (IKK) complex stimulation and activation. Phosphorylation of IkBα subunit is done by IKKα/β, utilizing the IKK system, in order to do subsequent proteasomal degradation. Furthermore, IKKα/β has the ability to inactivate the death-provoking role through direct RIPK1 phosphorylation (Dondelinger et al. 2015).

Ubiquitinated phosphorylation of IkBα induces NF-kB translocation from the cytosol into the nucleus (Ebrahimi et al. 2019). NF-κB plays diverse functions such as inducing the expression of many anti-apoptotic genes c-FLIP (a pro-survival gene which is an inactivated caspase-8 homolog, which cannot catalyze proteolysis) and similarly induce the expression of genes which express inflammatory mediators (Serasanambati and Chilakapati 2016). Despite the fact that

caspase-8 action is related to heterodimerization with a long isoform of c-FLIP (c-FLIPL) (LaCasse et al. 2008), overexpression of c-FLIP may suppress apoptosis as multiple tumors indicated c-FLIPL overexpression (Safa and Pollok 2011; Ullenhag et al. 2007). Apart from c-FLIPL, there are many other target molecules for NF-kB such as E3 ligases cIAP1 and cIAP2, whose steric effects inhibit RIPK1 attachment to other death-inducing signal receptors by ubiquitination. Optimally, TNF-induced cell death achieves when NF-kB is blocked properly (Fig. 3) (Dondelinger et al. 2015).

Within an hour, just-after the stimulation, internalization of the membrane-associated Complex I towards the cytosol happens because it has a short half-life. This internalization leads to the formation of Complex II by the addition of caspase-8 and fas-associated death domain (FADD) protein into the complex, as well as the disintegration of TNFR1 (Fig. 3) (Micheau and Tschopp 2003). It is supposed that RIPK1 de-ubiquitination happens inside Complex I but Complex I to II conversion mechanism yet unidentified (O'Donnell et al. 2007). De-ubiquitination of RIPK1 in Complex I primarily needs an enzyme named as de-ubiquitinating enzyme cylindromatosis. This enzyme also plays its role for RIPK1 ubiquitination in Complex II (Moquin et al. 2013). Moreover, to hinder the assembling process of Complex II, direct phosphorylation of RIPK1 is done by IKKα/β (Dondelinger et al. 2013). It is worth mentioning that without receptor stimulation, chemotherapeutic compounds cause assembling of a complex named ripoptosome (Tenev et al. 2011). Consequently due to various stimuli, the formation of the ripoptosome or Complex II occurs.

Complex II, especially Complex IIa, is an inducer for apoptosis. While in virus-induced infections, inhibition of caspase-8 occurs (Upton and Chan 2014) causes recruitment of RIPK3 due to RIPK1 by utilizing the RIP homotypic interaction motif (RHIM) which leads to the organization of Complex IIb (necrosome) (Fig. 3). A complex similar to amyloid created by RHIMs of RIPK1 and RIPK3 helps signaling mechanism of necroptosis. In fact, the RHIM characterized by significantly preserved flanking β-strand dominant residues as well as a tetra-peptide core (Li et al. 2012a). Caspase inhibition is essential for an effective necroptosis because at the border of kinase domains the cleavage of RIPK1 and RIPK3 mediated by caspase-8 (Feng et al. 2007; Lin et al. 1999). For this reason, dissociation of RIPK1 and RIPK3 splits the kinase domain through the RHIM and ultimately this process hinders its activation inside Complex II. Despite the fact that in RIPK3 phosphorylation, RIPK1 plays a fundamental role, but here, it is worth mentioning that RHIM-containing adaptors (TRIF and DAI/ZBP-1) are not included in kinases even they induce necroptosis. Therefore, there is a possibility that activation of RIPK3 does not happen via direct phosphorylation, while Complex I to Complex II conversion is essentially supported due to RIPK1 kinase activity (Feoktistova et al. 2011).

