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INVITED REVIEW

Extremely low frequency electromagnetic fields stimulation modulates autoimmunity and immune responses: a possible immuno-modulatory therapeutic effect in neurodegenerative diseases

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Abstract

Increasing evidence shows that extremely low frequency electromagnetic fields (ELF-EMFs) stimulation is able to exert a certain action on autoimmunity and immune cells. In the past, the efficacy of pulsed ELF-EMFs in alleviating the symptoms and the progression of multiple sclerosis has been supported through their action on neurotransmission and on the autoimmune mechanisms responsible for demyelination. Regarding the immune system, ELF-EMF exposure contributes to a general activation of macrophages, resulting in changes of autoimmunity and several immunological reactions, such as increased reactive oxygen species-formation, enhanced phagocytic activity and increased production of chemokines. Transcranial electromagnetic brain stimulation is a non-invasive novel technique used recently to treat different neurodegenerative disorders, in particular Alzheimer's disease. Despite its proven value, the mechanisms through which EMF brain-stimulation exerts its beneficial action on neuronal function remains unclear. Recent studies have shown that its beneficial effects may be due to a neuroprotective effect on oxidative cell damage. On the basis of *in vitro* and clinical studies on brain activity, modulation by ELF-EMFs could possibly counteract the aberrant pro-inflammatory responses present in neurodegenerative disorders reducing their severity and their onset. The objective of this review is to provide a systematic overview of the published literature on EMFs and outline the most promising effects of ELF-EMFs in developing treatments of neurodegenerative disorders. In this regard, we review data supporting the role of ELF-EMF in generating immune-modulatory responses, neuromodulation, and potential neuroprotective benefits. Nonetheless, we reckon that the underlying mechanisms of interaction between EMF and the immune system are still to be completely understood and need further studies at a molecular level.

Key Words: *electromagnetic fields; Alzheimer's disease; transcranial magnetic stimulation; autoimmunity; immunomodulation*

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Introduction

The etiology of neurodegenerative diseases is multifactorial. Genetic polymorphisms, increasing age and environmental cues are recognized to be primary risk factors. Although different neuronal cell populations are affected across diverse neurodegenerative disorders, hallmark protein modifications is a common feature that supports the differential disease diagnosis and provides a mechanistic basis to gauge disease progression (Bossy-Wetzel et al., 2004).

It is becoming increasingly clear that, particularly for chronic neurodegenerative disorders occurring late in life, a complex combination of risk factors can initiate disease development and modify proteins that have a physiological function into ones with pathological roles *via* a number of defined mechanisms (Moreno-Gonzalez and Soto, 2011).

Amyloid-beta plaques and tau protein tangles – hallmarks of the pathology – are most likely a non-specific result of the disease process, rather than a cause (Lee et al., 2007). A large body of evidence supports the direct contribution of inflammation in the development and progression of neurodegeneration (Tweedie et al., 2007). A common denominator in the occurrence of different pathogenic mechanisms is oxidative stress accompanied by redox dysregulation, which have a role in mitochondrial dysfunction, toxicity, missignalling by calcium, glial cell dysfunction and neuroinflammation itself. Each of these can influence one another at multiple different levels, and hence oxidative stress can both be secondary to them as well as have a primary part in their initiation (von Bernhardi and Eugenin, 2012).

In the last years, evidence are remarkably revealing that Alzheimer's disease (AD) has an autoimmune component (D'Andrea, 2005). In older patients the presence of anti-neuronal

autoantibodies in the serum frequently occurs; if blood-brain barrier (BBB) dysfunction comes up, these autoantibodies are able to reach their targets and determine deleterious effect (D'Andrea, 2003). In fact, a profound change in BBB permeability has been observed in AD. In these patients amyloid deposits have been observed in microvessels and this overload is associated with degenerating endothelium (decreased mitochondrial content, increased pinocytotic vesicles), damaged smooth muscle cells and pericytes, and basement membrane changes (focal necrosis, reduplication, increased collagen content, disintegrating) (Thomas et al., 1996; Wardlaw et al., 2003). All these components strengthen the possibility that the 'major pathological role of amyloid in AD may be to inflict vascular damage' and hence, impair BBB function (Franzblau et al., 2013; Attems and Jellinger, 2014).

Immunoglobulins (IGs) have been detected in serum, cerebrospinal fluid and amyloid plaques of patients with AD. IGs are associated with vessel-associated amyloid, which has been linked to a faulty BBB (Franzblau et al., 2013). As a consequence, the presence of neuronal autoantibodies associated with a BBB dysfunction seems to be a relevant part of AD neuropathology (Attems and Jellinger, 2014).

Additional data about relationship between autoimmune diseases (*e.g.*, thyroid dysfunction, diabetes) and AD has been proven. In fact, patients with AD have a significant increase in the values of anti-thyroglobulin and anti-microsomial autoantibodies compared to healthy controls (Genovesi et al., 1996).

Moreover, typical features of autoimmunity have been associated with both AD and diabetes (*e.g.*, high levels of advanced glycation end products and their receptor have been detected in tissues and in the circulation in both disease) (Mruthinti et al., 2006).

In summary, these data in the context of the underlying mechanisms of many autoimmune diseases indicated that AD has proven autoimmune mechanisms, which provide a link between vascular pathology (altered BBB function) and neuronal cell death. Furthermore, according to these data, BBB dysfunction precedes neuronal degeneration and dementia (Rhodin and Thomas, 2001).

Electromagnetic Brain Stimulation and Immunomodulation in Neurodegenerative Diseases

Over the past decades, neuroscientists and clinicians have been exploring the properties of the brain's electromagnetic activity for both diagnostic and therapeutic purposes. In the 1990s, research on electromagnetic radiation was motivated by the need to better understand the potential harmful effects of environmental magnetic fields (Bennett, 1995; Bracken and Patterson, 1996); actually, it is becoming increasingly clear that interactions between magnetic fields and biological systems deserve to be studied in their own right because these interactions appear to be fundamental to life processes and could represent a therapeutic agent in several diseases.

In our opinion, one of the more striking observations related to the effects of EMFs on biological systems concerns the presence of a "window effect," showing that biological effects occur only at particular combinations of frequency and field intensity (Panagopoulos and Margaritis, 2010). These effects have been reported especially for changes in calcium ion flux in cells and tissues. Related window effects are reports of signal-specific quantitative and qualitative response to EMFs in several different tissues (Azanza and del Moral, 1994).

ELF-EMFs interact readily with the central nervous system (CNS). While the high-frequency EMFs encountered in industry can expose workers to an increased risk of AD (Hakansson et al., 2003), amyotrophic lateral sclerosis and multiple sclerosis (MS) (Johansen, 2004), EMFs of weak and very weak intensity can exert interesting and proven therapeutic effects on the CNS (Sandyk, 1992; Sandyk and Iacono, 1994; Boggio et al., 2012). The level of radiation is typically in the range of 1 millitesla (mT) in most studies.

Transcranial magnetic brain stimulation (TMS) is a commonly-used neurostimulation and a neuromodulation technique, based on the principle of electromagnetic induction of an electrical field in the brain. This field can be of sufficient magnitude and density to depolarize neurons, and when TMS pulses are applied repetitively they can modulate cortical excitability, decreasing or increasing it, depending on the parameters of stimulation, even beyond the duration of the train of stimulation (Fregni and Pascual-Leone, 2007; Ridding and Rothwell, 2007).

The last decade has seen a rapid increase in the applications of TMS to study cognition, neurobehavioral relations and the pathophysiology of several neurologic and psychiatric disorders. Evidence has accumulated that demonstrates that TMS provides a valuable tool for modulating brain activity in a specific, distributed, cortico-subcortical network through control and manipulation of cognition, neuromotoricity and behavior (George et al., 2007; Guerriero et al., 2015).

Since the immune system plays a primary role in the control of many diseases and tumor growth, many laboratories have investigated the influence of ELF-EMF stimulation on blood mononuclear cells, various cellular components and cellular processes; other studies have examined electromagnetic effects on specific genes expressions and signal transduction pathways, but the experimental data obtained are currently controversial (Cossarizza et al., 1993; Onodera et al., 2003).

The mechanisms by which ELF-EMFs elicit cellular responses are somewhat still unknown, and it is still unclear which cellular components mediate these fields' effects. However, there are several hypotheses to explain EMF interaction with the living matter.

It is assumed that some type of initial interaction occurs at the level of the cell membrane and that specific signal amplification processes carry the membrane-mediated effect into the cell (Frey, 1993). Molecular studies of the membrane signaling processes have shown, for example, that the involved cells can use mechanisms such as intracellular second-messenger (*e.g.*, Ca^{2+}, cyclic adenosine monophosphate [cAMP], cyclic guanosine monophosphate [cGMP]) cascades, positive feedback, and linear membrane channel-gating (Grundler et al., 1992). Some of the most important calcium-related processes such as synaptic neurotransmitter and synthesis and release and levels of cAMP (Matthews and Gersdorff, 1996), essential for the functioning of the neurons that are influenced by EMFs (Rosen, 1992). In addition, amplification

via calcium flux could also provide the means by which the membrane-mediated effects of EMFs could be carried into the cell (Karabakhtsian et al., 1994).

As described below, EMFs proved to exert a certain immune function modulation. Modulation of neural activity by ELF-EMFs could possibly counteract the aberrant pro-inflammatory responses present in neurodegenerative and neuropsychiatric disorders reducing their severity and, possibly, their onset.

Thus, in the next sections we will address the influence of ELF-EMFs on autoimmunity and immune cells, supposing that ELF-EMF may act on the basis of mechanisms centered on immunomodulation. This could have particular relevance for the treatment of neurodegenerative disorders, such as AD.

Low-frequency Electromagnetic Fields Stimulation and Autoimmunity

Regarding a possible relationship between EMF and autoimmunity, the researches conducted by Sandyk and colleagues deserve great interest. In the 1990s, Sandyk amply demonstrated the efficacy of pulsed ELF-EMFs of a few mT in alleviating the symptoms of MS through their action on axonal and synaptic neurotransmission (Sandyk and Iacono, 1993; Sandyk and Dann, 1995). Weekly treatment administered for years with very weak ELF-EMFs can alter the clinical course of chronic progressive MS, arresting progression of the disease for as long as four years (Sandyk, 1995a, 1997). This observation prompts the hypothesis that, in addition to effects on axonal and synaptic neurotransmission, effects may also be exerted on the autoimmune mechanisms responsible for demyelination.

Other proposals that to use pulsed ELF-EMFs of a few mT aims to modify the autoimmune pathology of the disease by eliciting profound membrane changes (Bistolfi, 2002) (the so-called Marinozzi effect) (Marinozzi et al., 1982) in the MS plaque cells.

While the action of ELF fields of a few pT is characterized by an improvement in neurotransmission, the use of ELF fields of a few mT aims to exert an action of local immunomodulation on the cells of the MS plaque through the induction of the Marinozzi effect. It therefore follows that the targets of ELF fields in the mT range will be the plaque cells (T-lymphocytes, macrophagic monocytes, microglia cells and dendritic cells), those cells disseminated in the seemingly normal nervous tissue (macrophages and microglia cells) (Bistolfi, 2007).

More specifically, the target should be the plasma membrane of these cells, which is almost always carpeted with microvilli and protrusions of various types. Since the plasma membrane is central to the relationships among immune cells (Lassmann et al., 2007) and since the plasma membrane itself is the elective target of ELF-EMF, a possible induction of the Marinozzi effect could slow down the activity of autoimmune cells in the plaque. It may determine an effect of local (on the brain) or regional immunomodulation (on the entire CNS) (Baureus Koch et al., 2003).

In far 1998, Richards et al. (1998) expressed the hope that electromagnetic fields might find application in the therapy of MS, both to manage symptoms and to achieve long-term effects by eliciting beneficial changes in the immune system and in nerve regeneration.

Our personal hypothesis is that – as observed in MS - similar effects could be present and relevant during EMF brain stimulation in patients with other CNS neurodegenerative disorders and be responsible for their therapeutic effect.

Low-frequency Electromagnetic Fields Stimulation and Immunomodulation

ELF-EMF effects on macrophages, nitric oxide and heat shock proteins

Macrophages are responsible for eliminating infectious agents and other cellular debris (Tintut et al., 2002). The recruitment of monocytes/macrophages to inflammatory sites and neoplastic tissues and their activation therein is crucial to the success of an immune reaction, in part because further cell migration is intimately related to leukocyte function. Resting macrophages have low levels of phagocytic activity and become fully active through the binding of pathogens or by local cytokine release. Once activated, macrophages exhibit an increased level of phagocytic activity and an increased production of reactive oxygen species (ROS) enabling the killing of microbes within phagosomes. The first step is the phagocytosis of the infectious agent, which is then transferred to the phagosome where it is killed by ROS and reactive nitrogen oxide species. The main protagonist of this process is nitric oxide (NO), which in turn induces the formation of cGMP, which in turn triggers a cascade of intracellular signaling. In the other hand, ROS also act as a signaling molecule and targets a wide range of physiological pathways. Activation of these cellular pathways also causes the secretion of inflammatory cytokines including IL-1b and TNF-alpha (Laskin and Laskin, 2001). Therefore when stimulated with bacterial toxins, NO and ROS stimulate cells to synthesize heat shock proteins (HSPs) (Polla et al., 1996).

Several studies have shown the effect of ELF-EMFs on macrophages. Kawczyk-Krupka and colleagues aimed to determine the effect of ELF-EMFs on the physiological response of phagocytes to an infectious agent. Human monocytic leukemia cell lines were cultured and 50 Hz, 1 mT EMF was applied for 4–6 hours to cells induced with Staphylococcus aureus. The growth curve of exposed bacteria was lower than the control, while field application increased NO levels. The increase was more prominent for Staphylococcus aureus-induced cells and appeared earlier than the increase in cells without field application (Kawczyk-Krupka et al., 2002). Increased cGMP levels in response to field application were closely correlated with increased NO levels (Azanza and del Moral, 1994).

Another study on mouse macrophages after short-term (45 minutes) exposure to 50 Hz EMF at 1.0 mT showed a significant uptake of carboxylated latex beads in macrophages, suggesting EMFs stimulate the phagocytic activity of their macrophages (Frahm et al., 2006). Tetradecanoylphorbol acetate (TPA) was used as positive control to prove the activating capacity of cells, as TPA is known to activate the protein kinase C and induce cellular processes including pinocytosis and phagocytosis (Laskin et al., 1980). On the basis of these data, ELF-EMF seems to potentially play a role in decreasing

the growth rate of bacteria and other pathogens eliminated by phagocytosis.

A significant increase of free radical production has been observed after exposure to 50 Hz electromagnetic fields at a flux density of 1 mT to mouse macrophages (Aktan, 2004). To elucidate whether NADPH- or NADH-oxidase functions are influenced by EMF interaction, the flavoprotein inhibitor diphenyleneiodonium chloride (DPI) was used. EMF-induced free radical production was not inhibited by DPI, whereas TPA-induced free radical production was diminished by approximately 70%. Since DPI lacks an inhibitory effect in EMF-exposed cells, 50 Hz EMF stimulates the NADH-oxidase pathway to produce superoxide anion radicals, but not the NADPH pathway. Furthermore, the oscillation in superoxide anion radical release in mouse macrophages suggests a cyclic pattern of NADH-oxidase activity (Rollwitz et al., 2004).

An important aspect of these phagocytic cells is that they produce high levels of free radicals in response to infection, and the effect of ELF-EMF on free radicals has been widely proposed as a probable direct mechanism for the action of ELF-EMF on the living systems (Simko and Mattsson, 2004).

NO, a free radical, is an intra-cellular and inter-cellular signaling molecule and it constitutes an important host defense effector for the phagocytic cells of the immune system. It is synthesized by NO synthase, which has two major types: "constitutive" and "inducible". Inducible nitric oxide synthase (iNOS) is particularly expressed in macrophages and other phagocytic cells that are stimulated during an immune response to infection (Aktan, 2004). Although high concentration of NO can be beneficial as an antibacterial and antitumor agent, an excess of NO can be fatal and can lead to cell injury. For example the excessive activity of iNOS has detrimental effects on oligodendrocytes, cells responsible for the myelination of neuron in the CNS (Klostergaard et al., 1991). The roles of NO in the pathophysiology of disease are still being defined, but there is a growing body of evidence that the neutralization of iNOS activity may have a therapeutic value (Parmentier et al., 1999).

Some studies have focused on the potential toxicity of the ensuing high-output NO-synthesis serving as a mean to eliminate pathogens or tumor cells, but the expression of iNOS, contributes to local tissue destruction during chronic inflammation. NO increases the ability of monocytes to respond to chemotactic agents more effectively, and it is considered to be one of the principal effector molecules involved in macrophage-mediated cytotoxicity (Desai et al., 2003).

It has been observed that exposure to ELF-EMFs modifies both NOS and MCP-1 chemokine expression and that these modifications are related to each other and are furthermore mediated by increased NF-κB protein expression (Goodman et al., 1994). EMF represents a non-pharmacological inhibitor of NO and an inducer of MCP-1, the latter of which activates one of these molecules and leads to inhibition of the former and *vice versa*, establishing a mechanism that protects cells from excess stimulation and contributes to the regulation of cellular homeostasis (Biswas et al., 2001). Moreover *in vitro* study observed a slight decrease was observed in iNOS levels was observed in cells induced with Staphlococcus aureus after ELF-EMF stimulation (Azanza and del Moral, 1994).

HSPs are evolutionarily conserved proteins known to play a key role in cellular defense against the effect of stressors and their function in modulating apoptosis has been well assessed (Beere, 2004). Concerning the relationship between EMF stimulus and HSPs expressions, Goodman et al. (1994) first demonstrated that HSP expression was enhanced by exposure to electromagnetic fields. Tokalov and Gutzeit (2004) showed the effect of ELF-EMF on heat shock genes and demonstrated that even a low dose of ELF-EMF (10 mT) caused an increase in HSPs, especially hsp70, implying that the cell senses ELF-EMF as a physical stressor.

ELF-EMF stimulation and oxidative stress

Oxidative stress derives from two primary sources: 1) chronic ROS creation that is generated from the mitochondrial electron transport chain during normal cellular function; 2) high levels of acute ROS generation resulting from nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, particularly associated with the activation of the CNS immune system (Barja, 1998). In both circumstances, oxidative stress comes up when an imbalance between ROS production and clearance of radical species occurs.

ROS have been implicated as second messengers that activate protein kinase cascades, although the means by which ROS regulate signal transduction remains unclear. ROS release and cytokine production, such as IL-1β, are common cell activation markers in immune relevant cells. ROS is involved in the activation of IL-1β signal transduction pathway (Li and Engelhardt, 2006). To neutralize the detrimental effects of ROS, cells have evolved a hierarchy of sophisticated antioxidant response mechanisms regulated by NF-E2-related factor 2 (Nrf2) transcription factor (Tasset et al., 2010).

Environmental factors including EMFs, stressors or diseases that augment the former or lower the latter can amplify and drive the process. Thus, in practical terms, oxidative stress is determined by excessive exposure to oxidant molecules when there is insufficient availability of antioxidant mechanisms, with the resulting free ROS oxidizing vulnerable cellular constituents, including proteins, nucleic acids and lipids, inducing microglial activation, inducing pro-inflammatory and suppressing anti-inflammatory cytokines and related signaling pathways and ultimately causing both synaptic and neuronal damage and dysfunction (Bonda et al., 2010). Whereas most environmental electromagnetic radiations cause oxidative stress in the brain (Sahin and Gumuslu, 2007), ELF-EMF seems to have an antioxidant and neuroprotective effect (Medina and Tunez, 2010).

As shown by Tunez et al. (2006), ELF-EMF induces the antioxidant pathway Nrf2, which is closely associated with its protective effect against neurotoxicity induced by 3-nitropropionic acid (3-NP) (Tunez et al., 2006). This effect may be due to the induction of Nrf2, increasing its concentration in the nucleus as a result, at least in part, on its translocation from the cytoplasm to the nucleus. These changes in antioxidant systems were associated with a reduction of cell and oxidative damage biomarkers. In fact given that Nrf2 regulates the expression of antioxidant protein systems, its decrease may

plausibly be related to a reduction in antioxidant system levels. Thus, the depletion of Nrf2 showed that 3-NP induced a significant decrease in antioxidant enzyme activity in the striatum and an intense depletion of glutathione levels. This was accompanied by clear and intense oxidative damage characterized by lipid and protein oxidation, an increase in cell death and damage markers and neuronal loss. Thus, the reduction in Nrf2 in both cytoplasm and nucleus may have been due to significant cell loss induced by 3-NP (Tunez et al., 2006).

Animal studies have demonstrated that ELF-EMF exposure, in the form of TMS (60 Hz, 0.7 mT) applied to rats for 2 hours twice daily, can be neuroprotective (Tunez et al., 2006; Tasset et al., 2012). Administered prior to and after a toxic insult to the brain, for example in the systemic injection of 3-nitropropionic acid to induce an animal model of Huntington's disease (Tunez and Santamaria, 2009), ELF-EMF can mitigate oxidative damage, elevate neurotrophic protein levels in brain and potentially augment neurogenesis (Arias-Carrion et al., 2004).

EMF 1.0 mT exposure of mouse macrophages showed a significant increase in extracellular IL-1b release after only 4 hours of exposure, which was continuously increased after 12–24 hours of exposure. This data suggests that EMF stimulation is able to increase cytokines in murine macrophages. Cossarizza and colleagues described the increased release of IL-2, IL-1, and IL-6 in peritoneal lymphocytes after long-term exposure to ELF-EMF (Cossarizza et al., 1989). On the other hand, investigation on cytokine production by Pessina et al. showed no effects after EMF on peritoneal blood cells (Pessina and Aldinucci, 1998).

Beyond these results, such studies reiterate the importance that the cellular effects of ELF-EMFs depend, in a large part, on their intensity and exposure time, as well as on the phenotype of the cellular target and interactions with intracellular structures. The level and timing of exposure can potentially be scheduled to optimize endogenous compensatory mechanisms following an adverse reaction.

ELF-EMF effects on pro-inflammatory chemokines

Chemokines are produced by a variety of cells including monocytes, T lymphocytes, neutrophils, fibroblasts, endothelial cells and epithelial cells (Murdoch and Finn, 2000). Chemokines play a relevant role in inflammatory events, such as trans-endothelial migration and accumulation of leucocytes at the site of damage. In addition, they modulate a number of biological responses, including enzyme secretion, cellular adhesion, cytotoxicity, T-cell activation and tissue regeneration (Zlotnik and Yoshie, 2000).

Since their discovery, chemokines have emerged as important regulators of leukocyte trafficking, and MCP-1, one of the best-studied chemokines, is known to exert multiple effects on target cells, such as increased cytosolic calcium levels, superoxide anion production, lysosomal enzyme release, production of anti-inflammatory cytokines and adhesion molecules in monocytes. MCP-1 is involved in the induction of polarized type Th2 responses and in the enhancement of IL-4 production. A possible feedback loop for Th2 activation would be the production of IL-4 and IL-13 by Th2, which stimulates MCP-1 production and leads to further recruitment of Th2 cells (Moser and Loetscher, 2001).

The fine control of inflammatory mediator levels is critical to neuronal homeostasis and health. For example, a deficiency in neuronal TGF-β signaling promotes neurodegeneration and AD, whereas augmented TGF-β can act as an anti-inflammatory cytokine and has potential neuroprotective action in AD and following other insults to the central nervous system (Ren et al., 1997).

Studies have shown the anti-inflammatory effects of ELF-EMF *in vivo*; for instance, Selvam used a coil system emitting a 5 Hz frequency to treat rats with rheumatoid arthritis for 90 minutes, producing significant anti-exhudative effects and resulting in the restoration of normal functional parameters (Vianale et al., 2008). This anti-inflammatory effect was reported to be partially mediated through the stabilizing action of ELF-EMF on cell membranes, reflected the restoration of intracellular Ca^{2+} levels in plasma lymphocytes (Selvam et al., 2007). Other investigators have suggested that ELF-EMF can interact with cells through mechanisms that involve extracellular calcium channels (Cho et al., 1999).

Moreover, incubating mononuclear cells with an iNOS inhibitor showed a significant reduction of iNOS and an increase of MCP-1 levels, and these effects are consistent with iNOS and MCP-1 level modifications observed in mononuclear cells exposed to ELF-EMF. Selective inhibition of the NF-κB signaling pathway by ELF-EMF may be involved in the decrease of chemokine production. If so, ELF-EMF exposure, interfering with many cellular processes, may be included in the plethora of stimuli that modulate NF-κB activation (including pro-inflammatory cytokines such as tumor necrosis factor-α and IL-1β, chemokines, phorbol 12-myristate 13-acetate, growth factors, lipopolysaccharide, ultraviolet irradiation, viral infection, as well as various chemical and physical stresses) (Vianale et al., 2008).

Lymphocyte activity and electrotaxis: a possible link to ELF-EMF stimulation

Recent studies have shown that cells can directionally respond to applied electric fields, in both *in vitro* and *in vivo* settings, a phenomenon called electrotaxis. However, the exact cellular mechanisms for sensing electrical signals are still not fully well understood, and it is thus far unknown how cells recognize and respond to electric fields, although some studies have suggested that electro-migration of some cell surface receptors and ion channels in cells could be involved (Cortese et al., 2014). Directed cell migration is essential to numerous physiological processes including immune responses, wound healing, cancer metastasis and neuron guidance (Kubes, 2002). Normal blood lymphocytes and monocytes respond to a steady electric field in Transwell assays. All lymphocyte subsets, including naive and memory $CD4^+$, $CD8^+$ T cells and B cells migrated toward the cathode. Electrotaxisis highly directional and the uniform migration of circulating lymphocytes suggests that other leukocyte subsets (*e.g.*, tissue memory cells) may undergo electrotaxis as well.

Lymphocytes respond to electric fields with activation of Erk-kinases and Akt, which are involved in chemo-attractant

receptor signaling and in electrotactic signaling in other cells (Sotsios et al., 1999; Zhao et al., 2006). Activation of these pathways suggests that electrotaxis and chemotaxis engage common intracellular cell motility programs in responding lymphocytes. In fact, electric field exposure induces Erk1/2 and Akt activation in lymphocytes, consistent with the activation of the MAPK and PI3K signaling pathways implicated in coordinated cell motility. Furthermore, it has been proven that an applied electric field induced the electrotactic migration of endogenous lymphocytes to mouse skin (Lin et al., 2008). These data thus define electrotaxis andpotentially present an additional mechanism for the control of lymphocyte and monocyte migration.

ELF-EMFs can either inhibit or stimulate lymphocyte activity as a function not only of the exposure (Petrini et al., 1990), but also of the biological conditions to the cells are exposed, with mitogen-activated cells being more responsive than resting cells (Conti et al., 1986). To explain this ambivalence of the effects of ELF magnetic fields on the immune system, Marino and colleagues have presented the hypothesis that the biological effects of ELF magnetic fields are governed by non-linear laws, and that deterministic responses may therefore occur that are both real and inconsistent, thereby yielding two conflicting types of results (Marino et al., 2000). A particular role in the interaction of ELF-EMFs with lymphocytes seems to be played by the mobilization of intracellular Ca^{2+} from the calciosomes and of extracellular Ca^{2+} through the membrane channels (Conti et al., 1985). The action of ELF-EMFs on lymphoid cells, however, can also be exerted on the functions of the plasma membrane: the duration of the ligand-receptor bond (Chiabrera et al., 1984), the clustering of membrane proteins (Bersani et al., 1997), the activity of enzymatic macro-molecules (Lindstrom et al., 2001), and the active ion pumps (Ca^{2+} ATPase and $Na^{+}K^{+}$ ATPase).

Conclusions

Several studies have shown that ELF-EMF exposure is able to activate primary monocytes and macrophages from different species and also in cell lines. This activation potential is comparable to the activation by certain chemicals resulting in physiologically relevant cellular responses.

In the past, several findings have demonstrated the efficacy of pulsed ELF-EMFs of a few mT in alleviating the symptoms of MS through their action on synaptic neurotransmission and autoimmunity (by determining cell membrane changes in plaques).

Moreover, ELF-EMF exposure contributes to a general activation of macrophages, resulting in changes of numerous immunological reactions, such as increased ROS formation, in an enhanced phagocytic activity, and in an increased IL-1β release. Therefore, we can deduce that EMFs activate physiological functions of immune cells. However, the underlying mechanisms of interaction between EMF and immune system are still to be completely understood and need further studies at the molecular level.

Animal studies have demonstrated that ELF-EMF exposure, in the form of transcranial magnetic stimulation (60 Hz, 0.7 mT) applied to rats for 2 hours twice daily, has been seen to be neuroprotective (Sahin and Gumuslu, 2007; Medina and Tunez, 2010).

The effects of low flux density magnetic fields are exerted on altered functional states, in the sense of hyper- or hypo-function, rather than on normal functional states. The neurophysiological interpretation is that neurotransmission is favored at various sites: partially synapses, the cerebellum, and interhemisphere transcallosal connections, an idea which is strongly supported by the rapid regression seen in certain symptoms in patients with MS (Sandyk, 1995b). Based on all these evidences such effect could be attributed to the correction of perturbations of synaptic conductivity and immunomodulation (Bistolfi, 2007), resulting in clinical therapeutic effect as observed in neurodegenerative disorders such as AD (Mruthinti et al., 2006; Attems and Jellinger, 2014).

However, so far there is still no general agreement on the exact biological effect elicited by EMFs on the physical mechanisms that may be behind their interaction with biological systems. Of course the biological effects of EMFs are dependent on frequency, amplitude, timing and length of exposure, but are also related to intrinsic susceptibility and responsiveness of different cell types (Tenuzzo et al., 2006). Level and timing of exposure can be potentially scheduled to optimize endogenous compensatory mechanisms following an adverse challenge.

In the light of results reviewed here, we conclude that there is growing evidence of the potential role of EMFs in biological modulation of autoimmunity, immune functions and oxidative stress. As a consequence, the hypothesis that ELF-EMFs explicit their therapeutic effect through modulation of immune relevant cells is of clear interest, in particular in neurodegenerative diseases.

It is notable to underline that the effects of ELF-EMFs are not unique as they depend on their intensity, exposure time and cellular targets; further efforts towards more scheduled and well defined level and timing of exposure should be warranted.

Hence, it is necessary to proceed with substantial research on this issue, paying particular attention to the choice of the appropriate biological model and controlled experimental conditions.

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References

Aktan F (2004) iNOS-mediated nitric oxide production and its regulation. Life Sci 75:639-653.

Arias-Carrion O, Verdugo-Diaz L, Feria-Velasco A, Millan-Aldaco D, Gutierrez AA, Hernandez-Cruz A, Drucker-Colin R (2004) Neurogenesis in the subventricular zone following transcranial magnetic field stimulation and nigrostriatal lesions. J Neurosci Res 78:16-28.

Attems J, Jellinger KA (2014) The overlap between vascular disease and Alzheimer's disease--lessons from pathology. BMC Med 12:206.

Azanza MJ, del Moral A (1994) Cell membrane biochemistry and neurobiological approach to biomagnetism. Prog Neurobiol 44:517-601.
Barja G (1998) Mitochondrial free radical production and aging in mammals and birds. Ann N Y Acad Sci 854:224-238.
Baureus Koch CL, Sommarin M, Persson BR, Salford LG, Eberhardt JL (2003) Interaction between weak low frequency magnetic fields and cell membranes. Bioelectromagnetics 24:395-402.
Beere HM (2004) "The stress of dying": the role of heat shock proteins in the regulation of apoptosis. J Cell Sci 117:2641-2651.
Bennett WR (1995) Electromagnetic fields and power lines. Sci Am 2:68-77.
Bersani F, Marinelli F, Ognibene A, Matteucci A, Cecchi S, Santi S, Squarzoni S, Maraldi NM (1997) Intramembrane protein distribution in cell cultures is affected by 50 Hz pulsed magnetic fields. Bioelectromagnetics 18:463-469.
Bistolfi F (2002) Are microvilli and cilia sensors of electromagnetic fields? Physica Medica XVIII: 85-94.
Bistolfi F (2007) Extremely low-frequency pulsed magnetic fields and multiple sclerosis: effects on neurotransmission alone or also on immunomodulation? Building a working hypothesis. Neuroradiol J 20:676-693.
Biswas SK, Sodhi A, Paul S (2001) Regulation of nitric oxide production by murine peritoneal macrophages treated in vitro with chemokine monocyte chemoattractant protein 1. Nitric Oxide 5:566-579.
Boggio PS, Ferrucci R, Mameli F, Martins D, Martins O, Vergari M, Tadini L, Scarpini E, Fregni F, Priori A (2012) Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease. Brain Stimul 5:223-230.
Bonda DJ, Wang X, Perry G, Nunomura A, Tabaton M, Zhu X, Smith MA (2010) Oxidative stress in Alzheimer disease: a possibility for prevention. Neuropharmacology 59:290-294.
Bossy-Wetzel E, Schwarzenbacher R, Lipton SA (2004) Molecular pathways to neurodegeneration. Nat Med 10 Suppl:S2-9.
Bracken TD, Patterson RM (1996) Variability and consistency of electric and magnetic field occupational exposure measurements. J Expo Anal Environ Epidemiol 6:355-374.
Chiabrera A, Grattarola M, Viviani R (1984) Interaction between electromagnetic fields and cells: microelectrophoretic effect on ligands and surface receptors. Bioelectromagnetics 5:173-191.
Cho MR, Thatte HS, Silvia MT, Golan DE (1999) Transmembrane calcium influx induced by ac electric fields. FASEB J 13:677-683.
Conti P, Gigante GE, Cifone MG, Alesse E, Fieschi C (1985) Effect of electromagnetic field on two calcium dependent biological systems. J Bioelectr 4:227-236.
Conti P, Gigante GE, Cifone MG, Alesse E, Fieschi C, Bologna M, Angeletti PU (1986) Mitogen dose-dependent effect of weak pulsed electromagnetic field on lymphocyte blastogenesis. FEBS Lett 199:130-134.
Cortese B, Palama IE, D'Amone S, Gigli G (2014) Influence of electrotaxis on cell behaviour. Integr Biol 6:817-830.
Cossarizza A, Monti D, Bersani F, Paganelli R, Montagnani G, Cadossi R, Cantini M, Franceschi C (1989) Extremely low frequency pulsed electromagnetic fields increase interleukin-2 (IL-2) utilization and IL-2 receptor expression in mitogen-stimulated human lymphocytes from old subjects. FEBS Lett 248:141-144.
Cossarizza A, Angioni S, Petraglia F, Genazzani AR, Monti D, Capri M, Bersani F, Cadossi R, Franceschi C (1993) Exposure to low frequency pulsed electromagnetic fields increases interleukin-1 and interleukin-6 production by human peripheral blood mononuclear cells. Exp Cell Res 204:385-387.
D'Andrea MR (2003) Evidence linking neuronal cell death to autoimmunity in Alzheimer's disease. Brain Res 982:19-30.
D'Andrea MR (2005) Add Alzheimer's disease to the list of autoimmune diseases. Med Hypotheses 64:458-463.
Desai A, Miller MJ, Huang X, Warren JS (2003) Nitric oxide modulates MCP-1 expression in endothelial cells: implications for the pathogenesis of pulmonary granulomatous vasculitis. Inflammation 27:213-223.
Frahm J, Lantow M, Lupke M, Weiss DG, Simko M (2006) Alteration in cellular functions in mouse macrophages after exposure to 50 Hz magnetic fields. J Cell Biochem 99:168-177.
Franzblau M, Gonzales-Portillo C, Gonzales-Portillo GS, Diamandis T, Borlongan MC, Tajiri N, Borlongan CV (2013) Vascular damage: a persisting pathology common to Alzheimer's disease and traumatic brain injury. Med Hypotheses 81:842-845.
Fregni F, Pascual-Leone A (2007) Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. Nat Clini Prac Neurol 3:383-393.
Frey AH (1993) Electromagnetic field interactions with biological systems. FASEB J 7:272-281.
Genovesi G, Paolini P, Marcellini L, Vernillo E, Salvati G, Polidori G, Ricciardi D, de Nuccio I, Re M (1996) Relationship between autoimmune thyroid disease Rand Alzheimer's disease. Panminerva Med 38:61-63.
George MS, Nahas Z, Borckardt JJ, Anderson B, Foust MJ, Burns C, Kose S, Short EB (2007) Brain stimulation for the treatment of psychiatric disorders. Curr Opin Psychiat 20:250-254; discussion 247-259.
Goodman R, Blank M, Lin H, Dai R, Khorkava O, Soo L, Weisbrot D, Henderson A (1994) Increased levels of hsp70 transcripts induced when cells are exposed to low frequency electro-magnetic fields. Bioelectrochem Bioenerg 33:115-120.
Grundler W, Kaiser F, Keilmann F, Walleczek J (1992) Mechanisms of electromagnetic interaction with cellular systems. Naturwissenschaften 79:551-559.
Guerriero F, Botarelli E, Mele G, Polo L, Zoncu D, Renati P, Sgarlata C, Rollone M, Ricevuti G, Maurizi N, Francis M, Rondanelli M, Perna S, Guido D, Mannu P (2015) An innovative intervention for the treatment of cognitive impairment-Emisymmetric bilateral stimulation improves cognitive functions in Alzheimer's disease and mild cognitive impairment: an open-label study. Neuropsychiatr Dis Treat 11:2391-2404.
Hakansson N, Gustavsson P, Johansen C, Floderus B (2003) Neurodegenerative diseases in welders and other workers exposed to high levels of magnetic fields. Epidemiology 14:420-426; discussion 427-428.
Johansen C (2004) Electromagnetic fields and health effects--epidemiologic studies of cancer, diseases of the central nervous system and arrhythmia-related heart disease. Scand J Work Environ Health 30 Suppl 1:1-30.
Karabakhtsian R, Broude N, Shalts N, Kochlatyi S, Goodman R, Henderson AS (1994) Calcium is necessary in the cell response to EM fields. FEBS Lett 349:1-6.
Kawczyk-Krupka A, Sieron A, Shani J, Czuba ZP, Krol W (2002) Biological effects of extremely low-frequency magnetic fields on stumlated macrophages J774.2 in cell culture. Electromagn Biol Med 21:141-153.
Klostergaard J, Leroux ME, Hung MC (1991) Cellular models of macrophage tumoricidal effector mechanisms in vitro. Characterization of cytolytic responses to tumor necrosis factor and nitric oxide pathways in vitro. J Immunol 147:2802-2808.
Kubes P (2002) The complexities of leukocyte recruitment. Semin Immunol 14:65-72.
Laskin DL, Laskin JD (2001) Role of macrophages and inflammatory mediators in chemically induced toxicity. Toxicology 160:111-118.
Laskin DL, Laskin JD, Weinstein IB, Carchman RA (1980) Modulation of phagocytosis by tumor promoters and epidermal growth factor in normal and transformed macrophages. Cancer Res 40:1028-1035.
Lassmann H, Bruck W, Lucchinetti CF (2007) The immunopathology of multiple sclerosis: an overview. Brain Pathol 17:210-218.
Lee HG, Zhu X, Castellani RJ, Nunomura A, Perry G, Smith MA (2007) Amyloid-beta in Alzheimer disease: the null versus the alternate hypotheses. J Pharmacol Exp Ther 321:823-829.
Li Q, Engelhardt JF (2006) Interleukin-1beta induction of NFkappaB is partially regulated by H2O2-mediated activation of NFkappaB-inducing kinase. J Biol Chem 281:1495-1505.
Lin F, Baldessari F, Gyenge CC, Sato T, Chambers RD, Santiago JG, Butcher EC (2008) Lymphocyte electrotaxis in vitro and in vivo. J Immunol 181:2465-2471.
Lindstrom E, Still M, Mattsson MO, Mild KH, Luben RA (2001) ELF magnetic fields initiate protein tyrosine phosphorylation of the T cell receptor complex. Bioelectrochemistry (Amsterdam, Netherlands) 53:73-78.

Marino AA, Wolcott RM, Chervenak R, Jourd'Heuil F, Nilsen E, Frilot C, 2nd (2000) Nonlinear response of the immune system to power-frequency magnetic fields. Am J Physiol Regul Integr Comp Physiol 279:R761-768.
Marinozzi G, Benedetto A, Brandimarte B, Ripani M, Carpano S, Camporiondo MP (1982) Effetti dei campi magnetici pulsanti su colture cellulari. Giorn Ital Oncol 2:87-100.
Matthews G, Gersdorff H (1996) Calcium dependence of neurotransmitter release. Semin Neurosci 8:329-334.
Medina FJ, Tunez I (2010) Huntington's disease: the value of transcranial meganetic stimulation. Curr Med Chem 17:2482-2491.
Moreno-Gonzalez I, Soto C (2011) Misfolded protein aggregates: mechanisms, structures and potential for disease transmission. Semin Cell Dev Biol 22:482-487.
Moser B, Loetscher P (2001) Lymphocyte traffic control by chemokines. Nat Immunol 2:123-128.
Mruthinti S, Schade RF, Harrell DU, Gulati NK, Swamy-Mruthinti S, Lee GP, Buccafusco JJ (2006) Autoimmunity in Alzheimer's disease as evidenced by plasma immunoreactivity against RAGE and Abeta42: complication of diabetes. