



Review

Redox cell signalling triggered by black carbon and/or radiofrequency electromagnetic fields: Influence on cell death

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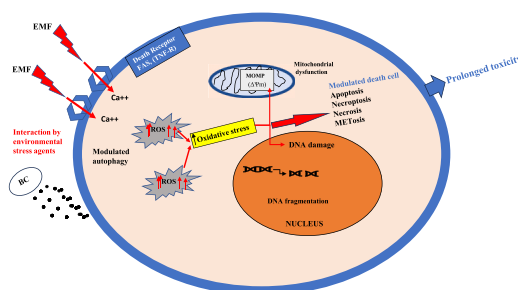
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HIGHLIGHTS

- Environmental stressors like BC and/or RF-EMF can produce oxidative damage in cells.
- Pre-clinical models of BC and/or RF-EMF exposure can clarify cell death pathways.
- Exposure and risk assessment may help to prevent non-communicable diseases.

GRAPHICAL ABSTRACT



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ABSTRACT

The capacity of environmental pollutants to generate oxidative stress is known to affect the development and progression of chronic diseases. This scientific review identifies previously published experimental studies using preclinical models of exposure to environmental stress agents, such as black carbon and/or RF-EMF, which produce cellular oxidative damage and can lead to different types of cell death. We summarize in vivo and in vitro studies, which are grouped according to the mechanisms and pathways of redox activation triggered by exposure to BC and/or EMF and leading to apoptosis, necrosis, necroptosis, pyroptosis, autophagy, ferroptosis and cuproptosis. The possible mechanisms are considered in relation to the organ, cell type and cellular-subcellular interaction with the oxidative toxicity caused by BC and/or EMF at the molecular level. The actions of these environmental pollutants, which affect everyday life, are considered separately and together in experimental preclinical models. However, for overall interpretation of the data, toxicological studies must first be conducted in humans, to enable possible risks to human health to be established in relation to the progression of chronic diseases. Further actions should take pollution levels into account, focusing on the most vulnerable populations and future generations.

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1. Air quality: scope in the pathogenesis of chronic diseases

The accelerated growth of developing cities worldwide has led to a reduction in air quality. Inhaled airborne particles, or particulate matter (PM), generated from various sources, affect human health and constitute harmful substances that are associated with many diseases in modern society (Offer et al., 2022). As a result, the World Health Organisation (WHO) warns of the risk of air pollution to global health (Who, 2022). Experimental studies using *in vitro* and *in vivo* models of airborne exposure to PM have demonstrated an association between the exposure and chronic non-communicable diseases affecting the brain, lung, heart, liver and kidney (Chen et al., 2022). Inhaled pollutants induce redox-sensitive signalling pathways that can lead to protective adaptations and epigenetic changes, induce innate or adaptive immune system responses, cause mitochondrial depolarization and lead to cell death (Mudway et al., 2020). The capacity of atmospheric pollutants to generate oxidative stress *in vivo* may be the primary and central causal pathway linking inhaled pollutants and adverse health effects (Kelly and Fussell, 2015).

Atmospheric pollutants are generated by the combustion of fossil fuels in the transport and energy sectors, as well as by the burning of biomass for domestic heating and cooking (Nagappan et al., 2021). These activities generate black carbon (BC) particles, of approximate size 0.00001–1 mm (Niranjan and Thakur, 2017; Wang et al., 2014; China et al., 2013), which induce redox-sensitive signalling through the generation of reactive oxygen species (ROS) (free radical oxidants); the ROS, in turn, affect molecular pathways in cells and subcellular organelles (Liu and Tang, 2020) and cell lines in experimental systems (Shang et al., 2022). The damage caused to cells by BC can lead to different types of cell death, and the intensity of oxidative stress plays a very important role in determining which cell death pathway occurs (Peixoto et al., 2017). Cell death is generally characterized by loss of plasma membrane integrity, cell fragmentation and reduced or absent mitochondrial function (Galluzi et al., 2019). Apoptosis and necrosis represent the two biochemical extremes of cell death pathways (D'Arcy, 2019), although in some cases both may coexist (Jiang et al., 2018) because of the effect of BC. Apoptosis is a physiological process that is intrinsically regulated by non-inflammatory factors (such as oxidative stress) that act at the cell membrane level (activating death receptor cells) and the mitochondrial membrane level (Brenner and Mak, 2009), altering the function, which will be regulated by ROS and by Ca and Ca-associated proteins (Smaili et al., 2000). Activation of the caspase cascade, extrinsically and intrinsically aided by p53 activation due to DNA damage, indicates activation of apoptosis (Wang et al., 2017), which can be reversed by repair. *In vitro* and *in vivo* research has demonstrated the capacity of particulate pollutants to induce redox-sensitive pathways and transcription factors (Pourazar et al., 2005) that can induce cell death. However, various aspects of the impact and synergistic interactions with other possible environmental agents remain to be investigated. Although the toxicity of PM is known to be determined by the size and nature (chemical composition) of the particles (Wu et al., 2021), different sources of environmental non-ionizing radiation could modify PM-cell interactions. It has been hypothesised that external electromagnetic fields (EMFs) can alter the cellular effects of particulate matter, depending on the frequency used, by modifying the dielectric constant (Michel et al., 1993; Sihvola, 2002). The bioelectrical properties of the cell membrane can also vary depending on electromagnetic parameters such as frequency and modulation (Lin et al., 2023). Further research is required to address the individual and combined impacts of both environmental agents on cell metabolism and also the mechanisms involved, to determine the role of these agents in mortality caused by chronic non-communicable diseases.

In vivo and *in vitro* experimental studies of radiofrequency electromagnetic fields have indicated that exposure to mobile phones (and similar equipment) and radar can cause oxidative stress and DNA damage (Dasdag et al., 2015a,b). In addition, some epidemiological

studies carried out on humans exposed to radiation from mobile phone communication systems have detected indicators of oxidative stress, such as increased blood lipid peroxidation and decreased superoxide dismutase and glutathione peroxidase activity at the level of red blood cells (Moustafa et al., 2001). Likewise, indications of oxidative stress have been observed in experimental studies in rats, with lysis of red blood cells after exposure to 2450 MHz RF (Hassan et al., 2010). In long-term studies in rats, exposure to 1800 and/or 2100 MHz RF caused oxidative DNA damage (Alkis et al., 2021) and alterations in oxidant-antioxidant parameters also caused by exposure to 900 MHz RF (Dasdag et al., 2008). However, no consensus has been reached regarding the extent of exposure and mechanisms of RF-EMF that induce oxidative stress or whether the effects are persistent and lead to cell and organ damage (Jeong et al., 2018). Nonetheless, a group of WHO-appointed RF-EMF experts rated oxidative stress as an important biomarker that should be systematically reviewed because of the health implications (Henschenmacher et al., 2022).

Researchers investigating the effects of non-ionizing radiation on living organisms have tried to explain how exposure to EMFs can induce oxidative stress, by considering that repeated exposure could cause irregular opening of electrosensitive or voltage-gated ion channels (VGIC) and abnormal cation movement, which could alter the biochemical properties of membranes, leading to alteration of the electrochemical balance and homeostasis of cells and oxidative stress (Pall, 2022; Panagopoulos et al., 2021; Panagopoulos et al., 2015; Georgiou and Margaritis, 2021). The oxidative stress that can be induced by EMFs causes cell damage, with evidence of effects at the mitochondrial level due to the overproduction of ROS in the male and female reproductive systems (Gautam et al., 2022; Santini et al., 2018), at the myocardial level (Li et al., 2023; Kiray et al., 2013), in the nervous system (Lin et al., 2021; Gupta et al., 2018) and in the immune system (Yao et al., 2023; Lu et al., 2012). Chronic oxidative stress is known to be linked to the development and progression of cancers and metabolic and neurodegenerative diseases (Tirendi et al., 2023; Caturano et al., 2023; Olufunmilayo et al., 2023). Recent studies have revealed an association between RF-EMF exposure and the possible risks of non-communicable, oncological (Pareja-Peña et al., 2022), metabolic (Jelodar et al., 2021), reproductive (Yahyazadeh et al., 2020) and neurological (Tuteja et al., 2020) diseases. Identification of the extrinsic environmental factors (e.g. non-ionizing radiation) that contribute to the increasing prevalence of non-communicable diseases may allow us to gain a better understanding of the pathophysiological mechanisms (Di Ciaula, 2018) and to prevent high levels of mortality (Fitipaldi and Franks, 2023).

Paradoxically, EMF exposure can have bidirectional effects, depending on the type of exposure to the electromagnetic parameters of non-ionizing radiation sources. Thus, EMFs can be used therapeutically to induce antioxidant action at the level of the myocardium (Goraca et al., 2010), keratinocytes (Calcabrini et al., 2017), the nervous system (Shirbandi et al., 2023) and the immune system (Groiss et al., 2021), activating the anti-apoptotic system. EMF can also exert a therapeutic function through death signalling pathways in cancer by inducing apoptosis and ferroptosis (Yuan et al., 2020).

The arguments that led us to carry out this study of the biological effects of black carbon and electromagnetic fields are explained below: 1) Epidemiological studies in humans and *in vivo* and *in vitro* experimental models link both environmental agents (BC and EMF) in relation to pollutant control. Thus, rigorous real-time spatio-temporal air quality monitoring of ambient PM 2.5 particulate matter concentrations is being carried out, especially for BC present in diesel cars and heating systems (Salas-Sánchez et al., 2020; He et al., 2023a,b; Xu et al., 2023). On the other hand, anthropogenic electromagnetic noise can affect biological processes, including human health (Engels et al., 2014; Eroglu et al., 2006). A recent study carried out in Germany in people living close to mobile base stations showed the existence of a significant level of different chromosomal aberrations in the group exposed to non-ionizing radiation (Gulati et al., 2024). 2) Both external environmental agents

(BC and EMF) act on cell metabolism by altering the oxidative/antioxidant machinery and possibly causing cell damage. Biochemical experts specializing in oxidative stress have recently commented that exposure to physical factors, such as RF-EMF, or exposure to chemical mutagens can lead to production of ROS and trigger oxidative stress, which increases the risk of chronic diseases (Mallah et al., 2022). Oxidative stress can damage macromolecules, stimulate inflammation and lead to the accumulation of mutations (Zhang et al., 2022). 3) The environmental interaction between wireless communications and BC particles present in the atmosphere as pollutants could modify the electromagnetic properties of the particles, thus significantly altering their cellular toxicity and the consequent effects on cell death. Our own analysis and other studies carried out in recent years indicate potentially significant health effects caused by the combined action of electromagnetic fields and fine or coarse BC particles. In the context of thermal inversion, the toxicity of atmospheric BC would be increased by modifications of the dielectric constant and the conductivity owing to RF from wireless communication (López-Álvarez et al., 2023). EMF and BC can both cause oxidative stress, inflammation, immunotoxicity and ultimately cell death after exposure in experimental models, as demonstrated in environmental health studies in each of these fields. It is also possible that these environmental pollutants act together in the pathogenesis of chronic diseases such as cancer and metabolic and neurodegenerative diseases (Offer et al., 2022; Chen et al., 2022; Pareja-Peña et al., 2022; Jelodar et al., 2021; Yahyazadeh et al., 2020; Tuteja et al., 2020). In our opinion, the use of models of individual or combined exposure to BC and/or EMF in cell cultures and/or interaction with different cell types in in vivo studies will provide relevant preliminary information on which to base future toxicological studies in humans. Therefore, critical analysis of the published data regarding exposure, assays and models used for comparative assessment of the effects caused by environmental toxicity mechanisms is required.

The objective of this review was to examine published articles that, based on the use of preclinical experimental models (in vitro and in vivo), document redox signalling mechanisms that occur after exposure to environmental stress agents, such as black carbon and/or RF-EMF, which produce cellular oxidative damage and can trigger different types of cell death. This review article therefore documents and considers in vivo and in vitro studies concerning the mechanisms and pathways of redox activation induced by exposure to EMF and/or BC and that lead to apoptosis, necrosis, necroptosis and pyroptosis. It also considers autophagy and other forms of cell death, such as ferroptosis and cuproptosis, which are important in relation to environmental toxicity in humans. It also examines the possibility of synergistic interactions (potentiation or attenuation) between BC and EMF at the cellular level that has different effects on tissues to those resulting from the separate action of each agent. The participation of both external environmental agents as risk factors for non-communicable diseases (Allen et al., 2023) led us to also consider the possible combined interaction between both environmental stress agents, considering the chemical and bioelectrical interactions and finally the impact on cell metabolism leading to triggering of different types of cell death.

2. Redox mechanisms triggered by black carbon can induce different types of cell death

The WHO reported guidelines regarding environmental levels of BC stating “Illustrative annual mean concentrations where statistically significant associations with health outcomes have been found were 1.08–1.115 $\mu\text{g}/\text{m}^3$ for black carbon and 0.5–0.8 $\mu\text{g}/\text{m}^3$ for elemental carbon” (Khreis et al., 2017; Luben et al., 2017; Who Global air quality guidelines, 2021). Based on the literature review conducted and expert opinion on the health impact of ultrafine BC (uBC) particles (smaller than 10 nm in size), there is general agreement that concentrations below 1000 particles/cm (24-hourly-average), typically observed in environments unaffected by anthropogenic emissions, can be considered

low (de Jesus et al., 2019). It is proposed that 24-hour average concentrations exceeding typical levels observed in background urban areas (10,000 particles/cm) or 1-hour average concentrations exceeding levels typically found in all urban areas microenvironments (20,000 particles/cm) can be considered high (Who Global air quality guidelines, 2021). The mechanisms of toxicity by which BC can induce cell death include the inflammatory pathway, oxidative stress and DNA damage (Peixoto et al., 2017; Møller et al., 2014). Different forms of cell death are caused by exposure to BC, including apoptosis, necrosis-like or necroptosis, necrosis, pyroptosis, newly discovered forms of programmed cell death such as cuproptosis (Zhao et al., 2024), ferroptosis and autophagy-dependent cell death (Wang et al., 2021a, b), and other forms such as macrophage extracellular traps (METs), although in general they can initially be activated in the same way (Deng et al., 2014). The BC components, exposure time and also the characteristics of individual cells will define the cytotoxic response, and chemical analysis of the components and their concentrations is therefore necessary in order to establish cause-effect relationships (Dambruoso et al., 2014). However, according to experts on this topic, the amount of ROS and the intensity of oxidative stress caused by BC can be decisive factors and play an important role in determining the cell death pathway (Peixoto et al., 2017).

Black carbon is defined as a group of highly aggregated carbon particles with important light absorbing properties in the UV-visible range. Although the most frequently cited studies involve PM_{2.5} particles, because these are very harmful to health, due to the wide range of ambient black carbon (BC) in the 10 nm–1 mm size range (Niranjan and Thakur, 2017; Wang et al., 2014; China et al., 2013), studies involving smaller particles or even nanoparticles are also cited. Emission of BC can cause differences in the oxidative potential at the cellular level, triggering high, medium or low levels of redox activity relative to the size of the particles (Nagappan et al., 2021) and the emission sources (Li et al., 2019). The damaging mechanisms caused by the oxidative stress induced by BC can act at cellular and subcellular levels, depending on the physicochemical characteristics of the surface of the particles (Jin et al., 2016; Zheng et al., 2017) and on soluble compounds such as transition metals or organic compounds (Nan et al., 2023). In this respect, the different redox effects on mitochondria, caused by particles, or on the cell membrane, caused by NADPH-oxidases (Cui et al., 2023; Shang et al., 2022; Calabró et al., 2021), or the activation of inflammatory cells capable of generating ROS and reactive nitrogen species (RNS), are all very important factors (Glencross et al., 2020). In addition, gases such as ozone modify the physicochemical characteristics of BC, naturally increasing redox activity (An et al., 2019a,b) in the environment or experimentally increasing hydrophilicity, leading to an increase in the oxidative potential (Xu et al., 2015). When only low amounts of ROS are generated and the cell damage is not severe, with the cell maintaining metabolic activity, the cells undergo apoptosis to protect other cells from inflammation and prevent the proliferation of damaged cells (Guo et al., 2012).

Autophagy constitutes a dynamic process involving removal of cell debris and also cellular equilibrium. Previous studies have shown that atmospheric particulate matter (APM) induces autophagy and increases LC3II expression in human vascular endothelial cells (Wang et al., 2021a, b; L. Wang et al., 2021). The autophagic capacity and autophagic flux have been systematically studied in order to clarify the exact cause of autophagosome accumulation in human umbilical vein endothelial cells (HUVECs) in response to a standard urban particulate matter, PM SRM1648a. It was observed that after 24 h of exposure, PM SRM1648a significantly increased LC3II expression with apparent autophagosome accumulation in HUVECs. Mechanistically, the blockage of autophagic flux can be explained by the detrimental effects of PM SRM1648a on lysosomal function, including lysosomal destabilization and alkalization, and inactivation of hydrolases, which are involved in blocking the fusion between autophagosomes and lysosomes, further disrupting the autophagic degradation and removal of cell debris. These observations

constitute evidence that PM SRM1648a destroys the balance of lysosomal stability and thereby causes autophagic flux dysfunction, ultimately contributing to endothelial cell damage (Wang et al., 2021a, b; L. Wang et al., 2021). The toxic and harmful potential of these particles, of very small sizes equal to or <2.5 , is maximal, as it has been demonstrated that they can facilitate the transport of toxic compounds into the bloodstream and damage developing organs in neonates (lungs, liver, brain) affecting their growth (Climate & clean air coalition). Maintaining acceptable levels of air quality should therefore be a priority worldwide, with a special focus on the new generations, in the context of environmental health.

The respiratory system is the main target organ affected by PM_{2.5}, and exposure to PM_{2.5} increases the risk of developing pulmonary fibrosis (PF). Lung epithelial cells (BEAS-2B) and fibroblasts (NIH-3T3) were used as in vitro exposure models to explore the mechanisms of PF (Liu et al., 2024). PM_{2.5} exposure was found to cause mitochondrial damage in BEAS-2B cells and increased the fibrotic phenotype in NIH-3T3 cells. Exposure to PM_{2.5} inhibits mitophagy in BEAS-2B cells, which hinders the removal of damaged mitochondria and triggers cell

death. In this process, nuclear retention of the mitophagy-related protein Parkin prevents its recruitment to mitochondria, resulting in inhibition of mitophagy. By contrast, fibroblasts exhibit increased levels of autophagy, which can isolate PM_{2.5} and lead to abnormal fibroblast proliferation and migration. Fibroblasts also include fibrotic phenotypes causing collagen deposition and increased α -actin activity. These findings identify PM_{2.5} as a trigger for PF and outline the molecular mechanism of autophagy in PM_{2.5}-induced PF, providing new insights into lung damage (Liu et al., 2024). Meta-analysis of epidemiological studies has suggested that BC is a valuable air quality indicator for assessing the health risks associated with particulate matter emitted from primary combustion, which may induce acute respiratory inflammation (Janssen et al., 2011) and chronic obstructive pulmonary disease (Niranjan and Thakur, 2017). Such meta-analysis has also shown that apoptosis is an important mechanism of pulmonary transmission induced by airborne particles. Studies using in vitro experimental environmental BC-models have indicated that oxidative stress can induce cellular apoptosis through two pathways (Niranjan and Thakur, 2017; Deng et al., 2014; Dagher et al., 2006). In vitro studies on human

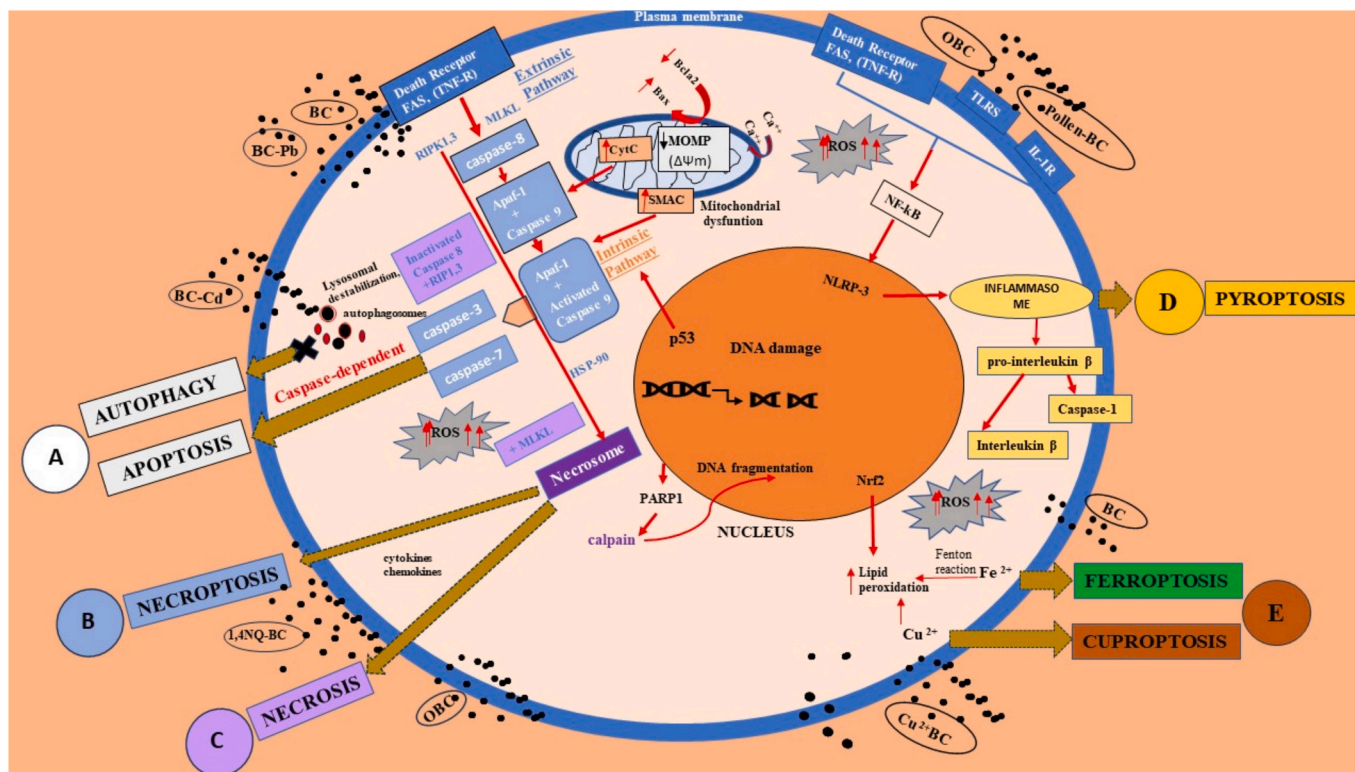


Fig. 1. Cell death pathways caused by BC exposure. **A)** Apoptosis can be initiated by the extrinsic pathway and/or intrinsic pathway. The extrinsic caspase-dependent pathway is activated by cell death receptors expressed in the plasma membrane and by activation of tumor necrosis- α TNF-R by secretion of caspase-8. The intrinsic mitochondrial pathway is mediated through cytochrome c released into the cytosol by mitochondrial dysfunction (decrease in membrane potential) and the second mitochondria-derived activator of caspases (SMAC), which promotes formation of the apoptosome (Apaf-1 and caspase 9) and activation of caspases that orchestrate cell death. Both pathways cause activation of caspase-3. Additionally, the synergistic cytotoxic effects of BC-Pb or BC-Cd that cause an increase in ROS that activates the extrinsic and intrinsic mitochondrial pathways of apoptosis are regulated through the Bax (BCLa2) gene, via the p53-Bax-caspase pathway. Blockage of autophagic flux can be explained by lysosomal destabilization, which is involved in blocking the fusion between autophagosomes and lysosomes, further disrupting autophagic degradation and removal of debris. **B)** Necroptosis is induced by activation of tumor death receptor 1 (TNF-R1) and regulated through expression and phosphorylation of the RIPK1a RIPK3 protein, which when combined with inactivated caspase 8, activates the necrosome, thus leaving programmed necrosis. In addition, the BC-associated secondary particle 1,4NQ causes necroptosis by activation of RIPK1, RIPK3, MLKL and HSP-90. This is accompanied by high levels of reactive oxygen species (ROS), increased levels of calcium ions in the cytosol and release of cytokines and chemokines. **C)** Necrosis. Extreme levels of ROS induce high levels of oxidative stress caused by BC or O-BC activating the necrotic death pathway. Mitochondrial dysfunction with reduced ATP, lack of Ca^{2+} homeostasis, DNA damage and PARP activation together induce production of proteins such as calpain, finally leading to rupture of the plasmatic membrane triggering necrosis. **D)** Pyroptosis, increased oxidative stress and inflammasome activation, through NLRP3 and the caspase 1 subunit with increased IL-1 β . BC or BC with ozone (OBC) through the pathway that integrates the signal ROS-NLRP3-caspase1-IL-1 β . **E)** Other types of cell death: Ferroptosis. An imbalance between antioxidant systems and intrinsic oxidation can cause iron-dependent cell death. Environmental BC is a potent inducer of ferroptosis that mediates redox imbalance and follows Nrf2-dependent signalling. Cuproptosis. Excess copper also induces cell death; copper-dependent death occurs via direct binding of copper to lipoylated components and loss of iron-sulphur cluster proteins, leading to cell death.