For instance, phosphorylation of RIPK3 leads to the recruitment and phosphorylation of a pseudokinase, which does not act as an enzyme, named as effector MLKL (Murphy et al. 2013). Oligomeric assemblage and translocation of MLKL to the cellular membrane occurs just after RIPK3 phosphorylation (Fig. 2) (Cai et al. 2014; Zhao et al. 2012). Recently, it has indicated that oligomers of MLKL have a critical role in inducing necroptosis by enhancing cellular membrane channels which may help out its rupture (Dondelinger et al. 2014; Wang et al. 2014b). Activation of RIPK3 not only happens in response to TLR3/TLR4 stimulation or herpesvirus infection by TRIF or DAI/ ZBP-1 but also happens via TNFR-1 and further associated death receptors (Kaiser et al. 2013; Upton et al. 2012).

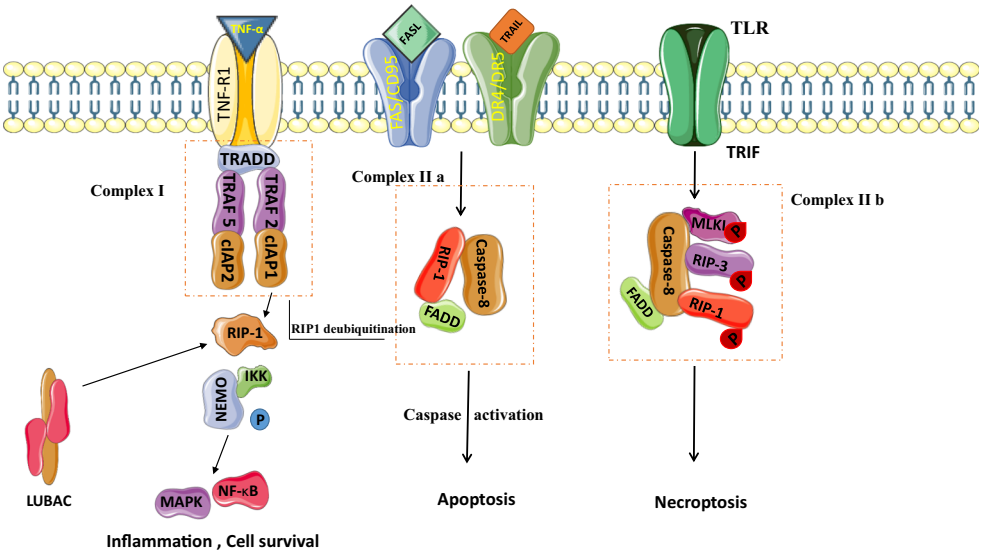

Fig. 3 Molecular mechanisms and regulatory pathways of inflammation, apoptosis, and necroptosis

Role of mitochondrial damage and ROS

Numerous researches confirmed that mitochondrial reactive oxygen species (ROS) plays a critical role in necroptosis induction (Florean et al. 2019). It showed that TNFα could interfere with RIP1 activation and cause ROS production due to mitochondrial dysregulation in the L929 cells (Ye et al. 2012). The relationship between RIP1-dependent activation and ROS production has been reported by several studies (Festjens et al. 2006; Shindo et al. 2013; Vanlangenakker et al. 2011). It was also observed that ROS would induce necroptosis in other cell lines, such as Jurkat T cells, HT-29, and THP-1 (Degterev et al. 2005; He et al. 2009; Temkin et al. 2006), recommending the cell line-specific role of ROS in necroptosis process (Temkin et al. 2006; Zhang et al. 2009). Besides, many studies have shown that mitochondrial permeability affects the necroptosis process with a focus on the CypD component. It was explained that overexpression of CypD inhibited TNF-mediated necroptosis in human leukemia THP-1 cells (Temkin et al. 2006); besides, it was shown that CypD knockout mouse embryonic fibroblast has partial resistance to pan-caspase inhibitor z-VAD, the second mitochondrial-derived activator of caspases mimetics, and TNF-α (He et al. 2009). On the whole, different necroptosis pathways depend on the cell type, mitochondrial condition, and mitochondrial ROS content.

Plasma membrane-linked NADPH oxidase 1 (NOX1) complex serves as an alternative origin for ROS generation. RIP1 has been shown to activate necroptosis via the TNFα pathway in L929 cells by NOX1 (Kim et al. 2007). Also, in L929, mouse embryonic fibroblasts, and HeLa cells, it was noted that TNFα induced NOX1 activity within a complex by RIP components, such as the TRADD (Kim et al. 2007; Yazdanpanah et al. 2009). Although knockdown of the NOX p22phos component does not prevent necroptosis in L929 cells, it is therefore unlikely that NOX1 is a crucial member of necroptosis initiation (Vanlangenakker et al. 2011). NOX4 is a member of the NOX family, and the study revealed NOX4 in HK2 cells, and mouse models increase cisplatin-mediated nephrotoxicity by enhancing ROS-induced RIP1-dependent necroptosis (Meng et al. 2018). Although these data suggest that NOX enzymes are contributed to the initiation of necroptosis in several ways, and their contribution alone is not sufficient and the role of mitochondrial ROS is significant (Brandes et al. 2014). One of the important factors in the production of cytosolic ROS is iron, which can be identified as bivalent or trivalent, and is required for the activity of many enzymes such as catalase, cytochrome p450, lipoxygenase, peroxidase, and detoxification in the cell. The majority of cellular iron is attached to proteins, such as transferrin, ferritin, or heme complex. Since labile forms of iron, seen as free or loose, are toxic to the cell, they must be inactivated and stored in the cell. According to these findings, proper transport or storage of iron protects the cell from necroptosis. Xie and their colleagues confirmed that L929 cell lines are more resistant to TNFα-mediated ROS formation and the labile iron pool, due to diminished the iron storage protein ferritin levels (Xie et al. 2005).

Chemicals-induced necroptosis

Medicines-induced necroptosis

Cisplatin-mediated ototoxicity is related to RIP3-dependent necroptosis and RIP3 expression in both the organs of Corti and spiral ganglion neurons significantly increased following cisplatin exposure (Choi et al. 2019). Also, the Nec-1 (Nec-1; necroptosis inhibitor) treatment could inhibit cisplatin-mediated cell death in HEI-OC1 cells, whereas the cisplatin-mediated cell death did not alter following treatment of Z-VAD (pan-caspase inhibitor) (Fig. 4).

Furosine treatment significantly increased the expression of RIPK1, RIPK3, P-MLKL, IL-1β, and TNF-α, indicating that furosine stimulated the necroptosis pathway and downstream inflammatory factors in liver tissue. Also, phospholipase A2 gamma plays an important role in furosine-induced cell necroptosis activity and subsequent damage in mouse primary hepatocytes (Li et al. 2019).

Microcystin-LR is a cyclic heptapeptide toxin that is generated by cyanobacteria in bloom proceedings (Hinojosa et al. 2019). Potential cell death induction by Microcystin-LR is importantly associated with its hepatotoxicity. Wu and their colleagues have shown that the expression of the necroptotic and apoptotic protein considerably upregulated following Microcystin-LR exposure (Wu et al. 2019). Mechanistically, dysregulation in the pro-oxidants' expression and activity of superoxide dismutase 1, amine oxidase A, NADPH oxidase 4, and glutathione peroxidase 1 is involved in Microcystin-LR-mediated overproduction of ROS. These results provide an innovative target in the Microcystin-LR-induced liver damage treatment.

Acetaminophen is an analgesic and antipyretic drug and its overdose can cause severe acute liver failure (Cover et al. 2006). Activation of hepatic RIP1 is an initial event throughout the acetaminophen-mediated acute liver failure. Pre-treatment or post-treatment with Nec-1 prevent acetaminophen-mediated acute liver failure. Furthermore, Nec-1 can suppress acetaminophen-related activation of c-Jun N-terminal kinase (JNK) and translocation of bax from the cytoplasm to the mitochondria in hepatocytes. According to the previous study, Nec-1 acts as an effective antidote that able to repress AIF-induced necroptosis during acetaminophen-induced acute liver failure (Zhang et al. 2014).

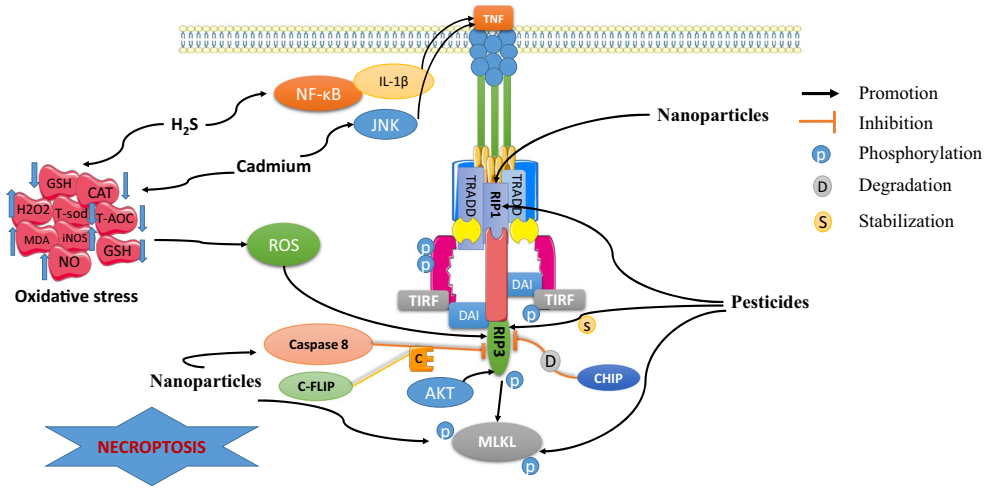

Fig. 4 Overview of environmental chemicals-induced necropoptotic cell death. H_2S exposure suppressed glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD) activities; increased nitric oxide (NO), hydrogen peroxide (H_2O_2), and malondialdehyde (MDA) content and induced oxidative stress. The expressions of related necroptosis (receptor-interacting protein kinase 1 and 3 (RIPK1 and RIPK3), mixed lineage kinase domain like pseudokinase (MLKL), transforming growth factor β-activated kinase 1 (TAK1); TGF-Beta Activated Kinase 1 (MAP3K7) Binding Protein 2 and 3 (TAB2, and TAB3) were significantly increased, and the mitogen-activated protein kinase (MAPK) pathway was activated. Besides, H_2S exposure activated the nuclear factor kappa B (NF-κB) classical pathway and induced tumor necrosis factor-α (TNF-α) and interleukin 1 beta (IL-1β) release. Cadmium significantly increased the mRNA and protein levels of c-Jun N-terminal kinase (JNK), phosphorylated c-Jun N-terminal kinase (P-JNK), tumor necrosis factor-α (TNF-α), and mixed lineage kinase domain-like (MLKL) in the chicken. Pesticides like endosulfan upregulated the expressions of RIPK1 and 3, MLKL, caspase 8, and caspase 3, which means the activation of RIPK1 pathways. In addition, pesticides promoted the increases of ROS, IL-1α, and IL-33 levels while antioxidant N-acetyl-L-cysteine effectively attenuated the cytotoxicity from pesticides

Cadmium-induced necroptosis

Cadmium is a principal environmental pollutant that able to induce cell death (Templeton and Liu 2010). It has been reported that cadmium at the IC50 concentration (50 μM, MTT assay) could induce apoptosis by increasing its indices such as loss of DNA content, nucleation density or DNA fragmentation, and increased caspase-3 activity. At the same time, a reduction in plasma membrane integrity, the ATP levels, mitochondrial membrane potential, and cell swelling were observed, which may suggest secondary necrosis, or similarly probable, necroptotic cell death occurrence. Although the use of Nec-1 as a necroptosis inhibitor is able to inhibit these changes partially, these cells are still sensitive to the zVAD-fmk pan-caspase inhibitor with a lesser extent, indicating that multiple cell deaths may respond simultaneously to cadmium intoxication (Krumschnabel et al. 2010).

Airborne particulate matter-induced necroptosis

It is shown that the climate, environment, and public health are affected strongly by airborne particulate matter (Kord Mostafapour et al. 2018). Airborne particulate matter by RIP/MLKL activation could lead to necroptosis induction in HBE cells and mouse lungs. Airborne particulate matter-related cytokines secretion (IL6 and IL8) and MUC5AC significantly decreased in HBE cells following the utilization of Nec-1 and GSK'872 (specific molecule inhibitors of necroptosis). In addition, Nec-1 could markedly inhibit airway inflammation and mucus overproduction in mice exposed to airborne particulate matter. Necroptosis induction by airborne particulate matter is associated with mitochondrial ROS-dependent early growth gene 1, which eventually stimulated inflammatory responses and mucin expression (Xu et al. 2018).

Hydrogen sulfide-induced necroptosis

Hydrogen sulfide (H_2S) is one of the main air pollutants. In a study, 1-day-old broilers were treated with H_2S gas (4 or 20 ppm) and the results showed that H_2S gas by decreasing the levels and activity of intracellular antioxidant enzymes such as GSH, CAT, and SOD and increased expression of ROS responsive genes, iNOS activity, and concomitant lipid peroxidation process could induce necrosis. Moreover, the results revealed that the expressions of RIPK1, RIPK3, MLKL, TAK1, TAB2, and TAB3 and proteins of MAPK cascade were elevated. Also, H_2S exposure triggered the NF-κB pathway and prompted the release of TNF-α and IL-1β in spleen samples (Chi et al. 2019).

Pesticides-induced necroptosis

Chlorpyrifos, a chlorinated organophosphorus pesticide, is broadly applied for agriculture (Hassani et al. 2015). It is well

shown that necroptosis plays a central role in chlorpyrifos-mediated immune-toxic effects. Neutrophils production increasing in carps is considered as a water pollution biomarker following exposure to chlorpyrifos. Neutrophils through neutrophil extracellular traps formation respond to several stimuli factors, such as PMA (phorbol 12-myristate 13-acetate), IL-8, or bacteria. Chlorpyrifos by necroptosis induction decrease PMA-mediated neutrophil extracellular traps production. Besides, chlorpyrifos through the protein kinase C-MAPK pathway activation inhibits PMA-induced respiratory burst and neutrophil extracellular traps formation, sequentially (Zhang et al. 2019).

Paraquat, a quaternary nitrogen herbicide, is a very pro-oxidant toxicant that prompts oxidative damage and multiple organ dysfunction (Liu et al. 2019). A recent study demonstrated that pretreatment of the paraquat-exposed animal with Nec-1 could prevent cardiac contractile failure through reducing RIP1/RIP3 interaction, downregulation of RIP1/RIP3/MLKL signaling pathway, which significantly inhibited the ROS generation. Therefore, the RIP1/RIP3/MLKL signaling pathway may be a novel therapeutic target for paraquat poisoning-mediated cardiac contractile dysfunctions (Zhang et al. 2018). Paraquat also induces SH-SY5Y cell line toxicity by mitochondrial stress, autophagy, and activation of necroptosis (Hirayama et al. 2018).

Endosulfan is an organochlorine pesticide with cardiovascular toxicity. It has been demonstrated that endosulfan induces necroptosis of human umbilical vein endothelial cells, through the RIPK pathway (Zhang et al. 2017). Moreover, cypermethrin is a synthetic pyrethroid insecticide and induces neurotoxicity in the SH-SY5Y cell line by activation of necroptosis (Raszewski et al. 2016).

Nanoparticles-induced necroptosis

Nanoparticles are tiny particles that have a size or at least one dimension between 1 and 100 nm (Zanganeh et al. 2019). In order to induce necroptosis via nanoparticles, it is of great importance to understand the basic controlling components of programmed cell death. Various researches have elaborated on structure, dose, surface charge, and the function of nanoparticles for the induction of necroptosis. Studies have mentioned that out of many characteristics of nanoparticles, the size of gold nanoparticles is of great importance and plays a role in monitoring the pathway of the programmed cell death (Sun et al. 2018). Interestingly, the smaller the size (< 1.4 nm) of gold nanoparticles, the more toxic it will be and the cell will mostly incline towards necrosis. But larger the size of gold nanoparticles, necrosis will be dominant. Toxicity will be insignificant in cells if the size of gold nanoparticles (> 15 nm) (Pan et al. 2009; Pan et al. 2007). Apart from size, the concentration of nanoparticles (such as silver nanoparticles) has a fundamental importance in ROS-mediated toxicity (Mishra et al. 2016; Rahman et al. 2009). As we mentioned in the case of gold nanoparticles, a similar case will be for silver nanoparticles. Smaller the size (< 13 nm) of citrated coated silver nanoparticles, more will be the production of reactive oxygen species, which induce toxicity. While larger will be the size, mild the toxicity will be (Tavakol et al. 2017).

Besides size and concentration, the surface charge of nanoparticles has a supplementary role in promoting toxicity and necrosis. Specifically, polar gold nanoparticles either with negative or positive charge have more tendency to prompt apoptosis while those with a neutral charge cause necrosis (Schaeublin et al. 2011). Formerly as we discussed, cationic carriers suchlike PEI, liposomes, and cationic chitosan have a distinctive mechanism for influencing necrosis (Wei et al. 2015). An investigation on mouse keratinocyte cell explained that the structure of nanoparticles has its own influence upon inducing programmed death of cells, for example, titanium oxide in its crystal form induces a specific kind of programmed cell death. Even the difference in the structure of nanoparticles has its various effects suchlike necrosis will be induced by crystal form of anatase and similarly, apoptosis will be caused by crystal form of rutile (Braydich-Stolle et al. 2009). Similarly, a study explained the function of the shape of nanoparticles in inducing toxic effects on the human lungs for example shape of nanoparticles of poly-aniline (PANI) has a unique character for inducing fibroblast damage. Necrosis induction is also linked with an aspect ratio of nanoparticles as an example, lower the aspect ratio more will be necrosis (Oh et al. 2011). Likewise, the exposure duration of nanoparticles upon cells is also associated with a kind of programmed cell death. In glioma cells, more will be the dose of nano-C60 fullerene, more will be the necrosis and low will be the dose, autophagy will be dominant (Harhaji et al. 2007). In this article, we tested various studies for the identification of underlying factors that contribute to nanoparticles induced necrosis development. But even so, there is a requirement for further investigations to explore nanoparticles induced necrosis criteria in detail. The cytotoxicity assessment of zinc oxide nanoparticles showed nanoparticles could induce cytotoxic effects on MCF-7 cells through necroptosis stimulation and cytoprotective autophagy inhibition. In this study, zinc oxide nanoparticles administration with apoptosis and autophagy inhibitors resulted in an increase in the necroptosis-related gene expression and the least viability. Furthermore, the necroptosis and apoptosis inhibition was accompanied by the upregulation of autophagy-related genes, presenting the highest cellular proliferation (Farasat et al. 2020). Conjugation of chloroquine, an autophagy inhibitor, to graphene oxide nano-sheets led to the necroptosis-mediated cell death through inhibition of autophagy flux induced necroptosis-mediated cell death in A549 human lung adenocarcinoma cells, whereas the cytotoxic effect was not observed on normal lung cells (Arya et al. 2018).

There are many mechanisms through which nanoparticles induce necrosis. Out of those, the primary one is through the production of ROS called a pro-oxidant pathway. ROS generated by this process causes damage to the membrane and DNA of mitochondria and this leads to cell necrosis (Bauer et al. 2011). An example that Nec-1, a necroptosis inhibitor, can decrease germanium nanoparticle toxicity explains the role of necroptosis in nanoparticles-induced cell death. By relating this example, we can explicate that by increasing the concentration of calcium intracellularly, nanoparticles cause ROS generation which leads to necroptotic cell death (Ma et al. 2011). Apoptosis and necroptosis of spermatogenic cells can be stimulated by silica nanoparticles by the generation of ROS. Findings explain that on the 45th-day silver nanoparticle exposure, the expression elevation of Fas/FasL/RIPK1/FADD/caspase-8/caspase-3 and RIPK3/MLKL has been observed (Ren et al. 2016). An additional pathway for inducing necrosis via silica nanoparticles' is by epithelial cell injury because of the production of cytokines (such as IL-6, IL-8), stimulation of von Willebrand factor, and triggering of the coagulation cascade (Bauer et al. 2011). In another study, the cytotoxic effect of the silica nanoparticles on hepatocellular carcinoma (HCC) cells was assessed. It was observed that silica nanoparticles induced cytotoxic effect through up-regulation of necroptosis-related genes, most significantly ZPB1 (as an important necroptosis mediator) (Niu et al. 2019).

Silver nanoparticles inside cells via following pro-oxidant pathways cause necrosis. They prompt necrosis through expressing genes for ROS, by oxidative degradation of lipids, and by reducing the concentration of antioxidant enzymes (GSH). These processes lead to DNA damage (Asharani et al. 2009; Tran and Le 2013). Production of ROS and silver cations causes silver nanoparticles-mediated necrosis. Apoptosis and necrosis via nanoparticles of polyvinylpyrrolidone silver happen in a size-dependent manner through the oxidation mediated signaling pathway (Li et al. 2012b). Similarly, one of the primary pathways of silver nanoparticles toxicity is their capability to produce ROS in BRL 3A rat hepatocytes and alveolar macrophages (Carlson et al. 2008; Hussain et al. 2005). Necrotic and pro-oxidant effects by silver nanoparticles cause anti-proliferative outcomes (Ciftci et al. 2013; Xia et al. 2006).

In the same way, gold and selenium nanoparticles stimulate necrosis by means of ROS generation and aggregation which induce oxidative stress. These processes cause oxidative damage to the defense mechanism of cells (HeLa and PC-3 prostate cancer cells) (Liu et al. 2013; Sonkusre and Cameotra 2017). By increasing intracellular ROS concentrations in macrophages and damage to DNA, zinc oxide nanoparticles induce necrosis. As we know that the immune system clear inhaled nanoparticles through this process (Wang et al. 2014a). Cationic nanoparticles by using some unique mechanisms influence necrosis. Cationic nanoparticles, in particular, chitosan (a polysaccharide nanoparticle), cationic liposomes, and polyethylene amine via interacting with sodium/potassium–ATPase, lead to acute cellular necrosis because of mitochondrial damage-mediated inflammation (Schaeublin et al. 2011).

Since the lysosome is a factory of digestive enzymes, so a further mechanism of nanoparticles for inducing necrosis is by lysosomal damage. Because of that, all those lysosomal enzymes will leak and cause cell death. Attachment with serum proteins, modification in the size, charge, and surface characteristics of nanoparticles occurs. As a result, the cellular uptake of nanoparticles will be altered (Sepand et al. 2020). For example, cadmium telluride quantum dots have an enormous surface-to-volume ratio which makes it highly absorbable nanoparticle for proteins. So due to this property of cadmium telluride quantum dots, the clathrin-mediated uptake by cells happens and causes lysosomal destruction which leads to necrosis (Lai et al. 2015).

The cytoskeletal destruction/collapse process starts from the endocytosis of zinc oxide nanoparticles. This endocytosis causes modification in the organization of cytoskeletal proteins (actin and myosin). By stimulating cytoskeletal destruction, zinc oxide nanoparticles, and nanowires induce cellular necrosis. These alterations are underlying risk factors for skin or mucosal cancer (García-Hevia et al. 2016). Even in the presence of advanced nanotechnology, still, it is complicated to elaborate and understand details related to necrosis due to a lack of precise cell death facts. Sometimes outcomes are inaccurate because, during the process of apoptosis, secondary necrosis dominates (De Stefano et al. 2012).

Cigarette smoke-induced necroptosis

Cigarette smoke is a composition of chemicals that includes reactive toxic elements like aldehydes, nitrogen and oxygen radicals, nicotine, cadmium, and other pro-oxidants. Following cigarette smoke exposure, a wide range of toxic effects including autophagy, immune- and oxidative-mediated reactions (DNA-damage, ROS generation, lipid peroxidation, an increase of cytokines release and inflammatory reactions, proteostasis-imbalance) were observed (Smith and Hansch 2000). It has been reported that cigarette smoke could induce cell death on bronchial epithelial cells by DAMPs released in the absence of caspase-3, -7, and -8 activity, which is comparable to necroptosis-mediated cell death (Pouwels et al. 2015). Overexpression of pro-inflammatory cytokines by epithelial cells is dependent on increased DAMP release due to cigarette smoke exposure in bronchial epithelial cells that are sensitive to necroptosis inhibition (Pouwels et al. 2015).

Conclusion and perspective

It has been demonstrated that living in a polluted environment may negatively affect our general health, and finally susceptible us to devastating disorders such as cancers, respiratory problems, cardiovascular, and infection diseases. Nowadays, our knowledge about the role of necroptosis in toxicity-related environmental exposures is insufficient and, just a small amount of chemicals have been investigated in this regard. This is mostly important for lipophilic and slowly metabolized environmental toxicants, as they can be stored in the body for a long time. However, many of the links between necroptosis, immune responses, and other cellular functions stimulated by chemical stressors are still unclear. This research for the first time explains the fact that necroptosis performs a fundamental role in the response of cells when exposed to environmental pollutants.

Here, we demonstrate that necroptosis could occur due to exposure to numerous synthetic or natural chemicals and chemicals-induced necroptosis may be influenced by various factors including cell type, exposure time, and dose (Fig. 4). Both dysfunctional/aberrant necroptosis and excessive activation of necroptosis could also be related to tissue/cellular damage and lead to pathological alterations. Moreover, additional identification and validation of more potential targets will be crucial for the development of drugs that may improve toxicants-induced pathological conditions.

Beyond necroptosis-associated pathological consequences, necroptosis may be exploited as an alternative target to overcome drug-resistant types of disease, where a failure in treatment may be caused by the acquired ability of cells to evade apoptosis and/or undergo autophagy depending on the cell types or the context of the stress. Thus, further fundamental research is necessary to identify the molecular mechanisms involved in the chemical-induced necroptosis pathway after exposure to environmental pollutants. This study provides a greater understanding of the role of necroptosis in chemical toxicity and its pathogenesis. Blocking of necroptosis pathways could be an exciting approach to introduce new interventions for reducing environmental pollution adverse health effects as the induction of necroptosis is one of the main strategies that contribute to chemical toxicity.

As a matter of fact, presently available data on relationship between exposure to commone environmental chemicals and risk of necroptosis supports the negative human *health* consequences of *such exposures*. Additional studies need to identify the target molecules mediating the signal transduction leading to necroptosis and facilitate the discovery of the mechanism of action of individual environmental toxicants.

Authors' Contributions M-R Sepand and N. Sanadgol conceived the study and designed the study; M-R Sepand, M. Aliomrani, and Y. Hasani-Nourian conducted the searches; N. Sanadgol, M-H Farzaei, and M-R Kalhori interpreted the finding; all authors contributed in writing and commented on the manuscript.

Funding Information This study was supported by the University of Zabol, Zabol, Iran, (UOZ-GR-9618-5) received by the corresponding author Dr. N. Sanadgol.

Compliance with ethical standards

Ethical approval and consent to participate Not applicable

Consent for publication Not applicable

Availability of supporting data Not applicable

Conflict of interests The authors declare that they have no competing interests.

Abbreviations cIAP, cellular inhibitor of apoptosis protein; COPD, chronic obstructive pulmonary disease; DAMPs, aamage-associated molecular patterns; FADD, Fas-associated protein with a death domain; IKK, IκB kinase; IL-1β, interleukin 1 beta; LUBAC, linear ubiquitin chain assembly complex; MAPK, mitogen-activated protein kinase; MLKL, mixed lineage kinase domain-like; NOX1, NADPH oxidase 1; Nec-1, necroptosis-specific inhibitor-1; NEMO, nuclear factor-κB essential modulator; NF-kB, nuclear factor kappa B; RHIM, RIP homotypic interaction motif; RIP, receptor-interacting protein; RIPK, receptor-interacting protein kinase; ROS, reactive oxygen species; PMA, phorbol 12-myristate 13-acetate; TAK, transforming growth factor β-activated kinase 1; TRAF, TNFR-associated factor; TLR, Toll-like receptor; TRADD, TNFα receptor-associated death domain; TNF, tumor necrosis factor; TNFR, Tumor necrosis factor receptor; TRAIL, TNF-related apoptosis-inducing ligand

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