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TOPICAL REVIEW

Can Electromagnetic Fields Modulate Inflammation and Cell Death by Acting on the Immune System?

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ABSTRACT Programmed cell death constitutes a fundamental part of the immune response to viral infection. This process forms part of the host defence mechanism and also enables establishment of biomarkers of disease severity. Natural or anthropogenic sources of microwaves emit energy and may alter the ecology of the SAR-CoV-2 virus (which causes COVID-19 disease) in the environment. Determining the associated effects on the immune system and on the health of hosts with COVID-19 disease is thus important. In this review paper, we consider studies analyzing the influence of electromagnetic fields on innate and acquired immune responses in humans, and above all on preclinical experimental animal models and in vitro models, and we also consider studies analyzing immunity acquired from COVID-19 infections associated with cell death. We focus on the effects of electromagnetic fields and the influence of oxidative stress on stimulation or immunomodulation, the inflammatory response, autoimmunity and the participation of intracellular calcium channels in the immunology of COVID-19 disease. Non-ionizing radiation can activate or reduce the inflammatory response, oxidative stress and the entry of intracellular calcium and can facilitate or reduce cell death. The review of experimental study findings indicates that exposure to non-ionizing radiation can also have a bidirectional effect on the immune system, either slowing down or enhancing the processes that lead to the cell death associated with COVID-19 disease.

INDEX TERMS Cell death, COVID-19, immune cells, electromagnetic fields, non-ionizing radiation.

I. INTRODUCTION

Biological and/or medical studies that provide possible evidence and well-founded arguments suggest a potential relationship between the severity of COVID-19 disease and radiofrequency radiation, including that used in 5G networks [1]. Thus, the wireless communication radiation (WCR) used in 5G is considered a source of environmental oxidative stress, and the bioeffects of ionizing radiation and the pathophysiology and evolution of COVID-19 disease have been implicated in health impacts. WCR may increase the adverse effects of patients infected by SARs-CoV-2 and exacerbate the severity of COVID-19 disease [1]. Epidemiological studies have indicated that the coexistence of COVID-19 disease and environmental pollution, such as particulate matter (PM), increased the severity of the disease [2], [3]; these studies have enabled establishment of a model of transmission [4]. In vitro models have indicated a

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greater toxic effect when non-ionizing radiation and ambient air pollution act together on immune cells exposed to 2.45 GHz, 12W EMF RF for 8, 24, 48 or 72 h [5], [6]. However, it is not yet possible to establish a direct causal relationship between the severity of COVID-19 disease and exposure to electromagnetic fields, as epidemiological studies are lacking. Nonetheless, some important similarities can be established between the etiopathogenic mechanisms of COVID-19 disease during its progression and the effects of electromagnetic fields [1]. Thus, infection with the virus and EMF exposure both produce oxidative stress via mitochondrial dysfunction and tissue damage [7], [8]. Immune cells become dysfunctional in COVID-19 disease and exposure to electromagnetic fields alters the response of immune cells [1].

On the other hand, various preclinical experimental models at cellular or animal levels have indicated that non-ionizing radiation may inhibit the oxidative stress [9] and inflammation caused by COVID-19 infection [10]. Within the electromagnetic spectrum, electromagnetic fields (EMFs), static magnetic fields and radiofrequency radiation are grouped together as non-ionizing radiation. These types of radiation can interact with biological systems in vivo or in vitro [11] and can trigger programmed cell death through various mechanisms [9]. A study using experimentally induced, extremely low frequency electromagnetic fields (ELF-EMFs), with exposure of MC4-L2 breast cancer cell lines for 2 h/day to 100 Hz 1 mT ELF-EMF for five days or in vivo assessment of inbred BALB/c mice bearing established MC-4L2 tumours exposed to 100 mT, 1 Hz ELF-EMF 2 h daily for a period of 28-day, showed that the increased damage due to overproduction of reactive oxygen species (ROS) or to an imbalance in Ca^{2+} homeostasis will finally increase apoptosis or cellular necroptosis [12]. The activating or inhibitory effects of environmental sources of EMFs on the immune system depend on the electromagnetic parameters used and the type of cell exposed to non-ionizing radiation [13]. There is some evidence that EMFs can suppress or activate the immune response and can increase autoimmunity and thus modulate (activate or inhibit) apoptosis [1]. Thus, on the one hand, pulsed electromagnetic fields (PEMFs) have been shown to inhibit the pro-inflammatory stimulus of IL-11β by stimulating cytoprotection and decreasing apoptosis [14].

Apoptosis is essential for the normal development and homeostasis of mammalian tissues [15], but it can also contribute to different types of pathological cell loss in neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease [16], as well as in heart failure [17] and in the abnormal cell growth that occurs in tumours [18]. Viral infections can trigger apoptosis, with both positive and negative effects on the spread and multiplication of the virus in the host. In turn, the host eliminates virus-infected cells through apoptosis, thereby blocking viral infection [19].

Disturbed immune responses in COVID-19 disease are indicated by T-cell exhaustion, dysfunctional monocytes, macrophages, B cells and natural killer cells [20] and excessive neutrophil production [21]. Clearly, both COVID-19 disease and exposure to non-ionizing radiation can lead to biological damage caused by oxidative stress and can thus trigger cell death [8]. In addition, the immune vulnerability of COVID-19 patients can be affected by other external environmental agents, such as continued exposure to EMFs, to which immune cells are sensitive [13]. Therefore, our hypothesis raises the possibility of modification of the host immune response due to COVID-19 infection and the simultaneous and continuous interaction with non-ionizing radiation sources.

It is possible that non-ionizing radiation could act in some way by modulating the pathogenesis of serious viral infections, such as altering the immunological response, preventing activation of the inflammasome and modifying the transit of calcium channels that lead to the different types of cell death caused by COVID-19 disease. Our motivation for carrying out this review study was to compare the possible mechanisms and pathways that have been suggested to lead to

TABLE 1. Description and definition of the type of electromagnetic fields (EMFs) used in this bibliographic review.

Terminology	Definition	Units
Radiofrequency (RF) [5,6,27,69,70,72,74,80,81, 82,98,99,109,133]	Oscillation of electric current and/or magnetic fields. Radiofrequency fields are produced by alternating electric current.	Hertz (Hz)
T Magnetic Fields (MFs)	Vector field that appears as the result of magnetic material or electric current	Tesla (T) & Hertz (Hz)
Static Magnetic Fields (SMFs)	A magnetic field that is represented by a constant or unchanged vector	Tesla (T)
Extremely Low Frequency Magnetic Fields (ELF-MFs) [12,28,40,53,54,55,56,57,5 8,73,74,76,91,93,94,95,96, 97,105,106,107,108,113, 116,117,134,135, 136]	Magnetic fields ranging from 1 to 300Hz	Tesla (T) & Hertz (Hz)
Pulsed electromagnetic field (PEMF) therapy. [26,42,68,73,97,106,107,1 08,114, 115]	Therapy that attempts to heal non-union fractures and depression based on electromagnetic fields	Tesla (T)
Wireless communications, including fifth generation (5G)	Transmission of data without wires	Tesla (T)

the response of immune cells induced by COVID-19 infection in the host and/or the effect of non-ionizing radiation in the different types of cell death. This information will enable a critical, necessary analysis of the direct or indirect effects of non-ionizing radiation on the response of immune cells (e.g. on autoimmune responses or calcium channels) associated with cell death due to COVID-19 infection. In this review, we simultaneously studied the response of immune cells (in in vitro or in vivo experimental studies in animals and humans) due to the interactions with non-ionizing radiation and/or COVID-19 infection. The objective was to outline a possible hypothesis enabling detailed study of the interaction or the role that environmental stress factors such as radiation (electromagnetic fields) may have in relation to cell death due to COVID-19 infection.

II. GENERAL EVALUATION OF THE INFLUENCE OF ELECTROMAGNETIC FIELDS ON CELL DEATH CAUSED BY COVID-19 INFECTION

The Nomenclature Committee on Cell Death (NCCD) has distinguished more than twenty types of cell death. However, in this review we focus on the types of cell death that are most important in relation to COVID-19 infection: apoptosis, necroptosis, pyroptosis and NETosis. Viruses can use a great multiplicity of mechanisms to regulate cell death, but these processes can become double-edged swords during viral infection [22], [23]. Thus, virus replication and propagation are prevented by elimination of infected cells through cell death. However, viral infection can alter the regulation of cell death and cause uncontrolled cell damage and a disordered immune response. One possible strategy to prevent the cell death caused by COVID-19 infection is to induce the immune system to modify the levels of inflammation. Thus, diffusion and multiplication of the virus are prevented by cell death and elimination of infected cells. Although EMFs were previously considered to cause only adverse health effects in humans, it is now known that the electromagnetic parameters used in relation to the frequency, intensity and amplitude of the field (table 1) determine whether the effects will be harmful, therapeutic or benign (table 1) [24].

Exposure to EMFs could modulate inflammatory responses by targeting signal transduction pathways and/or molecules involved in danger signalling in different cell types [25]. The use of therapeutic techniques involving exposure to the physical effects of EMFs could, in the long term, potentially cause immunosuppression or activation of immune cells and their effector activity. Environmental EMFs can exert stimulatory and inhibitory effects on immune system functioning depending on the electromagnetic parameters and frequency range, as well as the characteristics of the exposed cells [13]. Thus, some experimental findings have shown that increased white blood cell counts can be induced by exposure to 50 Hz radiation sources of field strength 100 kV in groups of male BALB/c mice in which the whole body was exposed or were sham exposed (control) to PEMF at 100, 1000, and 10000 pulses [26] or 0.18 GHz radiofrequency radiation of field strength 330 mW for 13.2 min/day, 4.10 min/day and 1.40 min/day [27]. By contrast, other studies showed the opposite effect in seven women and eight men, exposed to low frequency EMFs (50 Hz, 35 kV/m) for 20 hours a week; in these studies, conducted in 1999 and 2005, the mean EMF exposure in the workplace was 1.7 μT and 1.1 μT, respectively [28]. In a randomized crossover trial, comparing intervention (0.5–1.0 μT above ambient levels) and ambient magnetic field levels, during two 5-night measurement periods, night-time exposure to EMFs has been shown to have more severe effects on sleep outcomes in young women sleeping at home than daytime exposure to a 60 Hz magnetic field [29]. Thus, regarding the supposed inhibitory effects that long-term exposure to EMFs has on human peripheral blood neutrophils and mononuclear cells, 31 volunteers were analyzed before and 2 months after using a bed with the patented HOGO system, which insulated participants against EMFs. It was demonstrated that two months of bed rest isolated from EMFs (low and high frequency) improves immune function, decreases the levels of substances involved in oxidation and the molecules that promote inflammation and reduces the harmful effects caused by oxidation of lipids and DNA [30].

The potential use of ELF-EMFs and PEMFs to modulate immunity represents a new research frontier with clinical implications of interest. Harmful agents that cause insult to the body activate the immune system and downregulate the future response of immune cells. PEMFs and ELF-MFs show some potential for modulating danger signals leading to reduced inflammation. Although the mechanisms involved are not yet well defined, it seems that ELF-MFs induce ROS production, whereas PEMFs appear to control inflammation through upregulation of adenosine receptor (AR) pathways. These pathways are involved in all inflammatory conditions and could therefore represent important therapeutic targets in various (chronic) inflammatory diseases [25].

In our opinion, EMFs have been demonstrated to have some effect in modulating immune function. EMF-mediated modulation of immune cell activity could possibly counteract the aberrant pro-inflammatory responses in COVID-19 disease, thereby modifying the severity and possibly the onset of such responses. The main contribution of this review work is to consider the direct or indirect action of non-ionizing radiation on host immune cells in both stimulatory or inhibitory (bidirectional) directions. Thus, the effect of EMFs (in relation to electromagnetic parameters) may lead to a synergistic action that would either favour the immune response to COVID-19 infection or block the activity of inflammatory pathways. The review of experimental models of immune response in vivo/in vitro or in humans due to COVID-19 disease or due to exposure to radiation that cause cell death will allow us to analyze and help us to understand the mechanisms that act additively, synergistically or antagonistically in order to establish preventive control measures or therapeutic measures.

Thus, in the following sections we will consider how EMFs influence autoimmunity and immune cells, under the assumption that EMFs may act via mechanisms involving immunomodulation and possibly modulate cell death, either reducing or exacerbating the response (see tables 2 and 3).

III. EMF-INDUCED REDOX STRESS MAY MODULATE APOPTOSIS AND/OR NECROPTOSIS

EMFs constitute external stimuli that provoke a wide range of biological effects in immune cells that depend on the frequency of exposure, the specific absorption rate (SAR), the location of the signal exposure, the distance from the antenna, the duration of exposure and the increase in temperature [31]. In vivo studies have shown that experimental exposure to low-frequency radiation (ELF-MF) of intensity 4 and/or 7 mT in single or repeated exposure for minutes to days act on the homeostasis of the oxidant- antioxidant and activate an oxidative change [32], [33]. The bidirectional effect of repeated exposure to ELF-EMFs has recently been described in a study assessing whether repeated exposure to 1 and 7 mT EMFs can modify oxidative/antioxidative status in response to other stress factors. Rats were exposed to EMFs for 1 h/day during 7 days, one, two or three times. The level of exposure to the EMFs was found to be very important and determines when the response occurs: changes in the oxidative/antioxidative response to EMFs occurred to a lesser degree for a magnetic field strength below 1 mT than for a field strength of 7 mT. These findings confirmed that an EMF of field strength 1 mT constitutes a threshold level for the activation of antioxidant signalling pathways attempting to reduce oxidative stress and thus result in cellular adaptation. However, the lack of cumulative effects with repeated exposure cannot be guaranteed. On exposure to an EMF of field strength 7mT, cellular adaptation is insufficient to prevent harmful effects [34].

In recent years there has been an increase in research reporting the beneficial effects of EMFs via triggering of antioxidant activity [35], [36]. Exposure to 40 Hz, 7 mT EMFs for 15 min/day for 4 weeks (5 days a week) was found to have therapeutic effects, due to a protective effect, in fifty-seven post-stroke patients with brain damage [37]. Thus, excess oxidative stress occurs in patients with hypersensitivity to EMFs, caused by impairment of their oxidative detoxification systems. Mice were exposed to 35 kV/m SEF (0 Hz) and PFEF (50 Hz), after exposure for 7, 14 and 21 days, respectively [38], [39]. Conversely, ELF-EMF exposure can modify antioxidant action and decrease intracellular defensive activity, thus promoting DNA damage. On the other hand, low levels of ROS are involved in the activation of genes triggered by intracellular signals that act on cellular functions such as cell proliferation and apoptosis [40]. In addition to causing an increase in ROS by activation of free radicals, EMFs can also induce changes in calcium signalling cascades [41].

In recent studies with the experimental U937 cell line, it has been shown that PEMF-induced stimulation alternating (AC) (6.5rms mT, 35 Hz) magnetic field combined with 6 mT static (DC) component, or PEMF (45 $\pm$ 5) mT, 50 Hz may act on cell viability and also induce apoptosis. EMFs modulate the efficiency of cell death by altering the expression of calmodulin (CaM) and CaM-dependent proteins [42]. In summary, various in vitro and in vivo experimental studies highlighted here for their scientific quality [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42] show that the effect of ELF-MF (modulated or unmodulated) at the immune cell level depends on the oxidative status. Non-ionizing radiation in the 35–50 Hz frequency range and intensity of 1 to 7mT modulates antioxidant enzymes, increasing intracellular calcium levels, favouring therapy after cerebral vascular accidents, by modulating apoptosis caused by cytotoxic agents.

Infected host cells activate apoptosis and thus decrease spread of the virus in tissues. However, the virus strategy is activated by stimulating mechanisms that attempt to reverse the host's apoptotic defensive pathways [43]. Cells undergoing apoptosis exhibit characteristic features such as chromatin condensation, DNA fragmentation, externalization of phosphatidylserine in the plasmatic membrane and the appearance of cell contents surrounded by a membrane (apoptotic bodies) [44]. Apoptosis is important as a mechanism of non-inflammatory programmed cell death and has been studied in relation to COVID-19 disease, caused by infection with the SARs-Cov-2 virus [45]. Programmed cell death during infection is activated through two pathways: the intrinsic or mitochondrion-dependent pathway, and the extrinsic pathway caused by binding of a death ligand. Thus, extrinsic apoptosis occurs when a death ligand (such as tumour necrosis factor) binds to the death receptor and activates caspase-8. Intrinsic apoptosis is activated by internal stress stimuli that act at the mitochondrial level, involving the antagonist proteins BCL-2 and/or the BAK protein, causing permeabilization of the mitochondrial outer membrane (MOMP) and activation of caspase-9, the initiator of intracellular apoptosis. Apoptosis has been detected by TdT-mediated d-UTP (TUNEL) staining in lung samples from human patients with SARS-CoV-2 infection and attributed to acceleration of the progression of acute respiratory distress syndrome (ARDS) [46].

Natural killer (NK) cells have the primary function of eliminating infected or modified cells after cytolysis. This function may be direct or occur via the secretion of immune mediating substances that act on the activation or migration of T cells, neutrophils and macrophages at lesion sites. Inadequate NK function will have an important effect on infection [25]. Severe SARS-CoV-2 infection is characterized by an altered immune response [47]. The severity of COVID-19 disease is related to apoptosis, cell activation and exhaustion, elevated expression of the Tim-3 protein of NK cells (associated with the binding receptors of the SARS-CoV-2 spike protein) and elevated secretion of cytokines [48].

Depending on the frequency and amplitude, application of EMFs was timed to coincide with certain known intracellular chemical oscillators (phase-matched conditions). Thus, polarized, but not spherical, neutrophils labelled with anti-K(v)1.3, FL-DHP and anti-TRP1, but not

anti-T-type Ca^{2+} channels of non-ionizing EMFs have been reported to decrease calcium-transport alterations in human lymphocytes [49] and support natural killer cells. Pulsed sinusoidal 50 Hz ELF (PEMF) of amplitudes between 10 and 55 mT also induce an anti-tumour immune response and improve the immune function of the host [50], [51]. PEMF treatment attenuated IL-1β levels up to 10-fold in CSF within 6h after contusive injury and also significantly suppressed IL-1β within 17–24h after penetrating injury, thus modulating cytokines and traumatic brain injury [52]. Exposure to radiofrequency EMFs in the 600 kHz to 729 Hz band, of 8 hours a day, 6 days a week, for four weeks caused a significant increase in the number of NK T lymphocytes that inhibit cancer cells, in all subjects a sample of 15 end-stage cancer patients, and the RF EMF exposure increased the number and cytotoxicity of NK cells [53].