alveolar epithelial cell lines (A549) with PM 2.5 indicate that fresh BC (FBC) and ozone-oxidized BC (O-BC) can induce caspase-8 dependent apoptosis, in which both the cell death receptor-dependent pathway and the mitochondrial pathway participate (Xu et al., 2022). In this cell line, OBC significantly increased the cellular levels of ROS in a dose-dependent manner in 24 h (An et al., 2019a,b; Xu et al., 2022). Exposure to BC or O-BC in the A549 cell line can also induce cell death through other pathways. These include necroptosis (Xu et al., 2022), which is induced by activation of the death receptor tumor 1 (TNF-R1) and regulated through RIPK1a RIPK2 protein expression and phosphorylation, which when combined with the inactivated caspase 8, leads to assembly of the necrosome, thus leaving programmed necrosis (Chen et al., 2016). Overproduction of ROS provokes high levels of oxidative stress caused by fresh BC or O-BC associated with a sequence of intracellular events that can lead to the necrotic death pathway. These events include mitochondrial dysfunction with reduced ATP, lack of Ca^{2+} homeostasis, DNA damage and PARP activation, which induces proteins such as calpain; finally, rupture of the plasma membrane triggers necrosis (An et al., 2017) (See Fig. 1).

Recent in vitro and in vivo studies have shown that the association between heavy metals (Cu, Ni, Cd, Pb, Fe) and BC causes synergistic, toxic effects in alveolar epithelial cells provoking cell death and increased oxidative stress (Guo et al., 2009; Kong et al., 2017). Experimental studies in the human lung epithelial cell line (BEAS-2B) have shown that PM_{2.5} acts synergistically with Cd causing cytotoxic effects, altering the permeability of the cellular membrane, accumulating in cytoplasm with cell uptake of Cd and altering the cytoskeleton, even at low, non-toxic concentrations. The BC-Cd combination that causes an increase in ROS that activates the extrinsic and intrinsic mitochondrial pathways of apoptosis is again regulated through the BAX, BCLa2 and caspase 8 genes and p53 protein (Wang et al., 2021a, b; L. Wang et al., 2021). It is important to clarify that environmental PM_{2.5} particles can cause DNA damage at the nuclear level, triggering phosphorylation of the p-53 protein that activates apoptosis via the p53-Bax-caspase pathway (Pourazar et al., 2005). Particulate matter of this size can also induce mitochondrial dysfunction and damage (swelling, membrane pore opening, decreased membrane potential, decreased DNA copy number, decreased ATP synthesis) and calcium overload (Wang et al., 2019a,b) directly and not only via oxidative stress (see Fig. 1 and Table 1). Toxicological studies that have primarily focused on the toxic effects of pollutants are scarce and data on the impact and mixed mechanisms of black carbon and heavy metals are limited. Cd in particular was confirmed to cause autophagy and death in lung cells of mice, regulating autophagy that affects ferroptosis (Kang and Tang, 2017) induced by cadmium (Surolija et al., 2015). Thus, black carbon and cadmium nanoparticles, important environmental pollutants associated with cigarette smoke, can be associated with lung diseases that promote the formation of autophagosomes and ferroptosis, increasing malonaldehyde (MDA), reactive oxygen species (ROS) and the levels of divalent iron ions (Fe^{2+}), observed by comparing the exposure of the human 16HEB cell line (bronchial epithelioid cells) and mouse lung tissues (Mao et al., 2024). Ferroptosis is a newly discovered type of programmed cell death that results from the increase in lipid peroxidation to lethal levels that depend on oxidative stress (Cao et al., 2023). In vivo and in vitro studies have shown that oxidative stress caused by the imbalance between antioxidant systems and intrinsic oxidation can cause iron-dependent cell death leading to lung injury. Ferroptosis of the lung epithelium has pro-inflammatory effects; however, much of the current literature indicates that environmental PM is a potent inducer of pulmonary epithelial ferroptosis that mediates redox imbalance and follows Nrf2-dependent signalling (Wang et al., 2022; Yue et al., 2023; Dong et al., 2023; Qian et al., 2024). Experimental study of these new pathways of cell death such as ferroptosis related to particulate matter pollution and lung diseases is important. Additionally, metals are important cofactors of the toxicity associated with lung diseases (Hua et al., 2024) caused or aggravated by BC, one of the most common

Table 1

Summary of cell death pathways in relation to experimental models of exposure to environmental BC particles.

Type of cell death: pathway	Experimental details	Target group in vitro	Reference
Autophagy	SRM1648a PM	Human umbilical vein endothelial cells (HUVECs)	Wan et al, 2021
	BC-Cd	The human 16HEB and cell line (bronchial epithelioid cells) and mouse lung tissues	Mao et al., 2024
	Fine particulate matter	Lung epithelial cell (BEAS-2B) and fibroblast (NIH-3T3)	Liu et al., 2024
	Nano-Cu third day of gestation	Pregnant Sprague-Dawley rats	Kang et al., 2021
Apoptosis: ROS-intrinsic mitochondrial caspase -dependent	Black carbon Ultrafine BC (ufBC)	Neuroblastoma cell line (SH-SY5Y)	Shang et al., 2022
	Fresh BC (FBC)/ozone oxidized-BC (OBC) PM 2.5	Human alveolar epithelial cell line (A549)	An et al., 2019a,b
	BC (FBC)/ozone oxidized-BC (OBC) PM 2.5	Human alveolar epithelial cell line (A549)	Xu et al., 2022,
	BC + PB PM 2.5	Human alveolar epithelial line BEAS-2B	Jiang et al., 2018, 2020
Apoptosis: ROS-extrinsic cell death receptor and intrinsic mitochondrial caspase-dependent	BC + Cd PM 2.5	Human alveolar epithelial line BEAS-2B	Wang et al., 2021a, b; L. Wang et al., 2021
	M2.5 at different concentrations (0, 25, 100 and 250 $\mu\text{g mL}^{-1}$)	Human SH-SY5Y neuroblastoma cells	Wang et al., 2019a,b
	BC (FBC)/ozone oxidized-BC (OBC) PM 2.5	Human alveolar epithelial cell lines (A549)	Xu et al., 2022,
	1,4NQ-BC PM 2.5	Monocyte/macrophage murine line RAW-264.7	Cui et al., 2023
Necroptosis: ROS-TNF α -RIPK1/ RIPK3	Fresh BC (FBC)/ozone oxidized-BC (OBC) PM 2.5	Human alveolar epithelial cell lines (A549)	An et al., 2017
	BC + PB PM 2.5	Human lung epithelial line BEAS-2B	Jiang et al., 2018
Pyroptosis: ROS-NRPL3-caspase-1-IL-1beta	BC PM 2.5	Human nasal mucosal epithelial cells	Li et al., 2021
	Fresh BC (FBC)/ozone oxidized-BC (OBC) PM 2.5	Human corneal epithelial cells (HCECs)	Long et al., 2020
Ferroptosis	BC-Cd	The human 16HEB and cell line (bronchial epithelioid cells) and mouse lung tissues	Mao et al., 2024
	SRM1648a PM	Human umbilical vein endothelial cells (HUVECs)	Wang et al., 2021a, b
	PM (200 μg per mouse). NaHS (exogenous H ₂ S)	C57BL/6 and Nrf2 knockout	Wang et al., 2022
	Diesel exhaust PM2.5	Six-week-old C57/BL6 mice	Yue et al., 2023
	PM2.5-induced lung injury	Nrf2-knockout (KO) mice and Nrf2 siRNA transfection.	Dong et al., 2023
	PM 1649b	In vivo into murine C57BL/6 mice and airways or in vitro to human bronchial epithelial cells (HBECS).	Qian et al., 2024

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Table 1 (continued)

Type of cell death: pathway	Experimental details	Target group in vitro	Reference
Cuproptosis	Diesel soot particulate matter	C57BL/6 mice (male, 6–8 weeks old) and mouse dopaminergic neuronal cell line (MN9D)	Feng et al., 2024
	CuCl ₂	Pregnant mice	Zhao et al., 2024
	Decabromodiphenyl ether (BDE-209)	Female Sprague–Dawley rats	Wang et al., 2024

indoor environmental pollutants in chronic obstructive pulmonary disease (Zhang et al., 2024).

It is also known that exposure to some heavy metals causes toxicity of vital organs in the body. Some experts have indicated that combined exposure to low doses of BC (2.5 PM) and Pb in vivo and in vitro in the same cell line (BEAS-2B) has synergistic or additive effects and internalization as complexes in cells, thereby increasing oxidative stress and inducing severe apoptosis and necrosis (Jiang et al., 2018; Jiang et al., 2020). Thus, Pb potentiates the effect of BC on oxidative stress, DNA damage and apoptosis in the BEAS-2B human bronchial epithelial line (Jiang et al., 2020). A positive correlation can also be established between the potentiation of oxidative stress by BC and metal (Pb) co-exposure and the increase in apoptosis biomarkers. The BC particles resulting from the combustion of fossil fuels evade the body's defence mechanism and lodge in the lungs causing diseases such as lung cancer, chronic obstructive pulmonary disease (COPD), lower-respiratory infections (such as pneumonia). However, this mortality risk factor is potentially modifiable, by controlling air quality (Salas-Sánchez et al., 2020; He et al., 2023a,b; Xu et al., 2023). The harmful action of BC will be increased by heavy metals, increasing oxidative stress and different types of cell death and therefore numerous respiratory tract diseases. The in-depth study of the mechanisms of the different types of cell death associated with heavy metals is important because it would allow different therapeutic actions to be taken.

Some studies also show that excessive exposure to Cu can induce oxidative stress in multiple organs (Tang et al., 2018; Zhou et al., 2019; Wang et al., 2019a,b). When oxidative stress caused by Cu is severe and exceeds the cells' ability to repair itself, autophagy is triggered (Wang et al., 2018). Autophagy is a natural process involving removal of the degradation part of damaged organelles and proteins from the cytoplasm and is often accompanied by apoptosis (Xu et al., 2009). Studies conducted in animals exposed to copper for 180 days showed strong evidence that excess Cu can trigger autophagy and mitochondrial apoptosis by inducing oxidative stress in rat kidneys (Wan et al., 2020). Likewise, exposure in vivo in chickens to copper for 4, 8 and 12 weeks causes significant damage to immune organs, leaving apoptosis and autophagy via mitochondrial route in the Bursa of Fabricius (Guo et al., 2020). Prenatal exposure to nano-Cu induced autophagy via the PI3K/AKT/mTOR and AMPK/mTOR pathways, which associated with oxidative stress and inflammation in rat placenta (Kang et al., 2021). Cuproptosis is a newly described type of Cu-dependent programmed cell death (Tsvetkov et al., 2022). Cuproptosis is distinct from other known patterns of cell death and cannot be therapeutically acted upon by pharmacological or genetic inhibitors that might affect other forms of cell death such as apoptosis, necroptosis and ferroptosis (Tang et al., 2022). A new reproductive toxicity of Cu exposure in spontaneous abortion has recently been described as causing placental cuproptosis. In a recent study, researchers found that Cu exposure during pregnancy induced miscarriage by inducing placental cuproptosis in pregnant mice exposed to CuCl₂. In particular, exposure to Cu at 1.3 mg/kg/d (a real dose of environmental exposure) was sufficient to cause cuproptosis of

the placenta. Exposure to CuCl₂ disrupts the TCA cycle, causes proteotoxic stress, increases the import/decrease of Cu²⁺ ions, and results in the loss of Fe-S proteins in the mouse placenta, inducing placental cuproptosis and epigenetically regulates placental cuproptosis (Zhao et al., 2024). Other animal studies have also associated ovarian dysfunction with cuproptosis caused by exposure to inhaled substances such as decabromodiphenyl ether (Wang et al., 2024). In view of these studies, although cuproptosis has apparently not been found to have toxicological repercussions on many organs, the increasing environmental pollution and the fact that it preferentially affects reproductive and gestational organs make this process a priority target for environmental research with an eye on new generations. Poor quality air, water and food can act as a silent killer, affecting the survival of adults and of the younger generations.

Ultrafine BC particles (uBC) induce important neurotoxic effects by causing mitochondrial oxidative stress that generates mitochondrial damage and respiratory dysfunction in a neuroblastoma cell line (SH-SY5Y). Mitochondria are responsible for the production of most ROS in cells, and mitochondrial dysfunction is closely related to adverse nervous outcomes. Mitophagy is an important cellular process for eliminating dysfunctional or damaged mitochondria. Mitochondrial oxidative stress regulates uBC-induced mitochondrial dysfunction and PINK1/Parkin-dependent mitophagy. PINK1/Parkin-dependent mitophagy probably participates in regulating uBC-caused mitochondrial dysfunction, but not by controlling mitochondrial fusion and division related proteins (Shang et al., 2022). ROS overproduction and mitochondrial dysfunction often activate apoptosis via the mitochondrial-ROS pathway. The increase in ROS production, mitochondrial calcium overload and high levels of CypD are key factors in the regulation of mitochondrial membrane permeability (MMP) (Wang et al., 2019a,b). It is known that damage to numerous organs and degenerative pathologies are driven by ferroptosis (Jiang et al., 2021). Soot nanoparticles cause neurodegenerative diseases, including the development of Parkinson's disease (PD). A recent study investigated the effects of exposure to soot nanoparticles (SNPs) that are prevalent in PD symptoms, by using in vivo and in vitro PD models. In the experiments, in vivo animal behavioural assessment showed that exposure to SNPs exacerbated motor and cognitive impairment in PD mice. Molecular biology techniques further revealed that SNPs aggravated the degeneration of dopaminergic neurons. In vitro experiments revealed that exposure to SNPs intensified ferroptosis in PD cells by increasing ROS and iron ion levels, while reducing glutathione levels and mitochondrial membrane potential. The study findings showed that SNPs can exacerbate the onset and progression of PD by recruiting the YTH domain-containing protein family 1 (YTHDF1), increasing m6A methylation in the 5'UTR of ACSL4, amplifying ACSL4 protein expression, and accelerating the ferroptosis process in dopaminergic neurons (Feng et al., 2024). In our opinion, due to the aging population, further research on the role of BC in exacerbating PD and other neurodegenerative diseases such as Alzheimer's disease (AD) is necessary, as it may provide crucial data for formulating environmental safety standards and possible therapeutic strategies at the health care level to address these diseases. On the other hand, experimental studies using BC exposure in animals and cells constitute interesting models for obtaining information about the mechanisms of environmental neurotoxicity.

However, some research experts highlight that additional studies on the complex composition of BC should be carried out to investigate the toxicity of different secondary particles such as polycyclic aromatic hydrocarbons and sulphate and nitrate compounds, as some of the DNA damage and mitochondrial dysfunction may be due to the direct interaction between particles and target cells (Gao et al., 2017; Li et al., 2015). Thus 1,4-naphthoquinone-coated BC (1,4NQ-BC) is a secondary PM 2.5 particle obtained by the absorption of BC from polycyclic aromatic hydrocarbons (PAHs) during the process of combustion and that considerably increases its toxicity (Lohmann et al., 2005). In vitro experimental immunotoxicity studies in the RAW-264.7 cell line have

shown that this secondary particle (1,4NQ-BC) causes necroptosis in macrophages and increased expression of RIP1, RIP3, MLKL and HSP-90 mRNA. Macrophage necroptosis is important in immune defence as this secondary particle causes inhibition of the defensive capacity of macrophages to release extracellular traps directed towards pathogenic METs (Cui et al., 2023).

In addition to cellular redox activation, which triggers apoptosis, necroptosis or necrosis, BC PM_{2.5} can induce cell death through the inflammatory pathway, causing pyroptosis (Sangiuliano et al., 2014). In pollen-sensitized human nasal mucosal epithelial cells, BC PM_{2.5} causes increased oxidative stress and inflammasome activation (via NRPL3 and caspase-1 subunit) with increased IL-1 β and cytotoxicity (Li et al., 2021). Likewise, ozone-oxidized BC (OBC) causes apoptosis and cytotoxicity, and both OBC and fresh BC (FBC) also provoke in human corneal epithelial cells through a pathway that includes the ROS-NRPL3-caspase1-IL-1 β signal (Long et al., 2020).

The clinical and/or preclinical studies reviewed show that BC is an indicator of air quality (Janssen et al., 2011); however, we believe that cell damage is determined by the ratio between the oxidative stress level and cell death. Moreover, the cell damage caused by BC can evolve into one or another form of cell death, which is mainly determined by the level of oxidative stress (Peixoto et al., 2017). Different types of cell death can also appear simultaneously, such as apoptosis, which can progress to necrosis (An et al., 2019b), with each of these processes being one of the extremes of cell death. The activation pathways often seem to be either exclusive, such as apoptosis and necroptosis (Guo et al., 2009), necroptosis and Mets (Cui et al., 2023), or associated with inflammasomes, as in pyroptosis (Li et al., 2021; Long et al., 2020).

In summary, cell death pathways caused by the redox effect of BC are initially triggered at the cell membrane and/or the mitochondrial membrane level. In the latter situation, these pathways, which can be caspase-independent or caspase-dependent, will induce activation of the apoptosome and execution of the caspase cascade, in a reversible process of cell death (An et al., 2019a,b). If oxidative stress causes more intense cell damage, this can lead to activation of the necrosome and thus programmed necrosis and/or necrosis (Guo et al., 2009; Cui et al., 2023). Although the inflammatory component is present in necroptosis, high levels of inflammasomes will cause cell pyroptosis (Li et al., 2021; Long et al., 2020). In addition, oxidative stress can be accompanied by DNA damage, causing activation of antioxidant genes at the mitochondrial level in apoptosis (Wang et al., 2017), DNA fragmentation, membrane lipid peroxidation and reduced ATP production and destabilization of the mitochondrial membrane (Wang et al., 2019a,b). In situations of extreme levels of oxidative stress, cellular morphological changes such as swelling or rupture of the cell membrane are programmed through necroptosis (Guo et al., 2009; Cui et al., 2023) or necrosis (Jiang et al., 2018). At the same time, due to the interaction between BC and human cells, tissue clean-up processes such as autophagy (Kang and Tang, 2017; Surolia et al., 2015; Mao et al., 2024; Wang et al., 2018; Xu et al., 2009; Wan et al., 2020; Guo et al., 2020; Wang et al., 2021c) and mitophagy (Shang et al., 2022) are altered. Other types of cell death associated with heavy metals (Guo et al., 2009; Kong et al., 2017; Wang et al., 2021a, b; L. Wang et al., 2021; Jiang et al., 2018; Jiang et al., 2020) are enhanced or generated, such as cuproptosis (Tang et al., 2018; Zhou et al., 2019; Wang et al., 2019a,b; Zhang et al., 2024; Zhao et al., 2024; Wang et al., 2024; Tsvetkov et al., 2022; Zhao et al., 2024; Wang et al., 2024) and ferroptosis (Cao et al., 2023; Wang et al., 2022; Yue et al., 2023; Dong et al., 2023; Qian et al., 2024; Hua et al., 2024; Zhang et al., 2024; Jiang et al., 2021; Feng et al., 2024) caused by excessive oxidative stress by chemical or physical interaction with cellular machinery. Studying the interactions between the wide variety of environmental stressors associated with BC by using experimental models allows researchers to study the pathways of cell death through different assays and try to clarify the mechanisms of non-communicable diseases (see Fig. 1 and Table 1).

This review of experimental models exposed to BC provides

important preclinical information regarding the study of redox signaling caused by exposure to environmental BC particles and considering physical or chemical agents (see Table 1 and Fig. 1). On the basis of the studies considered, we suggest that ambient BC exerts adverse effects on human health by inducing different types of cell death in a mechanism that can lead to chronic diseases.

3. The interaction between RF-EMFs and biochemical processes can lead to cell death

The WHO and European Union have established limits of exposure of between 10 GHz and 300 GHz providing basic power density restrictions to prevent heating of tissues on or near the body surface. Electromagnetic fields at these frequencies are capable of heating exposed tissue and may cause burns on the whole body or on certain parts. Legislation limits the specific absorption rate (SAR) levels in occupational exposure to whole body <0.4 W/kg, head and trunk <10 W/kg and extremities <20 W/kg and in the general public whole body <0.08 W/kg, head and trunk <2 W/kg and extremities <4 W/kg (International Commission on Non-Ionizing Radiation Protection (ICNIRP), 2013; Directiva 2013/35/UE del Parlamento Europeo y del consejo de 26 de junio de 2013, n.d.; Karipidis et al., 2020). However, the European Union legislation does not consider non-thermal effects.

It has been hypothesised that radiofrequency fields may induce oxidative stress in various cell types and thus compromise human and animal health. In this section, we evaluate the literature relating this hypothesis (Henschenmacher et al., 2022; Schuermann and Mevissen, 2021) to cell death. Various experimental studies indicate that exposure of animals and biological samples to human-made sources of electromagnetic fields (EMFs) can cause oxidative molecular damage and trigger a stress response (Lai and Levitt, 2023). This section of the review presents experimental studies on radiofrequency field exposure and biomarkers of oxidative stress. However, the association between exposure to radiofrequency fields and fields and oxidative stress remains unclear (Henschenmacher et al., 2022). This review of the effects of RF exposure on oxidative stress is based on the studies and hypotheses of relevant researchers in this field, regardless of possible biological consequences yet to be established. It has been suggested that the effects of 5G radiofrequency in some non-communicable diseases such as diabetes are not negligible. Thus, an experimental study in diabetic rats demonstrated that 5G radiation (3.5 GHz, GSM-modulated) produced a decrease in antioxidant levels and an increase in oxidant action. An increase in neuron degeneration also occurs in the hippocampus of diabetic rats, demonstrating that 5G radiation causes oxidative damage in the brain (Bektas et al., 2022). In a human experimental study in pregnant women, a potentially oxidative effect in umbilical cord blood and placenta was identified among the effects of radiofrequency radiation emitted by Wi-Fi systems and mobile phones (Bektas et al., 2022). Samples were collected immediately after the women gave birth, and the study findings indicated that mobile phone exposure during pregnancy may be a significant risk for oxidative stress and DNA damage in cord blood and placenta (Bektas et al., 2022).

The response to cellular oxidative damage caused by EMF includes expression of genes that regulate the cell cycle, such as P53 and P21 (Dehghani-Soltani et al., 2021). There is also some evidence indicating that activation of the transcription factor NRF2 erythroid factor 2 related to factor 2 regulates cell defence against oxidative damage and is activated by EMF (Patruno et al., 2020). Molecular oxidative damage can potentially be repaired through the induction of heat shock proteins (Lee et al., 2012) or by DNA damage repair with changes in proteins (p53, NF κ B included MAPK pathway) (Eker et al., 2018) or lipid peroxidation (Lai, 2019) after EMF exposure (Lai et al., 2023). Finally, apoptosis constitutes the last link in the repair of oxidative molecular damage (Zielinski et al., 2020). In this respect, the parameters of real EMFs, such as intensity, frequency, duration of exposure, polarization, pulsation and modulation, play an important role in the bioactivity and

oxidative damage of cellular DNA (Panagopoulos, 2019; Lai et al., 2023), accelerate numerous pathologies (Bosch-Capblanch et al., 2022) and can cause cancer and reduced fertility (Kaur et al., 2023).

Expert researchers have commented on the action of electromagnetic fields generated by artificial sources and consider them to be fully polarized and coherent; the intensity of the radiation can exert forces on any electrically charged (or polar) particles or molecules, such as mobile or dissolved ions and charged macromolecules in any biological system (Pall, 2022; Panagopoulos et al., 2021; Panagopoulos et al., 2015). A model of the effect of polarized/coherent electromagnetic fields that is based on a forced ion oscillation mechanism to irregular activation of voltage-gated ion channels in cell membranes has been established (Panagopoulos et al., 2021). This biophysical action has been verified experimentally, showing that cellular exposure to electromagnetic fields causes the irregular opening of voltage-gated ion channels (VGICs) for calcium (Ca^{2+}), potassium (K^+) and sodium (Na^+) (Piacentini et al., 2008; Cecchetto et al., 2020; Zheng et al., 2021). This process can alter intracellular ionic concentrations, thus modifying the cellular electrochemical balance and inducing cell damage via overproduction of ROS (O'Hare Doig et al., 2017). Thus, EMF-radiofrequency fields generated by Wi-Fi (2.45 GHz) and mobile phones (at 900 and 1800 MHz radio frequency) have been shown to induce excessive oxidative responses and intrinsic mitochondrial apoptosis through a cation channel member of the subfamily of the transient receptor potential TRPV1 and induced cytosolic Ca^{2+} accumulation in a breast cancer cell line (MCF-7) (Çiğ and Nazıroğlu, 2015; Kahya et al., 2014). In model pentylentetrazol (PTZ)-induced epileptic rats, the effects of exposure to Wi-Fi (2.45 GHz) involved Ca^{2+} influx and oxidative stress-induced apoptosis in the hippocampal region and in the murine root ganglion (DRG), through activation of TRPV1 channels in vitro (Ghazizadeh and Nazıroğlu, 2014). All of these studies coincide in recognising the relationship between the irregular opening of cell membrane channels associated with oxidative stress and changes in cell metabolism due to radiofrequency exposure that can activate cell death pathways.

In an experimental study investigating the anti-apoptotic protein Bcl-2 in the brain and testes of rats following whole-body exposure to radiation emitted by 900 MHz mobile phones, no changes in this protein were detected 20 min after short-term exposure to RF/MW radiation (Yilmaz et al., 2008). However, in vitro studies with nerve cells have shown that RF radiation can increase caspase-3, induce proinflammatory differential responses and increase mitochondrial membrane potential of astrocytes (Zhao et al., 2007; Liu et al., 2012; Tsoy et al., 2019; Lu et al., 2014). In the first two of these in vitro studies (Zhao et al., 2007; Liu et al., 2012) experimental models were exposed at 1900 and 1950 MHz, for respectively twelve hours and forty-eight hours, and apoptosis was observed in both cases. On the other hand, the initial effect of radiofrequency at the cellular level is mediated at the plasma membrane by NADH oxidase, which rapidly generates ROS and voltage-gated calcium channels (Georgiou and Margaritis, 2021). The immediate effect of EMFs is quickly activated via a response to various frequencies and intensities and induces activation of ERK (the extracellular-signal-regulated-kinase cascade) mediated by MAPK cascades (mitogen-activated protein kinase) (Friedman et al., 2007). RF radiation (918 MHz) can suppress H_2O_2 -triggered oxidative stress, which induces phosphorylation of p38 mitogen-activated protein kinases (p38MAPK) and $\text{A}\beta_{42}$ activation by nicotinamide adenine dinucleotide phosphorophosphate (NADPH) oxidase and is regulated by ERK (Tsoy et al., 2019). Studies demonstrating activation of different cell death pathways caused by radiofrequency exposure at non-thermal SAR levels provide very important information in the study of contamination caused by non-natural, man-made sources of non-ionizing radiation.

However, altered levels of markers of oxidative stress, DNA damage or glial activation were not found in the brain of C57BL/6 mice exposed to 1950 MHz RF-EMF (Jeong et al., 2018) for 8 months or in vitro N9 microglial SH-SY5Y neuroblastoma cells exposed to 935 MHz RF-EMF (Zielinski et al., 2020). In addition, the effects of mobile phone

exposure on brains exposed to 900 MHz microwaves over periods of 10 months or one year indicated alteration of microRNA expression in the brain, apoptosis and altered total antioxidant capacity and catalase in glial cells (Dasdag et al., 2019; Dasdag et al., 2015a,b; Dasdag et al., 2009). Oxidative stress and decreased mitochondrial membrane potential (MMP) and caspase-dependent mitochondrial apoptosis occur in the hippocampus of albino rats after 28 consecutive days of exposure to 2.45 GHz RF (Gupta et al., 2018). Similarly, oxidative stress and caspase-dependent mitochondrial apoptosis occur in the rat hippocampus after exposure to 2 GHz RF for 8 weeks (Lin et al., 2021). Long-term exposure (one year) to 2.4 GHz RF could lead to adverse effects such as neurodegenerative diseases (non-communicable diseases) caused by altered expression of some miRNAs in the brain, and further studies on the effects of RF on the nervous system should be conducted (Dasdag et al., 2022; Dasdag et al., 2015a,b). ROS induced by RF could trigger various biological outcomes, such as autophagy, apoptosis and DNA damage. Thus, several experimental studies have shown that autophagy contributes to the RF-induced adaptive response. The effects of ELF-modulated 935 MHz RF-EMF on apoptosis, autophagy, oxidative stress and electron exchange in N9 microglial and SH-SY5Y neuroblastoma cells exposed to 4 W/kg or subjected to sham exposure for 2 and 24 h were evaluated (Zielinski et al., 2020). Exposure to RF-EMF for 24, but not for 2 h, increased protein levels of the autophagy marker ATG5, whereas LC3B-I and II and pERK were not altered in both cell types and exposure times investigated. A transient increase was observed in glutathione (GSH), but not in hydrogen peroxide or cytochrome c oxidase, indicating that short-duration RF-EMF at SAR levels accepted by current safety guidelines could cause autophagy and oxidative stress, depending on cell type and exposure duration (Zielinski et al., 2020). SH-SY5Y human neuroblastoma cells were exposed for 20 h to a 1950 MHz UMTS signal and then treated with menadione-induced DNA damage, assessed by applying the comet assay. The reduction did not occur when autophagy was inhibited by bafilomycin A1 and E64d. These findings suggest the involvement of autophagy in the RF-induced adaptive response in human neuroblastoma cells (Sannino et al., 2022). However, it is not clear whether exposure to environmental radiofrequency signals (RF) affects cell status or response to cellular stress such as apoptosis or autophagy. In another experimental study involving RF exposure alone or co-exposure to RF and chemical treatments known to induce either apoptosis or autophagy, two human cell lines (SH-SY5Y and HCT116) and two primary rat cortex cell cultures (astrocytes and co-culture of neurons and glial cells) were continuously exposed for three or five consecutive days using an 1800 MHz carrier wave modulated with various environmental GSM, UMT, LTE or unmodulated RF signals at constant temperature. Statistical analysis of the results indicated that RF-EMF exposure did not affect the overall behaviour of healthy, apoptotic or autophagic cells, even at SAR levels above guidelines (Joushomme et al., 2022). However, in vivo studies also showed that short-term exposure to RF-EMF leads to the autophagy pathway in the cerebral cortex and brainstem, at 835 MHz with a specific absorption rate (SAR) of 4.0 W/kg for 4 weeks or 12 weeks, and autophagosomes were observed in the striatum and hypothalamus of RF-exposed mice, based on neuronal transmission electron microscopy (Kim et al., 2017; Kim et al., 2016). In another study, the combined effects of 1-week exposure to electromagnetic pulse (EMP) at 650 kV/m for 1000 pulses and 4.9 GHz radiofrequency (RF) at 50 W/m² for 1 h/d in male mice were examined, and open field test, tail suspension test and Y-maze were used to evaluate anxiety, depression-like behaviours and spatial memory ability, respectively. Combined exposure to EMP and 4.9 GHz RF could alter emotional behaviour, which may be associated with Glutamatergic and GABAergic synapse system of hippocampus and autophagy in amygdala (Qin et al., 2023). EMF exposure during long exposure, of 12 weeks, may enhance learning ability, and has been shown (by higher hippocampal Ach levels) to interfere with long-term memory consolidation. Lipoic acid treatment improved both learning and memory by enhancing autophagy and hippocampal glutamate level and by the

reduced Ach levels and Sirt1 gene expression (Kim et al., 2018a,b; El-Kafoury et al., 2023). In another experimental vivo study, researchers explored the relationship between calcium channels and apoptosis or autophagy in the hippocampus of C57BL/6 mice after RF-EMF exposure at a specific absorption rate (SAR) of 4.0 W/kg for 4 weeks. RF-EMF may alter intracellular calcium homeostasis by decreasing calcium channel expression in the hippocampus; presumably by activating the autophagy pathway, while inhibiting apoptotic regulation as an adaptation process for 835 MHz RF-EMF exposure (Kim et al., 2018a,b). Autophagy can be activated by the effect of non-ionizing radiation and constitutes a cellular clearance system that can modify its homeostasis when environmental stressors such as radiofrequency act repeatedly. Disruption of the autophagy/cell death balance indicates the balance of the system between the cascade triggered by oxidative stress, metabolic activation and cell damage caused by sources of non-ionizing radiation. Therefore, all these in vivo and in vitro experimental studies allow us to validate and clarify the hypothesis that radiofrequency can induce cell damage by oxidative stress.

Ferroptosis is a recently described form of regulated cell death (RCD) caused by excessive oxidative stress. In vivo studies were conducted with a rat model to examine the association between ferroptosis and EMP-induced hippocampal neuronal damage. Moreover, in vitro studies were conducted with HT22 neurons to investigate the underlying mechanism of EMP-induced neuronal ferroptosis (Lai et al., 2022). Individual or combined exposure to MW and EMP radiation could impair learning and memory and damage hippocampal neurons in rats. Moreover, the adverse effects caused by the combined exposure were more severe than the individual exposure episodes, which may be due to cumulative rather than synergistic effects. Furthermore, ferroptosis in the hippocampus may be a common mechanism underlying learning and memory impairment induced by both single and combined MW and EMP exposure (Lai et al., 2023). Ferroptosis caused by radiofrequency is caused by a repeated and cumulative effect of oxidative stress. This can be validated in experimental models at the level of regions of the nervous system, such as the hippocampus, owing to the high vulnerability of the function of its cytoarchitecture to cellular damage. Likewise, exposure to 3500 MHz continuous wave RF-EMF in 40 male guinea pigs for 72 h led to ultrastructural changes in the auditory cortex cells, with swollen mitochondria and activation of caspase-9 and caspase-3 (Yang et al., 2022).

Spermatozoa are particularly vulnerable to oxidative stress, and non-ionizing radiation can interfere in the redox (oxidative/antioxidative) balance in the cells and thus alter their morphology and normal functioning (Gautam et al., 2022). As the concentration of Ca^{2+} increases, O_2 production is stimulated by the electron transport chain in mitochondria and/or activation of nitric oxide synthase (NOS), $\cdot\text{c}$ to generate more $\text{NO}\cdot$ (Brookes et al., 2004). Thus, exposure of human sperm to 1.8 GHz RF-EMF generates ROS in mitochondria and increased levels of 8-OH-dG, the main marker of oxidative DNA damage (De Iuliis et al., 2009). Long-term exposure to RF was found to increase ROS production and alter the antioxidant capacity by reducing GPx, CAT and SOD, and the resulting imbalance in redox status activated apoptosis through reduced expression of BCL-2 and increased BAX, cytochrome c and caspase 3 protein and DNA damage gene expression in rat spermatozoa (Kesari et al., 2011; Liu et al., 2015; Kumar et al., 2011; Akdag et al., 2016). Mice exposed to 900 MHz EMFs (4 or 8 h/day) for 35 days showed alterations in the electronic potential of the germ cell mitochondria membrane (Pandey et al., 2017). Exposure of mouse spermatogonia and spermatocyte cell lines to RF-EMF for 4 h induced mitochondrial ROS, DNA oxidation damage and fragmentation (Houston et al., 2018). Autophagy may play an important role in the adaptive response mechanism to protect against EMF and ensure cell survival (Liu et al., 2014). The autophagy induced by RF-EMFs pathway the AMPK/mTOR signalling pathway could prevent DNA damage in spermatozoan cells. In an experimental study mouse spermatocyte-derived cells (GC-2) were exposed to RF-EMFs 4 W/kg for 24 h. The findings showed that RF-EMFs

induced autophagy and DNA damage in GC-2 cells via ROS generation, and the autophagy signalling pathway AMPK/mTOR was activated by ROS generation (Li et al., 2018).

It has been demonstrated that apoptosis can be produced in human peripheral blood mononuclear cells PBMC by exposure to 900 MHz GSM RF-EMF radiation at a specific absorption rate of ~ 0.4 W/kg when the exposure lasts more than two hours (Lu et al., 2012). Apoptosis is induced through the mitochondrial pathway and mediated by activation of ROS triggered by alteration of the lipid, protein and DNA conformational balance (Lu et al., 2012). In an experimental study in which 40 Male BALB/C mice were exposed to TD-CDMA (3G) and LTE-advanced (4G) mobile phone radiation for six weeks, neutrophil numbers increased, but no effect on chemotaxis was observed: the authors concluded that radiation is likely to cause a decrease in phagocytosis and to induce apoptosis in neutrophils (Yinhui et al., 2019). Likewise, DNA damage and apoptosis was observed in mouse embryonic fibroblasts (NIH/3T3) after intermittent exposure (5 min on/10 min off, for various durations ranging from 0.5 to 8 h) to 1800 MHz GSM electromagnetic radiation (EMR) with an average specific absorption rate of 2 W/kg (Hou et al., 2015).

After normothermic exposure to 2.45 GHz RF, the promyelocytic cell line HL-60 was found to be the most vulnerable of ten different cell lines (Asano et al., 2017a). Microwave irradiation of the promyelocytic line HL-60 cells after continuous normothermic exposure for 48 h triggered caspase-independent apoptosis, and DNA fragmentation was thus induced by mitochondrial dysfunction related to apoptosis-inducing factor (AIF) expression. The caspase-dependent apoptosis was thus interrupted because the apoptosome was not activated due to the loss of apoptotic protease activating factor 1 (Apaf-1) and caspase 9 (Asano et al., 2017b).

In brief, this review study includes different experimental studies of autophagy associated with mechanisms of cell death and cell damage in different anatomical regions (nervous system, immune, embryonic and reproductive system) and/or cell units of different vulnerability (neurons, astrocytes, spermatozoa and/or cell lines). Different types of responses to the environmental stress caused by non-ionizing radiation were triggered in these models, activating the mechanisms of cell damage and death. Study and analysis of such models help us to better understand the interaction of RF in living beings. Although non-ionizing radiation does not produce ROS directly, cells potentially have some mechanisms whereby RF-EMFs cause oxidative stress (Henschenmacher et al., 2022; Schuermann and Mevissen, 2021) and indirectly induce some modifications in the redox state of the cell during attempted cell repair (Lai et al., 2023; Georgiou and Margaritis, 2021). The repair mechanisms are activated by molecular damage, such as DNA damage, lipid/protein peroxidation, alterations in cell cycles and induction of heat shock proteins (Kesari et al., 2011). The biophysical mechanisms of the EMF sources may act by activating the irregular opening of the VGIC channels (Panagopoulos et al., 2021; Panagopoulos et al., 2015). The intracellular increase in ions, especially calcium, is decisive in the overproduction of ROS (Liu et al., 2012) and can cause oxidative damage to the DNA (Houston et al., 2018) and alter calcium signalling at the level of the mitochondrial membrane (Çiğ and Naziroğlu, 2015; Kahya et al., 2014; Ghazizadeh and Naziroğlu, 2014) and the activity of NADPH oxidase in the cell membrane (Georgiou and Margaritis, 2021; Friedman et al., 2007). When the antioxidant mechanisms are overwhelmed by high levels of ROS in the nucleus (P53, P21) (Zielinski et al., 2020), the mitochondrial membrane (BCLa2/BAX) (Kesari et al., 2011; Liu et al., 2015; Kumar et al., 2011) and the cell membrane (NADPH) (Dasdag et al., 2015a,b), extrinsic and/or intrinsic caspase-dependent (Gupta et al., 2018; Lu et al., 2012; Yang et al., 2022; Hou et al., 2015) or caspase-independent (Asano et al., 2017b) apoptosis will be triggered. In vitro and in vivo experimental models have shown that oxidative stress induced by electromagnetic fields can activate adaptive autophagy that prevents apoptosis and cell damage, depending on the cell type and exposure time, and could alter intracellular homeostasis of

calcium by decreasing calcium channel expression and inducing AMPK/mTOR signalling (Zielinski et al., 2020; Sannino et al., 2022; Kim et al., 2017; Kim et al., 2016; Qin et al., 2023; Kim et al., 2018a,b; El-Kafoury et al., 2023; Kim et al., 2018a,b; Li et al., 2018). Ferroptosis, which occurs due to excess oxidative stress and has been described to be a result of neuronal damage in the hippocampus (Lai et al., 2022, 2023), is also considered (See Table 2 and Fig. 2). In our opinion, critical analysis of the relevant literature will improve the overall understanding of the mechanisms that modify bioelectric activity and that can cause oxidative damage at cellular and subcellular levels through the interaction of radiofrequency in preclinical experimental models.

In this section we have considered studies that describe a redox cellular response and different types of cell death associated with exposure to non-ionizing radiation. Although numerous experimental studies reflect the association between RF exposure and oxidative stress, there remains considerable uncertainty in this respect, with some authors considering it a hypothetical possibility (Henschenmacher et al., 2022), as several studies have shown no effect of EMF on oxidative stress in various models.

4. Prolonged redox signalling caused by the combination of BC and RF-EMF in immunotoxicity studies in vitro: impact on cell death

Air pollution is part of modern life (GBD and Risk Factors Collaborators, 2016), and in this respect the oxidative stress generated by exposure to air pollution may also contribute to increasing rates of human death due to non-communicable diseases (Rao et al., 2018). PM and/or EMF both generate free radical oxidants (reactive oxygen species) in experimental cell systems, causing oxidative stress and a reduction in endogenous antioxidants, finally triggering oxidative damage and cell death (Brenner and Mak, 2009; Meier and Vousden, 2007). On the other hand, in accordance with expert researchers working in this biophysical field, we hypothesise that the physico-chemical properties of both environmental agents (EMF and BC) must be considered, as the joint or simultaneous interaction between both could modify the biological response of immune cells via different mechanisms: 1) By modifying the dielectric constant of the BC during RF exposure. The biological effects of the interactions on cell metabolism would be different than if either of the agents acted separately (Michel et al., 1993; Sihvola, 2002); and 2) By altering the characteristics of the cell membrane during exposure to non-ionizing radiation, thus amplifying the toxic action of the BC and modifying the response to cell death (Lin et al., 2023). In this respect, the action described in Section 3, following the hypothesis that the effect of polarized/coherent electromagnetic fields is based on a mechanism of forced ionic oscillation for the irregular activation of voltage-gated ion channels in cell membranes (Panagopoulos et al., 2021), is very important in relation to the interaction between RF and cells. This process can alter intracellular ionic concentrations, thus modifying the cellular electrochemical balance and inducing cell damage through the overproduction of ROS (O'Hare Doig et al., 2017). Thus, radiofrequency EMF fields at 2.45 GHz, 900 and 1800 MHz have been shown to induce excessive oxidative responses and intrinsic mitochondrial apoptosis through a cation channel member of the TRPV1 transient receptor potential subfamily and also induce accumulation of cytosolic Ca^{2+} (Çiğ and Naziroğlu, 2015; Kahya et al., 2014).

On the other hand, from a biochemical point of view, the results of the NO response in the RAW macrophage cell line by combined exposure of RF and BC should be taken into account as indirect evidence of oxidative stress. Radiation acts by increasing the induction of NO even when macrophage viability levels were low and causing depletion of the cell machinery 48 h after RF exposure, despite the combined toxicity (Sueiro-Benavides et al., 2021). Some authors have suggested that electromagnetic fields could initially act as first messengers, modulating Ca-Calmodulin-dependent NO signalling pathways (Pall, 2018). There is

Table 2

Summary of cell death pathways in relation to experimental models exposed to radiofrequency electromagnetic fields.

Experimental details	Target group in vivo/ in vitro	Cell death pathway/ autophagy	Reference
935 MHz RF-EMF	N9 microglial and SH-SY5Y neuroblastoma cells	Autophagy	Zielinski et al., 2020
1950 MHz UMTS	SH-SY5Y human neuroblastoma cells	Autophagy	Sannino et al., 2022
1800 MHz, GSM, UMTS, LTE	Human cell lines SH-SY5Y and HCT116 and two cultures of primary rat cortex cells astrocytes and co-culture of neurons and glial cells	Autophagy	Joushomme et al., 2022
835 MHz RF-EMF	C57BL/6 mice	Autophagy	Kim et al., 2016; Kim et al., 2017 Kim et al., 2018a; Kim et al., 2018b Qin et al., 2023
at 650 kV/m for 1000 pulses and 4.9 GHz RF	C57BL/6 mice	Autophagy	
850–1900 MHz GSM	Male Wistar rats	Autophagy	El-Kafoury et al., 2023
1800 MHz	Mouse spermatocyte-derived cells	Autophagy	Li et al., 2018
900 MHz RF	31 adult male Wistar Albino rats exposed for 10 months (on glial cells in brain)	ROS- caspase-dependent apoptosis antioxidant capacity and catalase in glial cells on brain	Dasdag et al., 2009
918 MHz RF	Human and rat primary astrocytes	ROS- intrinsic mitochondrial caspase-dependent apoptosis P38-MAPK/NADPH-ERK	Tsoy et al., 2019
1800 MHz RF	Mouse microglial cells (N9)	ROS-intrinsic mitochondrial caspase-dependent apoptosis	Lu et al., 2014
1.900 MHz RF GSM	Neuron and astrocyte cell cultures	ROS-intrinsic mitochondrial caspase-dependent apoptosis	Zhao et al., 2007
1.950 MHz RF	Astrocytes and C6 glioma cells	ROS- intrinsic mitochondrial caspase-dependent apoptosis	Liu et al., 2012
3.500 MHz RF/ 5G	Auditory cortex of 40 male guinea pigs	ROS- intrinsic mitochondrial caspase-dependent apoptosis	Yang et al., 2022
2.450 MHz RF	Hippocampus of albino male rats	ROS- intrinsic mitochondrial caspase-dependent apoptosis	Gupta et al., 2018
2000 MHz RF	Hippocampus (CA1 and CA3) of 48 male (ICR) mice	ROS- intrinsic mitochondrial caspase-dependent apoptosis	Lin et al., 2021
Wi-Fi, 2.450 MHz RF	In vitro murine dorsal root ganglion (DRG) and in vivo hippocampus of pentylenetetrazol (PTZ)-induced epileptic rats	ROS-intrinsic mitochondrial caspase-dependent apoptosis Activation of TRPV1 channels in vitro	Ghazizadeh and Naziroğlu, 2014

(continued on next page)

Table 2 (continued)

Experimental details	Target group in vivo/ in vitro	Cell death pathway/ autophagy	Reference
900 MHz at RF	Human peripheral blood mononuclear cells (PBMC)	ROS- intrinsic mitochondrial caspase-dependent apoptosis	Lu et al., 2012
TD-CDMA (3G), and LTE-advanced (4G)	Exposure for six weeks, 40 male BALB/C mice	ROS- intrinsic mitochondrial caspase-dependent apoptosis	Yinhui et al., 2019
1800 MHz RF	Oxidative changes and apoptosis induced by 1800-MHz electromagnetic radiation in NIH/3T3 cells	ROS- intrinsic mitochondrial caspase-dependent apoptosis	Hou et al., 2015
1800 MHz RF	In vitro human spermatozoa	ROS-intrinsic mitochondrial caspase-dependent apoptosis	De Iuliis et al., 2009
1800 MHz RF SAR 0.15 and 1.5 W/kg	In vitro cultured mouse spermatogonial GC1 and spermatocyte GC2 cell lines	ROS-intrinsic mitochondrial caspase-dependent apoptosis	Houston et al., 2018
900 MHz RF SAR	Testicular germ cells in Swiss albino mice	ROS-intrinsic mitochondrial caspase-dependent apoptosis	Pandey et al., 2017
900 MHz RF SAR 0.9 W/kg	Spermatozoa in male rat	ROS-intrinsic mitochondrial caspase-dependent apoptosis	Kesari et al., 2011
900 MHz RF SAR 0.66 W/kg	Spermatozoa in male rat	ROS-intrinsic mitochondrial caspase-dependent apoptosis	Liu et al., 2015
10 MHz	Spermatozoa in male rat	ROS-intrinsic mitochondrial caspase dependent apoptosis	Kumar et al., 2011.
0.9–1.8–2.45 GHz-RF	Breast cancer cell line (MCF-7)	ROS-intrinsic mitochondrial caspase dependent apoptosis activation of TRPV1 channels in vitro	Çiğ and Nazıroğlu, 2015 Kahya et al., 2014
2.4 GHz-RF	Cord blood and placenta from 149 pregnant women	ROS and DNA damage in cord blood and placenta	Bektas et al., 2020
2.4 GHz-RF	16 adult male Wistar-Albino rats exposed for more than year	DNA damage in testes	Akdag et al., 2016
2.45-GHz RF	Promyelocytic HL-60 cell line	Apoptosis: ROS-mitochondrial caspase-independent	Asano et al., 2017a,b
1.5 GHz	HT22 neurons	Ferroptosis	Lai et al., 2022
1.5 GHz	Male Wistar rats	Ferroptosis	Lai et al., 2023

also evidence that RF acting in combination with BC particles prolongs the cellular inflammatory functions of NO-associated macrophages by 24 h (Sueiro-Benavides et al., 2021).

Macrophages and neutrophils are the first immune cells to respond when we inhale polluted air (toxic or pathogens) that reaches our lungs (Glencross et al., 2020). Therefore, conducting immunotoxicity studies to determine the mechanisms whereby environmental stress agents (biophysical and chemical) such as EMF and BC interact together is of great interest (Glencross et al., 2020; Yadav et al., 2023). The continuous and combined action of environmental pollution by BC and/or EMF on innate immune cells (first line of immune defence), additive, synergistic, antagonistic or facilitation effects (Kostoff and Lau, 2013) trigger cell

death pathways at the cellular or subcellular level.

The RAW 264.7 macrophage cell line produces a measurable immune response when cells are exposed separately to non-ionizing radiation (Lin and Lin, 2011) and/or environmental BC (Cui et al., 2023). The RAW264.7 cell line displays significant cytoprotective (increase in HSP70 after 48 h), cytotoxic (increase in NO after 72 h) and inflammatory actions (increase in TNF- α after 72 h) in response to exposure to multiple frequencies of radiation (2450 GHz and/or 900 MHz) and which are dependent on the exposure time (López-Furelos et al., 2018). The phagocytic activity caused by monocytes-macrophages was found to decrease on exposure to one or more frequencies (López-Furelos et al., 2018), with immunomodulation that was dependent on EMF exposure time. On the other hand, in the macrophage 264.7 cell line, BC-1.4NQ triggered cell death with significant redox activity and elevated levels of cytosolic calcium and HSP-90 (Cui et al., 2023). The toxic actions of each of these RF or BC agents have individual deleterious effects, but in combination have substantially different results (Kostoff and Lau, 2013).

There is some experimental evidence that the combined synergistic or simultaneous action of 2.45 GHz RF and BC in RAW 264.7 macrophages increases and prolongs the toxic effects. Thus, activation of the caspase-3 pro-apoptotic response occurred up to 72 h, in addition to activation of proinflammatory responses of TNF- α and interleukin 1 β , prolonging life expectancy of the cells, phagocytic activity and/or nitric oxide (NO) production up to 24–72 h respectively (Sueiro-Benavides et al., 2021). The increase in caspase-dependent apoptosis occurs at very low doses of BC, suggesting an RF-dependent mechanism that modulates the viability and efficiency of cell death (Wojcik-Piotrowicz et al., 2017) and that can act through pathways dependent on Ca-calmodulin (Pall, 2013). In addition, amplification of the pro-inflammatory macrophage response at high levels of NO (although low viability) and the feedback with TNF-alpha and interleukin 1 β (Brown et al., 2002; Vince et al., 2018) regulates the process of apoptosis (Sueiro-Benavides et al., 2021; Wallach et al., 1999; Lu and Xu, 2006). These modifications of macrophage functions can be attributed to the action of RF on the cellular membrane, exerting voltage-dependent biophysical modulation (Panagopoulos et al., 2021; Georgiou and Margaritis, 2021; Pilla, 2012; Ross et al., 2016) in the calcium channels of this immune cell in a cell machinery already altered by the effect of BC (Sakamoto et al., 2007), after this environmental stressor has been affected by RF (Michel et al., 1993; Sihvola, 2002).

Radiofrequency modulates oxidative stress caused by BC in the HL-60 cell line, with antiproliferative effects and prolonged levels of cytotoxicity (Benavides et al., 2023). In this experimental model of immunotoxicity, cell death (necrosis and/or apoptosis) occurs due to the separate or combined exposure to both toxins; however, there is a maximal early effect of exposure to radiation, as the maximum activity of caspase-3/7 is reached at 8 h due to the exclusive effect of radiation (early apoptosis), indicating imminent mitochondrial damage (Chuang et al., 2017). Redox stress with ROS production was detected as early as 24 h after exposure and was maintained for at least 48 h, so that gene expression was also activated in the mitochondrial membrane of BCL2a HL-60 promyelocytic cells with antioxidant-antiapoptotic action after 24 h of irradiation and/or exposure to BC (Lohmann et al., 2005). Activation of the caspase-3 gene expression after irradiation for 48 h finally ensured participation of the mitochondrial machinery through the intracellular intrinsic pathway. Although the extrinsic pathway of apoptosis was explored from 48 h after radiation exposure and the BC cell death receptor gene FAS-R was shown to be significantly elevated, it was not accompanied by significant levels of caspase 8 (Fritsch et al., 2019), but was accompanied by the coexistence of necrosis and possible activation of the necrosome (by inactivation of caspase 8) that would trigger necroptosis. The findings of this in vitro experimental study may indicate modification of the immune response due to the interaction between both environmental agents, since the high levels of oxidative stress and mitochondrial dysfunction that were generated persisted for 48 h (Benavides et al., 2023).

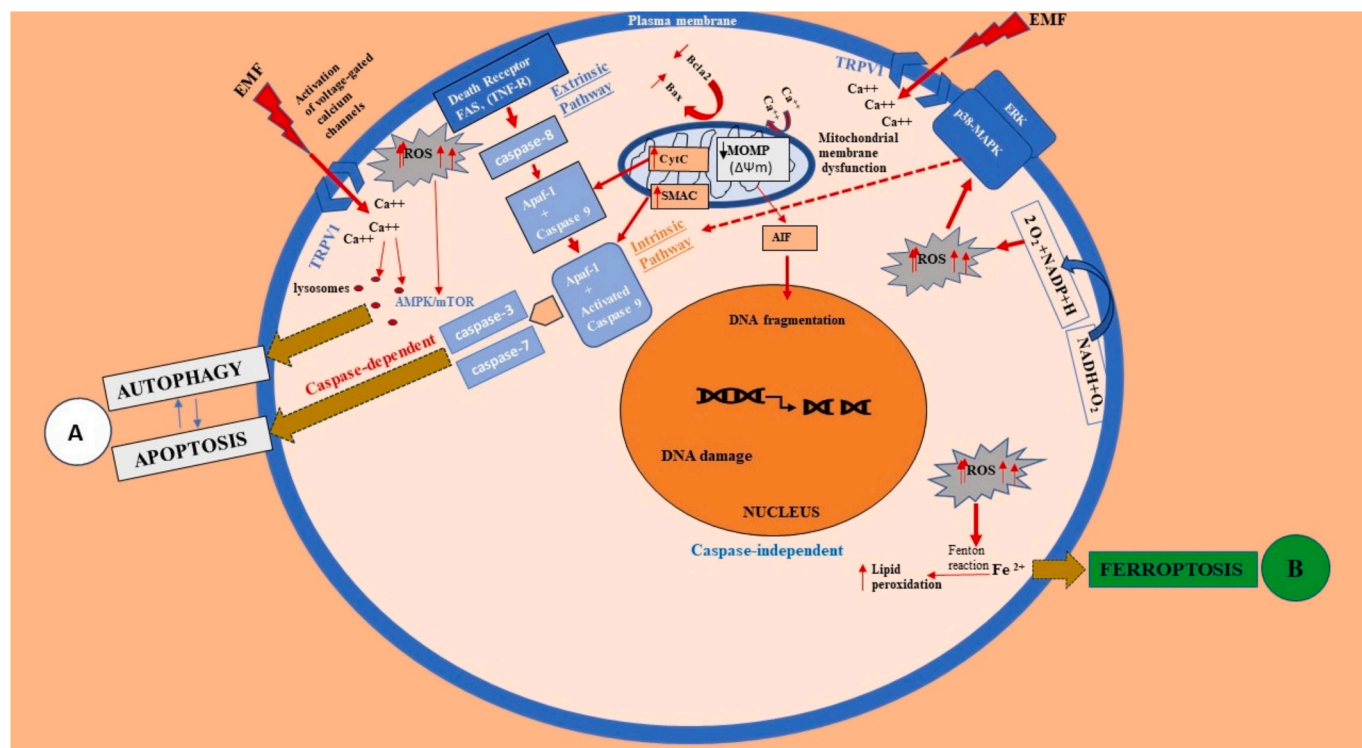


Fig. 2. Cell death pathways induced by microwave irradiation. (A) The stress caused by EMF activates the caspase-dependent and caspase-independent pathways. In the caspase-dependent pathway (extrinsic pathway), increased caspase 8 triggers and increases caspase-9 activation of apoptosome with increased caspase-3. EMF-triggered activation of membrane-dependent voltage channels (TRPV1) with increased calcium deposits and activation of the cell membrane NADPH system provoke intracellular activation of the ROS-p38-MAPK pathway promoting apoptosis. Mitochondrial dysfunction with increased Bax and decreased Bcl2 in the outer mitochondrial membrane increases oxidative stress and also favours apoptosis. The increase in AIF due to mitochondrial dysfunction activates DNA fragmentation and caspase-independent apoptosis. (B) RF-EMF may alter intracellular calcium homeostasis by decreasing calcium channels that activate the autophagy pathway while inhibiting apoptotic regulation as a process of adaptation for RF-EMF exposure.

In short, preclinical studies of immunotoxicity induced by the combined exposure of BC and non-ionizing radiation allow exploration of the potential redox damage in the immediate immune response. Both environmental toxins may cause oxidative damage in the cell membrane and at the subcellular level (in the mitochondrion), activating inflammatory factors (TNF alpha and Interleukin-1 beta) and modifying microbial functions (phagocytosis) and modifies activation of the different cell death pathways through caspase-dependent apoptosis or necrosis (see Fig. 3) (Sueiro-Benavides et al., 2021; Benavides et al., 2023).

In our opinion, the high levels of cell death, apoptosis, necrosis and necroptosis and the dysfunctional immune response of macrophages or reticulocytes in the models of combined immunotoxicity caused by exposure to the environmental agents BC and EMF may indicate a relevant role in the mechanisms of oxidative damage in chronic diseases.

5. Discussion and conclusions

Redox-sensitive signalling pathways associated with cell death have been established as pathophysiological mechanisms in several chronic non-communicable diseases, such as neurodegenerative, cardiopulmonary and metabolic diseases (Mudway et al., 2020; Kelly and Fussell, 2015). In this review paper, we attempt to provide an overview of the mechanisms involved in triggered cell death regulated by ambient air particulate matter (BC) and/or non-ionizing radiation, summarising the models, cell type, cell line and evaluating these mechanisms (see Tables 1, 2). The common link between all of these studies is the relationship between oxidative damage and different types of cell death.

However, in addressing this challenge, we believe that there are numerous knowledge gaps and that experimental validation of existing findings (by conducting toxicological studies) is required, as already

suggested by other researchers in the field (Henschenmacher et al., 2022; Pall, 2022; Panagopoulos et al., 2021; Gautam et al., 2022; Santini et al., 2018).

One of the greatest problems in understanding the toxicity of BC and/or EMF is establishing the intensity, duration and type of exposure to each different source (Nagappan et al., 2021; Niranjana and Thakur, 2017; Jin et al., 2016; Zheng et al., 2017; Lai et al., 2023). This has led to the use of numerous different methods and models in environmental toxicity modelling, and it is therefore very difficult to reach firm conclusions from the findings (see Tables 1, 2). The cellular responses will be determined by the different conditions within cells, tissues or whole organisms, and these effects will also be affected by the choice of animal model or cell line used. The characteristics of the model used must also be taken into account when investigating cell death pathways (Peixoto et al., 2017).

The toxic effects of BC particles, which undergo a bioactivation process, depends on the ability of cells to metabolise the particles (Jiang et al., 2018). This applies to metallic components that exert important cellular effects due to their interaction with environmental BC particles (Guo et al., 2009; Jiang et al., 2020) or to combined exposure with EMF (Sueiro-Benavides et al., 2021; Zmyslony et al., 2000). The oxidative stress effect caused by the RF-EMF effect appears to be more controversial (Henschenmacher et al., 2022; Lee et al., 2012). Differences in findings may be due to the great diversity of in vivo and in vitro models used to validate this redox action accompanied by cell death in numerous experimental studies, as described in this review.

Interpretation of the combined effect of both toxicants at the cellular level or by the interaction of both stress agents in the human body is even more complicated (Sueiro-Benavides et al., 2021; Benavides et al., 2023). Kostoff explains the potential health effects caused by the

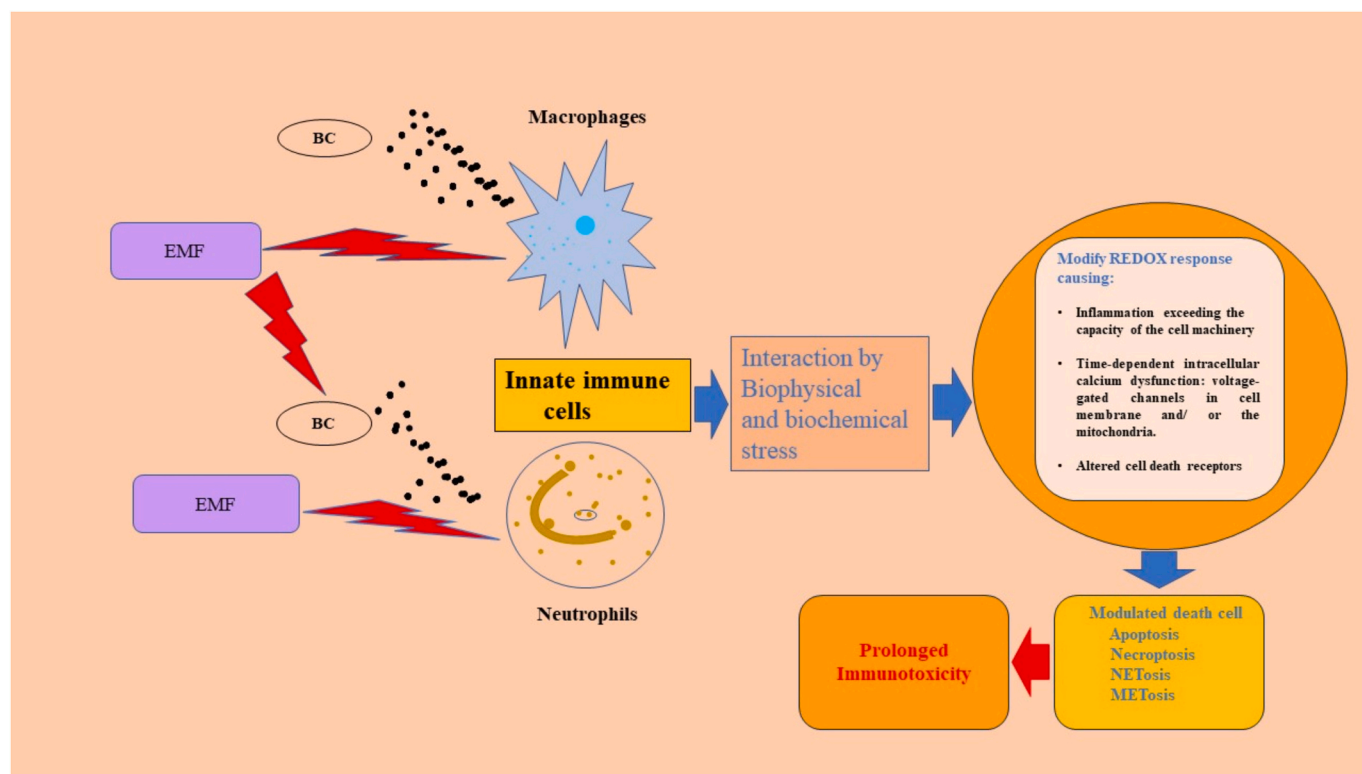


Fig. 3. Cell death due to interaction between BC and EMF stress agents. The immune cell response increases the REDOX response by biophysical and biochemical stress causing inflammation and time-dependent intracellular calcium dysfunction, and it also alters the cell death receptors, which act by modulating cell death and prolonging the immunotoxic effects.

combined action of biological systems and electromagnetic fields. EMFs can initiate health effects and can also act as co-promoters or potentiators of biochemical agents (Kostoff and Lau, 2013). Thus, the multi-stress combination may cause an increase in adverse effects, as in the experimental model in which cellular DNA damage in rat lymphocytes is reported to result from the combination of magnetic fields and iron (Zmysłony et al., 2000). On the other hand, in recent applications of combined nanoparticles and microwaves for therapeutic purposes, the heating effects and the release of copper ions from Cu-Cy upon MW stimulation are the main mechanisms for generating ROS that are “lethal bullets” causing destruction of cancer cells. Cu-Cy nanoparticles have a safe and promising clinical application prospect in MWD for deep-seated tumours and effectively inhibit tumor cell proliferation by inducing ferroptosis, which provides a potential solution for cancer resistance (Zhou et al., 2022). In this review we have taken into account the non-thermal effects (SAR <4 W/Kg) on the human body of the combined exposure of BC and electromagnetic fields, addressing relevant biophysical and biochemical aspects of this interaction and its possible implications for cell damage. However, the findings obtained in a human monocyte cell line model of combined RF and UFP exposure indicate oxidative stress, but not a stress-related response (Simko et al., 2006). Oxidative damage may also occur when RF acts as a co-promoter with chemical stressors (Kostoff and Lau, 2013), as the patterns of immunotoxicity caused by the combined effects of RF and BC on the redox activity trigger different types of oxidative cell death (apoptosis, necrosis and necroptosis) (Sueiro-Benavides et al., 2021; Benavides et al., 2023).

As indicated by immunotoxicity models, the chemical-physical interaction between BC and EMF may occur at the cellular level as a result of modification of the dielectric constant of the environmental particles. The interaction may therefore vary according to the frequency applied (Michel et al., 1993; Sihvola, 2002) and to modulation parameters and may alter the bioelectric properties of the cell membrane (Lin

et al., 2023). The toxic microenvironment that generates this multi-stressor combination provokes cell death in these in vitro models, and further testing is therefore needed to understand the mechanisms of cell damage in greater depth, as these may have different effects at the cellular level from those of each of the individual toxicants (Kostoff and Lau, 2013). In vivo models offer the advantage that they allow assessment of the interaction between different cell types and the immune system. However, although both in vivo and in vitro models are widely accepted as basic tools for experimental research, they have limitations that restrict extrapolation of the findings to human exposure (Peixoto et al., 2017). Further work is needed to improve understanding of cell death in cells and organisms exposed to BC and/or EMF. In the future, a combination of different approaches, with more detailed identification of the different chemicals and study of bioelectrical phenomena by EMF interaction, may help to clarify the mechanisms that induce cell death by both environmental agents (Kostoff and Lau, 2013).

On the other hand, the combined action of both environmental stress agents leads to dysfunction of the immune response in the RAW-264.7 macrophage cell line, prolonging the inflammatory response and favouring toxicity. In addition, it also alters the function of reticulocytes in the HL-60 line with impaired antimicrobial action, creating a microenvironment associated with inflammatory processes. These immune dysfunctions may be associated with an increase in rates of chronic non communicable and autoimmune diseases (Sueiro-Benavides et al., 2021; Benavides et al., 2023).

However, the aforementioned studies of the combined effects of non-ionizing radiation and BC used preclinical experimental models, and any clinical effects must be confirmed in humans.

Based on the analysis and information obtained with two toxic agents (BC and/or EMFs) in different in vivo experimental preclinical models, in vitro cell lines and combined experimental immunotoxicity studies, in which the RAW 264.7 macrophage cell line and the human promyelocytic cell line HL-60 displayed high sensitivity to both agents

with the subsequent oxidative stress, it can be concluded that the combined action of RF-EMF and BC can cause oxidative cell damage in the following ways:

- 1) Redox activity can act at the cell membrane level, or at the subcellular level in the cytoplasm, at the mitochondrial level or in nuclear DNA. Activation of cell death pathways by RF or BC occurs when antioxidant mechanisms caused by oxidative stress or other mechanisms, such as inflammation, exceed the capacity of the cell machinery to restore homeostasis.
- 2) Intracellular calcium dysfunction may play a very important role in activating cell death signalling pathways caused by both BC and RF. However, the biophysical action of radiation seems able to alter extracellular voltage-gated channels at the level of the cell membrane and also at the mitochondrial level. The increase in intracellular calcium deposits generated is an important metabolic factor that causes dysfunction of redox signalling and activates cell death. This effect seems to be time-dependent and modify the activity when both environmental agents act together.
- 3) Immunotoxicity studies have shown that the mutual interaction of both agents in the cell membrane alters the morphology of cell death receptors and causes changes in immune responses, having a significant impact on the immune defence mechanisms and defence systems in the human body.
- 4) Modulated programmed cell death or apoptosis or other pathways such as necrosis and/or programmed necrosis, or necroptosis, autophagy, ferroptosis or cuproptosis can also prolong the toxic action by modify the activity between both environmental stress agents.
- 5) The use of preclinical models to study the redox response caused by the effects of one or both environmental agents (BC and RF) and the effects of the activation of cell death pathways could identify potential environmental risks to human health. The indications of cell damage due to the combination of both environmental agents should encourage researchers to search for new experimental models that allow validation and detection of environmental toxins at pre-clinical levels. The vulnerability of some human cell populations (immune cells, reproductive germ cells and nervous system cells), the prevalence of certain diseases (autoimmune, infertility, neurodegenerative) and the impact according to gender and age should be taken into account in the development of these models.
- 6) After conducting this bibliographic review of the models that explore the pathways of cell death caused by environmental oxidative stress agents BC and EMF, we conclude that some obvious and important challenges must be overcome regarding evaluation of the mechanisms involved in the cytotoxicity of complex combinations of environmental stress agents as well as in the application of approaches that can reflect real human exposure. Finally, the overall interpretation of these results depends on the findings of future toxicological studies in humans so that further actions worldwide should take pollution levels into account to prevent adverse effects on health, focusing on the most vulnerable populations and future generations.

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CRediT authorship contribution statement

Elena López-Martín: Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. **Rosana Sueiro-Benavides:** Supervision, Resources, Data curation, Conceptualization. **José M. Leiro-Vidal:** Validation, Supervision, Formal analysis,

Conceptualization. **Juan A. Rodríguez-González:** Validation, Supervision, Software, Funding acquisition. **Francisco J. Ares-Pena:** Writing – review & editing, Validation, Supervision, Software, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Elena Lopez-Martin reports financial support was provided by FEDER Ministerio de Ciencia, Innovación Universidades-Agencia Estatal de Investigación. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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