The opposite effect has been described in another experimental animal model exposed to 60 Hz EMF of magnetic field strength 1 mT continuously for 13 weeks, which led to a decrease in or elimination of NK activity [54]. Future studies must investigate whether the production of NK cytokines is affected or their functions are affected by chronic exposure to ELF-EMFs. Human studies have focused primarily on NK cell counts after moderate exposure, with contrasting results. Thus, some authors observed that low, chronic exposure to a 50 Hz 0.2–6.6 μT EMFs led to decreased levels of immunological parameters (total lymphocytes and CD4 counts) in both humans and mice [28], [55], [56], while others observed an increase in the number of NK cells in the blood after ''safe'' ELF-EMF exposure [57]. Effects on NK activity were reported in a study [58] involving a group of 52 workers occupationally exposed to ELF-EMF. The NK function was evaluated in relation to the ability to lyse target cells in two groups of workers according to the intensity of ELF-EMF exposure, i.e. low magnetic field strength, less than 0.2 μT, and high field strength, greater than 0.2 μT. A subgroup of most exposed workers was selected for further study (12 subjects; TWA >1 μT). Workers exposed to high levels of ELF-EMF did not present any differences in the number of peripheral blood NK cells, but did show a reduction in lytic capacity relative to workers exposed to low levels. Further studies are required in order to determine whether chronic exposure to ELF-EMFs affects the cytokines released by NK cells, thus possibly modifying T-lymphocyte functions.

Experimental studies carried out in both animal models and human patients have shown that electromagnetic fields can exert a modulating effect on inflammation and on the activity of killer lymphocytes (NK), although there are some differences in the intensity and frequency of the source used in experimental studies [49], [50], [51], [52], [53], [54], [55], [56]. Nonetheless, researchers agree that effect of EMF exposure on the immune response will act as follows: 1) SPEMF or PMEF pulsed fields are the most likely to modulate the immune system to which lymphocytes and/or killer lymphocytes would be sensitive, acting at the membrane level in calcium channels. 2) 50 Hz ELF in the range of 1–55 mT can produce therapeutic effects with anti-tumour and anti-inflammatory activity. 3) Chronic exposure to PEMF or 60 Hz EMFs from 0.002 to 6.6 μT or >1 μT causes a decrease in NK count and a decrease in immunological parameters. 4) RF exposure in the range of 600 kHz–729 Hz for six days a week/4 weeks increases the cytotoxic activity of NK.

Autophagy and apoptosis are activated in peripheral blood mononuclear cells (PBMC) isolated from COVID-19 patients [59], indicating that dampening of the immune system by SARS-CoV-2 infection could affect disease outcome. Studies in an in vitro model showed that monocytes and B and T lymphocytes were susceptible to infection by SARS-CoV-2 as the double-stranded RNA of the virus accumulates as the virus replicates and apoptosis of T cells occurs. However, it is not known whether the lymphocytopenia is due to direct infection or recruitment of lymphocytes [60]. DNA damage and Fas overexpression has been observed on T cell surfaces, resulting in PBMC apoptosis in COVID-19 patients [61], [62]. In patients suffering from severe clinical cases of COVID-19 disease, an increase in apoptosis has been observed in mononuclear cells [63]. Apoptosis was observed in post-mortem samples obtained from the lungs of patients with COVID-19 disease and also in lung tissue from a primate model of SARs-CoV-2 infection, including alveolar 1 and 2 cells, vascular endothelial cells, macrophages and T cells. The intrinsic and extrinsic apoptotic pathways are activated as a result of SARS-CoV-2 infection [64]. Monocyte/macrophage expression and function are disturbed in COVD-19 patients, mainly in lung tissues [65], [66]. This process may partly involve the spike protein of the SARS-CoV-2 coronavirus, which induces oxidative stress, inflammatory response and apoptosis in macrophages. The SARS-CoV-2 coronavirus induces oxidative stress, an inflammatory response and apoptosis [67].

Electromagnetic fields have been shown to act through the anti-inflammatory pathway and lipid metabolism in susceptible immune cells. Thus, exposure to EMFs for one hour raises reactive oxygen species in THP1 human leukaemia cells previously been stimulated with liposaccharide (LPS). Using weak EMF exposure prevented the NAD(P) reducing enzyme system from being depleted in human leukaemia and peripheral blood mononuclear cells. The effect of EMF exposure on lipid metabolism was evident in the 2- to 6-fold increase in antioxidant enzymes (PRDX6 and DHCR24).

Innate immune cells react to EMFs by generating ROS, which are crucial intracellular messengers. In an experimental EMF application, exposure of human leukemic THP1 cells and peripheral blood mononuclear cells (PBMCs) to a pulsed EMF of either $<$ 50 μT (weak EMF; wk EMF), $<$250 μT (moderate EMF; md EMF) or $<$ 4.8 mT (strong EMF; stEMF) with a fundamental frequency of 16.7 Hz emitted in send/pause intervals of 10 min for up to 24 h with sampling after 1 h, 3 h, 6 h and 24 showed altered susceptibility of immune cells provokes severe cellular

stress and enhanced rates of apoptosis, as indicated by HSP70 and caspase-3 [68]. In vitro studies have shown that ROS and apoptosis are induced in human PBMCs by 900 MHz mobile phone radiation. The exposure was carried out at an average specific absorption rate of 1.35 W/kg in a dual wire patch cell exposure system in which the temperature of cell cultures was strictly controlled. After exposure for one hour to the radiofrequency field, a slight but statistically significant increase in caspase-3 activity was observed 6 h after exposure.

Increased ROS production induces apoptosis through the mitochondrial pathway mediated by activation of caspase-3 [69], thereby decreasing the mitochondrial potential. Cell death occurs in 37% of PBMCs after 8 hours of exposure to EMFs at a specific absorption rate (SAR) of ∼0.4 W/kg when the exposure lasts longer than two hours, due to an imbalance between ROS and antioxidant defence function [70]. As a result, the metabolic activity of human monocytes was accelerated after exposure to an additional estimated 900 MHz simulated signal from the global system for mobile communication (GSM), 27 V/m, SAR 0.024 W/kg in a specifically designed anechoic chamber containing a microplate with cultured cells placed inside an ASSAB incubator [71]. On the other hand, protein expression (measured by Western blot assay) after intermittent exposure of human B-cell lymphoblastoid cells to 1.8 GHz GSM radiofrequency radiation (RFR) with a SAR of 2 W/kg for 24 h led to significant inhibition of expression of the RPA32 protein and an increase in the expression of p73 after exposure to RFR. The crucial roles of these proteins in DNA repair and cell apoptosis may guide the biological mechanisms that radiofrequency radiation exerts on programmed cell death and on DNA lesion-recovery [72]. The effects of exposure to EMFs (7 Hz, 30 mT) and to 50 Hz, 45±5 mT PEMF for 4 hours for three times in 24 hours intervals on in vitro stimulated PBMCs isolated from acute lymphoblastic leukaemia in children have been reported [73].

By analyzing the expression of apoptosis genes such as Bcl-2 and apoptosis-inducing factor (AIF), EMF-induced cell death was confirmed in proliferating native cells. The response of healthy lymphocytes obtained from people reporting hypersensitivity to 50 Hz and 915 MHz (RF) (specific absorption rate (SAR) 37 mW/kg and 15 mT peak value) was verified. Significant changes in cellular chromatin condensation were demonstrated to be caused by both types of EMF [74]. Chromosomal analysis of peripheral blood lymphocytes from workers exposed to 50 Hz EMF revealed a significant increase in chromosomal aberrations and sister chromatid exchanges [75]. Cellular damage caused in human lymphocytes by gallodinium (Gd) was compared relative to exposure to 0.2–1.2 mM of Gd only or in combination with a 60 Hz ELF-EMF of 0.8 mT field strength. ELF-EMF Gd causes cell damage and apoptosis; however, ELF-EMF decreases the cellular and genetic toxicity of Gd [76]. It is difficult to compare the results obtained for immune response, oxidative stress and activation of apoptosis due to the different electromagnetic parameters used in the experimental studies [68], [69], [70], [71], [72], [73], [74], [75], [76]. We have therefore tried to focus on rigorous experimental studies, which produced the following data. An increase in ROS generates oxidative stress, activation of apoptosis or conformation of chromatin in monocytes after sustained exposure to non-ionizing radiation both from the GSM network (RF 900, 915, 1800 MHz to SAR 0.024-2 W/kg) and power frequency magnetic fields (frequency 50 or 60 Hz, intensity 0.8-45 mT).

Patients with comorbidities such as cardiovascular disease, hypertension and diabetes have high levels of oxidative stress activated by increases in the NADPH oxidase pathway. This also increases O_2 and OH production by increasing neutrophils/lymphocytes. Activation of these processes throughout the body increases oxidative stress [77]. Alterations in endothelial cells and tissue damage caused by ROS occur in polymorphonuclear cells at the site of inflammation [78]. Some authors have also described lymphocyte-mediated modulation of the immune system after artificial exposure to other hyperfrequencies used in telecommunications. Sixty-four female Sprague–Dawley rats exposed individually to 2450 MHz EMFs of different field strengths (0, 1.5, 3 and 12 W) during 90 minutes or 24 hours, and analysis of cellular stress levels was conducted by examining expression of heat shock proteins 70 and 90 and or glucocorticoids receptors in the thymus. The data obtained indicated that high-frequency electromagnetic radiation acts by modifying endothelial vascular permeability, the number of vessels, and also by modifying the tissue levels of heat shock protein 90 and glucocorticoid receptors [79]. Another study demonstrated that chromatid aberrations (gaps and breaks) in lymphocytes exposed to 3G mobile phone RF signals were up to 275% higher than in controls [80]. By contrast, other studies indicated that pre-exposure to the UMTS signal decreases the harmful effects caused by toxic agents that act on the genome exposed to 1950 MHz, and continuous wave (CW), wideband direct-sequence code division multiple access (WCDMA, 4.5 MHz bandwidth), and additive white Gaussian noise (AWGN, 9 MHz bandwidth) signals 20 hours exposure were considered. For each signal, specific absorption rates (SARs) of 0.15, 0.3, 0.6, 1.25 W/kg were tested [81], [82].

This is of great interest in the context of synergistic effects evoked by various agents. In summary, exposure to 2.45 Hz EMFs or 3G UMTS causes vascular vulnerability with increased endothelial permeability, vascularization, cellular stress (increase in HSP-90), glucocorticoid receptors and genotoxic action on lymphocytes due to chromatid aberrations. The influence of WCDMA modulation of the signals (pulsed fields), 4.5 MHz bandwidth at 0.3 W/kg SAR or AWGN, 9 MHz bandwidth at 0.15 and 0.3 W/kg has therapeutic, protective clinical effects. In addition, pre-exposure of human lymphocytes to 1950 MHz UMTS radiation leads to repair of DNA damaged by cytotoxic agents,

with a reduction in the number of micronuclei. All of these experimental findings indicate a bidirectional effect (positive and/or negative) of EMFs, and their potential therapeutic use, as knowledge of the biological effects of non-ionizing radiation may have some favourable effects on human health. For example, appropriate exposure to EMFs can decrease activation of apoptosis and repair DNA damage in immune cells.

Necroptosis is associated with events such as organelle inflammation and the release of intracellular contents by rupture of the plasma membrane. Necroptosis is a non-caspase-dependent form of cell death regulated by a mixed lineage kinase-like pseudokinase (MLKL). Caspase 8 is inactivated in necroptosis and causes autophosphorylation of RIPK1-RIPK3 and, in turn, phosphorylation of the MLKL protein. MLKL is activated by the action of protein kinase 3, which also acts with RIPK3 [83]. High serum concentrations of RIPK3 that cause necroptosis have been found in COVID-19 patients with ARDS [84]. Necroptosis constitutes a type of cell death that can secrete inflammatory cytokines and trigger an inflammatory response and could thus act in the etiopathogenesis of severe COVID-19 [85]. In an experimental study in which a murine model of shock was caused by TNF-α and IFN-γ, an increase in the activity of innate immunity (macrophages and neutrophils) as well as a decrease in lymphocyte cells (B and T) was observed relative to the controls. The large increase in TNF-α and IFN-γ cytokines in mice observed in this model can be considered to be similar to the clinical picture of COVID-19 disease [86]. Tumour necrosis factor receptor 1 (TNFRI/TNF) induces necroptosis associated with high levels of neutrophils in critically ill COVID-19 patients. Finally, in an inflammatory situation with high levels of TNF, sFasL may play a secondary role in the survival of neutrophils [87]. Intracellular content can also be released during necroptosis [88], [89]. This type of cell death can also be produced as a result of the effect of EMFs.

The modulated use of this biophysical agent at the immune cell level could alter the molecular phenomena leading to this type of tissue destruction. ELF-EMFs induce necroptotic programmed cell death, which is consistent with necroptosis being accepted as a type of cell death, as we will see below. The existence of necroptosis as an entity different from cell death to apoptosis began to be considered due to different characteristics in the context of cell injury, the elevation of proinflammatory cytokines and TNF-α in vivo. Thus, necroptosis has been related to high concentrations of TNFα and TRAIL (apoptosis-inducing ligand related to tumour necrosis factor (TNF) dependent on NF-κB and p38 stimulation and would ultimately cause a large increase in synthesis of proinflammatory cytokines [90]. Necroptosis was shown to have occurred by observation of a meaningful increase in phosphorylation of specific proteins of necroptosis (RIPK1,3 and MLKL), together with a statistically significant increase in the concentrations of cleaved caspases after exposure to ELF-EMFs, and which can only be explained by a mixed pattern of both types of apoptosis/necroptosis cell death due to ELF-EMF exposure [12], [91] (tables 2 and 3). As well as inducing apoptosis, ELF-MFs can also induce necroptosis either by activating caspases or causing a pro-inflammatory response by activating cytokines with high concentrations of TNFα and TRAIL (which depend on the NF-κB pathways) and p38 mediated by overproduction of ROS and calcium. However, ELF-EMF exposure can be used as a therapeutic tool if expression of genes that act in cell defence is activated early, making DNA repair more efficient in the cell system, by ROS detoxification and induction of synthesis of antioxidant proteins to decrease cell death [12], [91] (apoptosis or necroptosis).

Activation of TPH-1-like macrophages triggered by stimulation of the virus spike protein, mediated by ROS production and intracellular calcium release, may cause increased programmed cell death in this model in which cells are artificially stimulated [67].

Mouse macrophages exposed to 50 Hz ELF-MFs of magnetic field strength 1.0 mT were activated by triggering the oxidative stress process caused by increased ROS production after exposure [92]. In this context, 50 Hz 1.0 mT ELF-MFs modulate the expression of redox proteins, such as the levels of the subunit of the protein gp91phox NAD(P)H oxidase, which was significantly elevated in irradiated macrophages, relative to the control [93]. The study authors attempted to clarify whether NADPH- or NADH-oxidase is influenced by interactions between the EMF and the flavoprotein inhibitor diphenyleneiodonium (DPI). Production of free radicals was induced by EMFs but was not inhibited by DPI, while the production of free radicals induced by TPA was decreased by approximately 70%. As DPI does not have an inhibitory effect on cells exposed to EMFs, these authors state that 50 Hz EMFs at a flux density of 1 mT cause activation of the NADH-oxidase pathway (with production of superoxide anions) but not the NADPH pathway. Furthermore, it has been suggested that the NADPH-oxidase activity associated with the release of superoxide anions from radiation-activated macrophages follows a cyclical pattern of activity [94].

ELF-EMF stimulation (50 Hz, 1.0 mT for 45 minutes) in macrophages causes a reduction in pro-inflammatory cytokines, due to moderate oxidative stress (moderate ROS release). The components of the macrophage membrane are initially affected, and cell homeostasis, gene expression and activation of the alternative pathway are subsequently modified [95]. Applying the same electromagnetic parameters of frequency (50 Hz) and magnetic field strength (1.0 mT) of ELF-MF exposure for different periods of time has been shown to affect the expression of redox regulatory proteins in primary mouse bone marrow-derived macrophages and has been attributed to elevated levels of ROS [93] and after 24 h exposure to IL-1β production [96]. The authors of these studies detected changes in tissue oxidative-antioxidant status, without lesions caused by the oxidative effect, due to

positive stimulation of antioxidant enzyme expression and a significant increase in glutathione levels. PBMCs isolated from 20 children were stimulated with three doses of PEMF (7 Hz, 30 mT) for 4 h each at 24 h intervals (above 0.025 mT), leading to activation of the alternative pathway by triggering the release of moderate amounts of radicals that activated the uptake of intracellular antioxidants.

Owing to moderate oxidative stress, the PEMFs induced a pattern of decreased pro-inflammatory factors and elevation of anti-inflammatory cytokines. The effects of this type of PEMF non-ionizing radiation exposure affected the intrinsic pathway and the endoplasmic reticulum pathway, which together induce apoptosis in monocyte cultures of the Mono-Mac 6 cell line [97]. Increased immunogenic activity has been observed in monocytes exposed to 900 MHz pulse-modulated radiofrequency radiation (20 V/m, SAR 0.024 W/kg) twice (15 min each), i.e. at comparably low exposure levels [98]. Exposure of four different cell types to RFR (2 W/kg SAR) for 8 h revealed increased protein synthesis in activated primary human monocytes [99]. In RAW 264.7 macrophages, the combined effect of 2.45 GHz RF exposure for 24 h and high levels of black carbon (BC) increased phagocytosis. When, in addition to RF and BC, the cells were stimulated with LPS endotoxin for 24 and 72 hours, production of high levels of nitrites was observed. These findings, along with an increase in TNFα and pro-inflammatory cytokines after 24 hours and interleukin-1β and caspase-3 after 72 hours, indicated prolongation of inflammation, activation of the proinflammatory response, and pathways of inflammation and apoptosis by the combined action of RF and BC [6] (see tables 2 and 3).

TABLE 2. Effects of exposure to different types of EMF radiation on immune cells.

Immune cells	RF	ELF-MF	PEMF
Neutrophils	Activate [133]	Activate [134,135,136]	-
NK cells	-	Increased the number-reduction-suppression [28,53,54,55,56, 57,58]	-
Monocytes-Macrophages	Activation-reduction the number [6,70,98,99,109]	Increased the number-activation [93,94,95,96, 105]	Increased the number-activation-reduction [52,73,97,106, 107,108]
T cells	Activation [74,80,81,82]	Activation [74,76]	Activation
B cells	Activation-reduction [72]	-	-

Preclinical experimental studies carried out in different laboratories have concluded that the LF-MF interaction (at 50 Hz and 1 mT) induced a high level of immunogenicity in human or rodent monocytes-macrophages. Exposure caused oxidative stress and activation of the NAD(P)H oxidase subunit gp91phox enzyme system at the cell membrane level, as well as an increase in IL-1beta. Additionally, PEMF (7 Hz, 30 mT) activated apoptosis in patients with lymphoblastic leukaemia, and 900 MHz and/or 2450 MHz RF (SAR 0.02-2 W/kg) increased IL-1β, TNFα, cellular stress pathways caused by mitogens, DNA fragmentation and apoptosis [67], [68], [69], [70], [71], [72], [73], [74], [75], [76], [77], [78], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88], [89], [90], [91], [92], [93], [94], [95], [96], [97], [98]. The high immunogenicity of mammalian macrophages in response to EMFs and different forms of cell death could lead to testing of new therapeutic alternatives in the future.

IV. EFFECTS OF EMFs ON PRO-INFLAMMATORY CHEMOKINES/INFLAMMASOME

Pyroptosis has been recognized as a type of programmed cell death with inflammatory characteristics and which is activated within a complex in the cytoplasm known as the inflammasome. The inflammasome protein complexes are made up of an initiator sensor, an apoptosis-associated protein (ASC) and caspase 1, the main inflammatory caspase [100]. Inflammasomes have found to be involved in the recognition of conserved patterns of protein sequences through PPR-type receptors, which recognize pathogens [101]. The NOD-like receptor (NLR) includes the NLRPs that respond to exogenous signals from bacteria, fungi or viruses that contain pathogen-associated molecular patterns (PAMPs), or to endogenous signal molecules, known as alarmins or damage-associated molecular patterns (DAMPs), which are released by cells and are damaged by cancer, trauma, necrosis or ischaemia. These molecules are known to mediate the induction of inflammation associated with stress processes [102]. Excess activation of the NLRP3 inflammasome could trigger pyroptosis, a type of cell death that is activated after an amplified inflammatory response to virus infection [103]. Dysfunction of the renin angiotensin system (RAAS) may influence the production of the cytokine storm in COVID-19 disease. Thus, the available number of molecules that induce the hyperinflammatory response may increases when the angiotensin-converting enzyme (ACE2) is blocked, leading to progression of COVID-19 disease [104]. At present it is known that the application of EMFs decreases the appearance of iatrogenic infections caused by viruses and/or bacteria after surgical interventions [52], [105].

Therapeutic exposure to PEMF can modulate factors that regulate inflammation, decreasing or blocking the process by causing changes in the mRNA expression of inflammatory factors. Thus, in in vitro studies of inflammatory skin cells induced by trauma, PEMF exposure led to a severe decrease in the mRNA of levels of pro-inflammatory cytokines such as interleukin-1 in mononuclear cells [106]. In order to

investigate the potential of PEMFs (5 Hz) to regulate inflammation markers expressed by macrophages [107], a murine RAW cell line activated with LPS 264.7 macrophages was exposed to a pulsed square wave magnetic field of intensity 0.4 mT. Exposure to PEMF radiation at 5.1 Hz, but not other frequencies (5.1–30 Hz), induced a statistically significant decrease in TNF-α and NFκB factors that had previously been induced by LPS. The decreased expression of interleukin-1β and tumour necrosis factor, pro-inflammatory factors [108] as well as the increase in interleukin-10 with anti-inflammatory action, indicates PEMF treatment has an anti-inflammatory effect [108]. On the other hand, exposure of RAW 264.7 macrophages to single or combined RF (900 or 2450 MHz 12 W power) for 4, 24, 48, or 72 in a GTEM electromagnetic test chamber showed that the radiation had both protective and anti-inflammatory effects, and that combined exposure had cytotoxic effects, with all effects depending on the exposure time [109].

Rigorous experimental studies carried out in different laboratories [107], [108], [109] have confirmed that LF-EMFs and/or PEMFs could have therapeutic applications by decreasing iNOS levels and suppressing caspase-9, with resolution of chronic inflammation (decreased interleukin 1 beta) through the modulation of the TNF-α and NFkB pathway in cell lines infected with bacteria. Additionally, pulsed radiofrequency energy (PRFE) fields have positive effects on endogenous opioid precursors, also decreasing inflammation by decreasing pro-inflammatory cytokines. Unlike the single or combined activity of RF 2450 or 900 MHz, it causes a decrease in phagocytic activity and an increase in inflammatory activity of mouse macrophages. These preclinical studies indicate the possible action of LF-MF/PEMF/PREF on the immune system to modulate the evolution of inflammation in infectious processes.

The following sequence occurs: the SARs-CoV-2 virus infection reaches monocytes in the blood, causing activation of the NLRP3 and AIM2 inflammasomes and pyroptosis with release of cytokines [110]. Monocytes and macrophages act as sentinel cells whose function is to detect any infective agents invading tissues, thus forming inflammasomes that activate caspase 1 and gasdermin, triggering pyroptosis or death by inflammation and releasing powerful inflammatory substances. Inflammatory death is triggered by the uptake of the SARS-CoV-2 virus through the mediation of macrophages, monocytes and antibodies, so that these block production of the virus but also cause the high level of systemic inflammation that is part of the pathogenesis of COVID-19 disease [110]. In a murine coronavirus model (with mouse hepatitis virus (MHV)), NLRP3 deficiency inhibited caspase-1 and GSDMD activation [51], which shows that the coronavirus promotes engagement of the NLRP3 inflammasome. Microscopic study of lung pieces and monocytes from patients with COVID-19 disease indicated formation of the NLRP3 inflammasome in these patients [116]. Infection of human primary monocytes by SARS-CoV-2 indicated NLRP3-dependent caspase-1 cleavage of GSDMD as well as IL-1β maturation [111], [112].

Inflammatory cell death or inhibition of pyroptosis may be a valid therapeutic option for treating COVID-19 infection. Exposure to extremely low frequency EMFs during prenatal and postnatal periods has been found to alter pro-inflammatory cytokines levels. Thus, due to the effect of ELF-MF, the level of interleukin-17A increased in the rat spleen, inducing proliferation and subsequent inflammation of CD4+ T lymphocytes [113]. The PEMF (pulse waveform, 1.5 mT, 75 Hz, 10% duty cycle) treatment in mice has an anti-inflammatory effect via the P38/TNF-α/efferocytosis pathway. Thus, it reduces the production of TNF-α by inhibiting the phosphorylation of P38, which increases the phagocytosis of neutrophils by macrophages (pherocytosis) and finally the inflammation is resolved (synovitis) [114]. PEMF exposure, pulse waveform, 3.82 mT, 8 Hz, for 40 min/day, 5 days a week during 12 weeks, may be a promising non-invasive strategy for slowing down the progression of osteoarthritis (OA), with beneficial effects possibly involving inhibition of the NLRP3/Caspase-1/GSDMD signalling pathway [115]. Some studies have reported anti-inflammatory effects of EMF exposure through a coil system: thus, anti-exudative action and functional recovery of normal parameters were observed in a rat model of rheumatoid arthritis exposed to 1 mT, 50 Hz 5 Hz EMF for 90 minutes [116]. The anti-inflammatory therapeutics of ELF-EMF radiation in rats exposed to PEMF (5 Hz x4 microT x 90 min) is based on stabilization of the cell membrane by recovery of calcium levels within the cell in the lymphocytes [117] (tables 2 and 3).

Cytokine storms are caused by hyperinflammation and are associated with exacerbated release of cytokines, triggered when alterations in the regulation between the immune cells that affect the elimination of the virus occur. A cytokine storm will occur when the spike protein of the SARS-CoV-2 virus binds to ACE2, which is expressed on monocytes and macrophages [118], [119]. The hyperinflammatory state is the focus of interest for reducing the mortality rate by using a therapy that efficiently prevents excessive production of cytokines. Autoimmune thyroiditis patients were randomly assigned to receive either 10 sessions of LLLT, 830 nm, 50 mW output power, and 707 J/cm (2) fluence [120], [121]. Therapeutic application of light and EMFs has been proposed as a possible way of reducing hyper-inflammation triggered by COVID-19 disease. There is evidence that photobiomodulation and EMF exposure in human cells together reduce the response induced by the TLR4 receptor signalling pathway in both light (photobiomodulation) and magnetic fields as daily exposure to two 10-minute intervals of moderate intensity infra-red light significantly lowered the inflammatory response [10]. This receptor has been directly implicated in the onset of ARDS and the cytokine storm in relation to pathogenic viruses [121].

TABLE 3. Bioeffects of exposure to EMF radiation on patterns of cell death.

	RF	ELF-MF	PEMF
Apoptosis	Activate or increase [6,69,70,72, 74,81,82,5]	Activate or increase or decrease [40,74,75,76]	Activate or increase [42,68,73,97]
Necroptosis	-	Activate or increase [91,12]	-
Pyroptosis	Decrease [109]	Decrease/increase [105,113,116, 117]	Decrease [106,107,108, 114, 115]
NETosis	Activate [5]	Increase [134,135,136]	

Summarizing the previously described experimental studies [116], [117], [118], [119], [120], [121], the effect of LF-MF exposure is related to age, gender and health status, with the prenatal and postnatal inflammatory immune response (IL-17A) increasing in females due to maternal exposure. On the contrary, modulation of chemokines occurs in inflammatory processes of the skin by inhibition of the NF-kappaB signal pathway, inhibiting the inflammatory process. At the therapeutic level, PEMFs may have anti-inflammatory effects in synovitis (in macrophages), through the P38 signal pathway, and in osteoarthritis via the NLRP3/Caspase-1/GSDMD signal. The anti-inflammatory effects could be produced by stabilization of the lymphocyte membrane in the calcium channels. Identification of the signalling pathways in which EMFs could intervene in the inflammatory response of immune cells in infectious processes constitutes the first step in the potential use of this type of radiation as a therapeutic tool. The therapeutic approach should be effective in reducing the high levels of inflammation in COVID-19 disease.

Neutrophil extracellular traps (NET), also known as NETosis, refer to a network of chromatin structures, which are released by neutrophils. They function in degrading virulent factors, with the ultimate goal of killing bacteria or viruses [122]. The generation of NETs by neutrophils results in a single form of cell death called NETosis, which is followed by phagocytosis by macrophages [123]. Severe COVID-19 disease is marked by excessive, dysregulated neutrophil function [124] and yields increased levels of markers associated with neutrophil extracellular traps (NETosis), tissue deformation in lung autopsies from patients [125], [126]. Sera from COVID-19 patients have been shown to trigger NETosis, with increased levels of soluble markers detected in sera from COVID-19 patients correlated with disease severity [126], [127]. As already mentioned, the alterations and lack of regulation in the immune response in COVID-19 disease make it difficult to eliminate the virus and also cause a state of hyperinflammation that is associated with a greatly increased secretion of cytokines, i.e. the ''cytokine storm'', which is the prelude to tissue and systemic lesions [128]. As also discussed in the previous section, the cytokine storm is expressed in monocytes and macrophages [118], [119]. However, the immune response is also generated by the continuous migration of neutrophils to the infection site, and the appearance of extracellular neutrophil traps, such as microbial stimuli, causes excessive release of cytokines and chemokines that may result in cytokine storm and sepsis development during COVID-19 infection [125].

Achieving a balance between neutrophilia and controlled levels of NETosis can regulate most pulmonary infections [129], [130], [131]. However, NETs are double-edged swords: they limit infection, but also expose the DNA itself and intracellular proteins, potentially making the organism more susceptible to the appearance of diseases associated with inflammation and with autoimmune etiopathogenesis [132].

Neutrophils act in the immediate immune response, which gives them characteristics of great sensitivity, rapid response and ease of migration, which are of great interest in studying the modulation exerted by exposure to ELF-EMFs [25].

Exposure of 16 ostensibly healthy volunteers to smartphone RF waves from a commercial smartphone (carrier frequency, 900 MHz), via a call placed on the smartphone for 30 minutes, has been shown to trigger activation of neutrophils in vitro, leading to a significant decrease in neutrophil parameters included in the lobularity index, the myeloperoxidase index (MPXI) and the neutrophil cluster mean [133]. ELF-EMFs (300 μT) trigger the production of neutrophil extracellular traps or NETs induced by reactive oxygen species and the NADPH oxidase pathway. Increased NET production has been found to favour antimicrobial characteristics and to lead to damage of surrounding cells [134]. Low frequency fields at 50 Hz, 5 μT, 300 μT and 500 μT did not elicit appreciable stress stimuli that modified the intracellular calcium signal in the human promyelocytic cell line HL-60 or PLB-985 [135]. In another study, exposure to a LF-EMF 5 μT signal for 30 min activated neutrophils in vivo in humans (of age 50-70 years), and it was concluded that low-frequency EMFs could be used therapeutically to induce the immune response at the beginning of infection, thus reducing the symptoms of infectious diseases [136].

On the other hand, particulate atmospheric pollution and EMFs may prove harmful to human health. Exposure of the Hl-60 human promyelocytic cell line to black carbon particles and 2.45 GHz radiofrequency has been found to trigger toxicity, oxidative stress and necrosis and apoptosis [5]. Exposure of innate immune cells to ELF-EMFs or RF-EMFs [5], [25], [133], [134], [135] affects the immune responses associated with inflammation. The effect of RF at 900 MHz or LF-MF at 50Hz causes activation of neutrophils and increases the antimicrobial action triggering the formation of NETs that is dependent on the NADPH oxidase pathway and the

production of reactive oxygen species without affecting the calcium signal. Additionally, the interaction between neutrophils, EMF sources and environmental particles mediates the activation of mitochondrial-caspase-dependent necrosis and apoptosis.
(tables 2 and 3).

V. STIMULATION BY ELECTROMAGNETIC FIELDS AND AUTOIMMUNITY

Serum from adult COVID-19 patients has been found to contain autoimmune antibodies produced in response to cell death, tissue damage caused by the virus, and the immunogenic action of intracellular antigens. The high level of stimulation of the immune system caused by the SARS-CoV-2 virus induces synthesis of autoantibodies [137]. Autoantibody production may mainly occur through the following routes: 1) hyperstimulation of the immune system induced by the virus; and 2) the molecular similarity between the components of the virus and the host [138]. The state of immune hyperstimulation caused by the SARS-CoV-2 was recognized at the beginning of the COVID-19 pandemic [139]. The virus-induced hyperstimulation of the immune system is accompanied by molecular mimicry between human cells and the virus [140]. SARS-CoV-2 infection and NETosis are linked to the autoimmune response.

Neutrophil extracellular traps may be the source of autoantigens and lead to autoimmune responses. In diseases such as systemic lupus erythematosus (SLE), RA, myositis and MS, excessive production of NETosis is related to the autoinflammatory response [141], [142]. A sequence of events occurs in which activated neutrophils degranulate and NETs are released, eliminating chromatin, DNA, histones, enzymes and toxic proteases, thereby increasing lung damage and exacerbating the complications of COVID-19 disease [138]. There is some concern about the possible consequences of the COVID-19 pandemic regarding chronic autoimmune diseases [143], [144]. Some models show that viral infections cause molecular modifications, cell death and facilitate the autoimmune response by these autoAg-Ds complexes, particularly in female hosts, favouring autoimmune pathologies [145]. As already mentioned, COVID-19 disease can cause a significant lack of control of the immune response, increasing the release of cytokines. On the other hand, exposure to non-ionizing radiation sources in vivo animal models has been shown to have a negative feedback on the immune system, causing repeated and chronic exposure to immunosuppression. Likewise, dysregulation of the immune response due to the effect of EMF radiation can, on the contrary, cause a hyperactive response and an increase in autoimmunity [1].

Radiofrequency radiation can damage the immune system of animals. In an animal model, exposure of rats to RF radiation (frequency 2.45 GHz and intensity 0.1–0.5 mW/cm^2) daily for one month resulted in a persistent pathological autoimmune response [146]. Even at low intensities of 0.1–0.5 mW/cm^2, RF radiation can cause changes in immune cells and their responses [147]. In an in vitro model of epidermal keratinocytes, exposure to RF (61.22 GHz frequency, 770 W/kg SAR) for 15-30 minutes caused an increase in the secretion of interleukin 1β, which has a pro-inflammatory function [148]. In an immunosuppressed mouse model exposed to frequency = 42.2 GHz; peak incident power density = 31 +/−5 mW/cm^2, peak specific absorption rate (SAR) at the skin surface = 622 +/−100 W/kg; for 30 min daily for three days, elevation of TNF-α secreted by macrophage cells was observed [149].

Environmental atmospheric pollution caused by the interaction between environmental particles and/or EMFs has been found to cause immune dysregulation, modifying the antimicrobial, inflammatory and an autoimmune response. Thus, combined exposure to 2.45 GHz RF EMF and black carbon particle triggered oxidative stress, caspase-dependent necrosis/apoptosis in the human promyelocytic cell line Hl-60 during 24 or 48 hours [5]. It also modified the immune response of macrophages, activated apoptosis, accelerated toxicity and prolonged phagocytosis in macrophages of the RAW 264.7 cell line exposed to 2.45 GHz RF for 24 or 72 hours, indicating possible induction of hypersensitivity reactions and autoimmune disorders [6]. Other proposed methods involve low intensity, low frequency pulsed radiation intended to alter the pathophysiology of autoimmune neurodegenerative diseases such as multiple sclerosis, which cause profound changes in the membrane [150]. The target of the ELF-EMFs at pulsed magnetic fields of 50–100 Hz and a few mT (whose flux intensity is 9 or 10 times) includes myelin plaque cells (T lymphocytes, monocytes, macrophages, microcytic immune cells of the nervous system), and all of the inactive cells located in the constitutive tissue of the nervous system (microglia and monocytes/macrophages) slow down the autoimmune activity in the plaques [151]. This may lead to local (in the brain) or regional (in the entire CNS) immunomodulatory effects at static magnetic fields ranging from 27 to 37 μT and time varying magnetic fields with frequencies between 7 and 72 Hz and amplitudes between 13 and 114 μT (peak) [152].

Experimental studies indicated the possibility of autoimmune changes after continued exposure to low frequency electromagnetic sources. However, it is not clear whether high frequency EMFs (61.22 GHz; SAR, 770 W/kg or 42.2 GHz, 100 W/kg) can cause an inflammatory effect or favour the immunosuppressive effect by increasing the proliferation of splenocytes and alter the activation and effector functions of T lymphocytes. On the other hand, pulsed magnetic fields of 50–100 Hz at a few mT (whose flux intensity is 10 (9) times) could induce morphological changes in the plasma membrane of various types of cells favouring immunomodulation in autoimmune processes such as multiple sclerosis (MS). This action could be carried out through the effects on calcium channels (Fig 1).

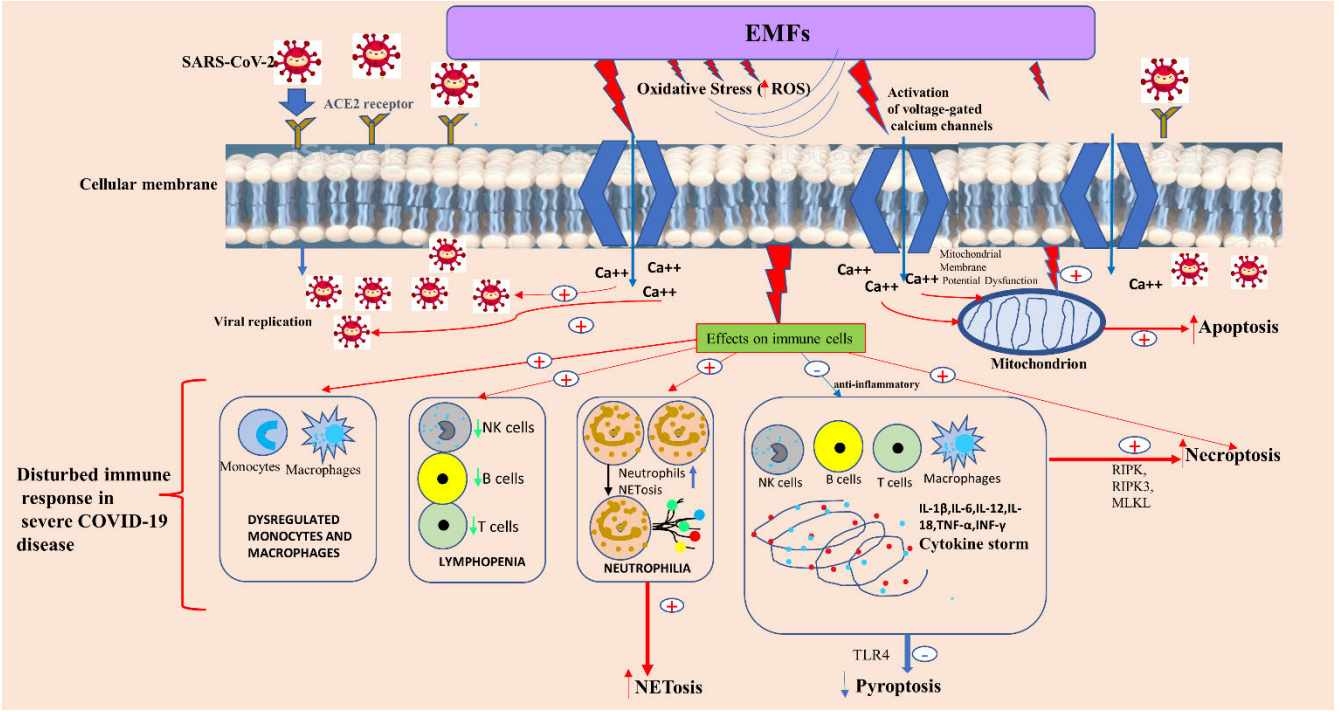

FIGURE 1. Diagram summarising the modulation exerted by electromagnetic fields (EMFs) on the immune system cells, including macrophages, monocytes, natural killer (NK) cells, T lymphocytes (T cells) B lymphocytes (B cells) and neutrophils, and the response to cell death caused by severe COVID-19 disease. EMFs cause cellular oxidative stress by increasing reactive oxygen species (ROS) which modify the response of the immune system to cell death (apoptosis, necroptosis, NETosis and pyroptosis) in cells already previously altered by COVID-19 disease (neutrophilia, lymphopenia, monocytic and macrophage dysregulation and cytokine storm). EMFs also cause opening of calcium channels with entry of intracellular calcium and increased entry and replication of virus. Oxidative stress and intracellular calcium entry alter mitochondrial membrane potential.

VI. EFFECTS OF EMF EXPOSURE ON INTRACELLULAR CHANNELS: THE ROLE OF PROGRAMMED CELL DEATH OF IMMUNE CELLS IN SEVERE COVID-19 DISEASE

There is some experimental evidence associating alterations in calcium homeostasis with cell death [153]. Increased cytosolic concentrations of Ca^{2+} ($[Ca^{2+}]$) have been detected in both early and late stages of the apoptotic pathway [154]. Other studies have shown that Ca^{2+} is released from the endoplasmic reticulum and that entry of Ca^{2+} is due to release of Ca^{2+} from apoptogenic Ca^{2+} channels [155], [156]. The Calcium-Sensing Receptor (CaSR) is involved in maintaining the balance of calcium metabolism by directly regulating excretion of this ion by the kidneys and acting indirectly in regulating the secretion of parathyroid hormone (PTH) from the parathyroid [157].

The CaSR, the calcium sensitive sensor, is expressed in immune cells promoting the inflammatory response and cell activation by the presence of calcium. These three elements (CaSR, calcium and vitamin D) seem to interact in a way that could have implications in the etiopathogenesis of severe COVID-19 disease as an acute respiratory syndrome and that would have implications in the prognosis of patients [158]. Proinflammatory signalling of the NLRP3 inflammasome is activated by calcium, leading to a significant number of systemic diseases [159], [160]. Nonetheless, the SARS-CoV-2 virus alters calcium homeostasis, thus favouring its virulence by boosting intracellular calcium influx [161]. CaSR may also act on viral infection by increasing immune cells and elevating the inflammatory response in patients with severe COVID-19 disease [158].

Exposure to EMFs has been found to modulate intracellular calcium entry; calcium levels are reduced in the mouse hippocampus and hypothalamus, with an increase in calcium in the cytosol of stem cells and a decrease in the expression of calcium-binding proteins [162], [163], [164]. On the other hand, low-frequency radiation from EMFs is related to increased calcium concentration at the tissue level, at the level of the hippocampus in the mouse and also in the PC12 cell line of rats [36], [165], [166], as well as to enhanced activation of voltage-dependent calcium channels and modulation of their electrical properties [165], [167]. When HEK 293 cells are exposed to electromagnetic fields (RF-EMFs) and static magnetic fields (SMF), constant and significant elevation of the calcium concentration occurs [168]. The voltage-gated calcium channel (VGCC) sensor is the primary target of low-intensity electromagnetic fields. Under normal physiological conditions, this voltage sensor controls the opening of the VGCC in the plasma membrane, acting on the partial depolarization response [169]. Four different classes of VGCCs are activated by exposure to ELF-EMFs: types L, T, N and types P-Q VGCCs [170]. Channels other than calcium, sodium,

potassium and chloride channels are also activated by ELF-EMF exposure.

Each of these channels have voltage sensors similar to voltage-gated calcium sensitive to ELF-EMF but with a more modest role in biological effects than VGCC and increased intracellular calcium [171]. EMF-induced VGCC activation and biological effects have been found to produce the main pathophysiological effects by elevation of the internal calcium concentration that causes excessive signalling in the peroxynitrite pathway, which is activated by elevation of ROS, with oxidative stress with an alteration in mitochondrial function and an increase in NF-kappaB activity and the cytokines. An NO signalling pathway and Nrf2 stimulation have also been identified via which the activation of the VGCC induced by exposure to electromagnetic fields can occur and can produce therapeutic effects [169]. This biological effect could be explained by a theoretical model based on the hypothesis that an external oscillating electric field will exert a force on free ions on both sides of a plasma membrane, enabling the ions to move across the membrane. Thus, the external oscillating force will cause vibration of each free ion and if the amplitude exceeds a critical value, the oscillating ions can give a false signal to open or close voltage-gated channels, thus altering the electrochemical balance of the plasma membrane and, consequently, the entire function of the cell [172]. All man-made EMF/EMR, in contrast to natural EMF/EMR, are polarized and have increased biological activity. Polarization appears to be a trigger that significantly increases the likelihood of initiating biological or health effects. This is because polarized fields have the ability to produce interference effects, amplify intensity, force charged/polar molecules and free ions. This causes the cells to oscillate in parallel planes, in phase with the applied bias field. Forced ionic oscillations exert additive electrostatic forces on electrosensitive ion channel sensors in the cell membrane, causing irregular activation and disruption of the electrochemical balance of the cells [173].

PEMF exposure to a sinusoidal 50 Hz PEMF with a magnetic flux density of 1 mT has been found to decrease calcium oscillations inside the cell, and calcineurin has been shown to be related to the protein activity but not expression [174].

PEMF exposure can also potentially restore equilibrium in ROS, and antioxidant free radicals induce currents that stabilize calcium within the cell by oxidative stress [175]. ROS exert greater regulation of protective and restorative genes than of dysregulatory and apoptotic genes [70]. However, EMFs have been shown to stimulate ROS production, cause immunosuppression and a decreased immune response to infections.

These impacts are associated with an inhibitory effect on intracellular calcineurin [176]. On the other hand, it has recently been found that EMF exposure can increase the infectivity of viruses by increasing intracellular calcium, which can act indirectly by contributing to the inflammatory process and thrombosis [1]. We wonder if the increased intracellular calcium flux caused by the SARS-CoV-2 virus [46] and enhanced by exposure to EMFs [168], [177] could play a relevant role in the different cell death processes [178] that take place in severe COVID-19 disease (Fig 1). Numerous in vivo experimental studies at the level of the hippocampus and hypothalamus have reported that EMF radiation at 835 SAR 1.6–4 W/kg can alter calcium homeostasis at the neuronal level. With ELF-EMF, Ca^{2+} channels facilitate the vesicle endocytosis and synaptic plasticity, causing neurotoxicity by activating apoptosis through the mitochondrial pathway, increasing glutamate, GABA and NR2B. Participation of the endoplasmic reticulum has been demonstrated in cells exposed to RF, and different direct and indirect theoretical models that explain the activation of the channels through voltage sensors from a physical point of view have been established [169], [170], [171], [172], [173]. Exposure to ELF-MFs increases reactive species causing DNA damage and inhibiting calcineurin [175], [176] also due to the effect of PEMFs [174]; it also modulates ion channels affecting the ionic conductance of the membrane and the concentration and expression of proteins [177].

VII. DISCUSSION

After analyzing the scientific publications included in this literature review, we can confirm the initial hypothesis, which suggests that COVID-19 infection modifies the host immune response and is also simultaneously and continuously affected by interaction with non-ionizing radiation sources. The review of studies describing the response of immune cells (in in vitro or in vivo experimental studies in animals and humans) due to interaction with non-ionizing radiation and/or COVID-19 infection has allowed us to perform a parallel reconstruction of how the mechanisms of inflammation and/or cell death act when subjected to the stress of infectious agents such as viruses and/or physical EMF. This is necessary because experimental publications that establish relationships between the two are practically non-existent. The objectives of this review article are as follows: 1) To compare the mechanisms and pathways of the host immune response induced by COVID-19 infection and/or the effect of non-ionizing radiation that lead to the different types of cell death. 2) To critically analyze the direct and/or indirect intervention of sources of EMF radiation in the cellular immune response associated with cell death in COVID-19 disease.

External sources of EMFs can act as stimuli that elicit a wide variety of immune responses related to the different electromagnetic parameters involved, such as frequency of exposure, specific absorption rate (SAR), location of signal exposure, distance from the antenna, duration of exposure and temperature increase [31]. There is experimental evidence that different levels of EMF exposure in living organisms can lead to changes in the homeostasis of the oxidative/antioxidative response at the tissue level [32], [33], [34]. The feedback from non-ionizing radiation to the cellular redox pathway can be positive, enhancing antioxidant action [35], [36], [37], or negative, exerting an

intense oxidative action [38], [39]. EMFs interacting with the cellular oxidative stress pathway can trigger activation of genes related to cell death [40], [41], [42]. The experimental biological effects of non-ionizing radiation on cellular functions related to antioxidant enzymes and cell death encourage us to consider several possibilities in relation to viral infection, particularly in the case of COVID-19 disease.

Apoptosis, in relation to COVID-19 disease, caused by infection with the SARs-Cov-2 virus, is important as a mechanism of non-inflammatory programmed cell death. Thus, infected host cells activate apoptosis and thus decrease the spread of the virus in tissues [45]. Severe COVID-19 disease is characterised by an altered immune response [47] and is also associated with activation of apoptosis and depletion of immune cells [48]. EMFs can act over a wide range (see table 3) and can cause an increase/decrease in apoptotic activity. Thus, environmental sources of EMFs could modify the host immune response and/or alter the apoptotic pathway in infectious processes such as COVID-19 disease [1]. In this review, experimental evidence has been found in animal models, in humans and also at the cellular level, indicating that exposure of immune cells to different sources of EMF radiation caused modifications in the immediate immune response of natural killer cells [49], [50], [51], [52], [53], [54], [55], [56], lymphocytes [68], [69], [70], [71], [72], [73], [74], [75] or monocytes-macrophages [67], [68], [69], [70], [71], [72], [73], [74], [75], [76], [77], [78], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88], [89], [90], [91], [92], [93], [94], [95], [96], [97], [98] by interfering with the mechanisms of the programmed cell death pathway. The improved knowledge of the mechanisms of cell death in COVID-19 disease [61], [62], [63], [64], [65], [66], [67] could help in the search for new therapeutic tools.

Necroptosis is another type of cell death associated with inflammation and cytokine release in severe COVID-19 disease [84], [85]. In addition, EMFs can also induce necroptosis by triggering a proinflammatory response through cytokine activation, mediated by overproduction of ROS and calcium [86], [87], [88], [89]. On the other hand, EMFs can also be used as a therapeutic tool in cellular defence, by enhancing the efficiency of DNA repair, ROS detoxification and even death by apoptosis and/or necroptosis [12], [91].

Excessive activation of the inflammasome may trigger pyroptosis [100], a type of cell death that is activated by an amplified inflammatory response to severe COVID-19 disease [103]. Recent research has documented the application of EMFs and reported a decrease in the occurrence of iatrogenic infections caused by viruses and/or bacteria after surgical interventions [52], [105]. The identification of signalling pathways in which EMF may be involved in the inflammatory response of immune cells in infectious processes is the first step in the challenge of identifying a new therapeutic strategy. Thus, several preclinical studies [107], [108], [109] discussed in this review indicated the possible action of LFMF/PEMF/PREF on the immune system to modulate the evolution of inflammation in infectious processes. Experimental studies have also related differences in age, sex and health status to increased immunity and prenatal inflammatory response (IL-17A) in maternal exposure to LF-MFs [116], [117], [118], [119], [120], [121]. In addition, PEMFs may have an anti-inflammatory effect on osteoarthritis through NLRP3/caspase-1/GSDMD signalling [115]. The challenge would be to achieve a sufficiently effective therapeutic approach to reducing the high levels of inflammation in COVID-19 disease (see table 3).

NETosis, neutrophil extracellular traps, are networks of chromatin structures, which are released when neutrophils degrade virulent factors, killing bacteria or viruses [122]. Excessive neutrophil activation and dysregulation of neutrophil function occur in severe COVID-19 disease [124]. The findings of this review also show that exposure to ELF-MEF or RF-MEF [5], [25], [133], [134], [135] causes neutrophil activation and enhances antimicrobial action that triggers the formation of NETs dependent on the NADPH oxidase pathway and the production of reactive oxygen species. In addition, the interaction between neutrophils, EMF sources and environmental particles mediates mitochondria-caspase-dependent activation of necrosis and apoptosis [5]. The information obtained in this review indicates that modulation of neutrophils by EMFs modifies the neutrophil response to NETosis production in the context of inflammation.

Linked to the excessive neutrophil activation, there is also a significant risk in COVID-19 infection that is clearly seen in NETosis, triggered by the autoimmune neutrophil response and autoantibody formation due to hyperstimulation of the immune system [137], [138], [139], [140]. There is a great deal of concern in the healthcare community about the possible consequences of the COVID-19 pandemic and the formation of autoantibodies leading to increased lung damage and complications [138]. There is also concern regarding chronic autoimmune diseases, which are caused by intense autoinflammatory response and excessive production of netosis such as systemic lupus erythematosus, rheumatoid arthritis, myositis and multiple sclerosis [141], [142]. Experimental studies indicated the possibility that continuous exposure to low levels of EMF radiation can cause autoimmune changes [146], [147], [148], [149], [150], [151], [152]. However, high-frequency EMFs may provoke an inflammatory effect or promote immunosuppression [146], [147], [148], [149]. By contrast, PEMFs could induce changes in the cell plasma membrane promoting immunomodulation in multiple sclerosis [150], [151], [152].

Much of the immunomodulatory actions of EMFs at the tissue level are carried out through effects on calcium channels. This can be explained by a theoretical model in which the electrical field will exert a force on free ions moving on both sides of the plasma membrane [172]. The forced ionic oscillations will cause irregular activation and disturb the electrochemical equilibrium of the cells [173]. PEMFs can indirectly affect calcium channel-related protein activity,

such as calcineurin [174]. PEMFs can also enhance the balance between free radicals (ROS) and antioxidant enzymes by inducing currents that stabilise calcium in the cell caused by oxidative stress [175], in some cases leading to immunosuppression and decreased immune response to infections (see figure 1).

Thus, the experimental findings obtained in this review indicate a bidirectional effect (positive and/or negative) of EMFs and their potential therapeutic use, as non-ionizing radiation may have some or no favourable effects on human health (see tables 2, 3). As attack from viruses and exposure to non-ionizing radiation will persist in the environmental context in the coming years, it will be necessary to develop new experimental models to assess the impact of the combined interaction of both biological/infectious and/or biophysical/technological agents at the level of the host immune system. The scope of these studies may have important implications for pathophysiology and human health and may also help to establish a route towards the development of new therapeutic tools.

VIII. CONCLUSION

This review highlights the large number of studies involving different EMF parameters and experimental conditions, which hamper direct comparison of the findings. It is therefore difficult to reach conclusions regarding the impact of non-ionizing radiation sources on COVID-19 disease. Nonetheless, we conclude the following:

1. All models used to study the interaction between electromagnetic radiation and the immune system of mammals (in or in vitro) show that non-ionizing radiation can activate or reduce the inflammatory response, oxidative stress and can have positive or negative manifestations in COVID-19 disease, depending on the radiation frequency, intensity or modulation and the exposure time.
2. Intracellular calcium entry can also be modulated by beneficial or adverse effects of EMF on inflammation and/or cell death [170]. Both sides of the coin [179] must also be taken into account in regard to progression to severe COVID-19 disease (Figure 1).
3. The COVID-19 pandemic has generated great advances in the study of the pathophysiology of viral diseases. However, further research regarding the influence of natural or artificial sources of EMFs on communicable viral diseases is required as this could have important implications for human health.
4. In light of the data reviewed, future research should be directed towards validating experimental models that demonstrate the direct or indirect biological effects of non-ionizing radiation on host immunity in relation to COVID-19 infection. Scientific findings could be applied to limit the environmental risks that act together with viral infections as well as assess new therapeutic tools.

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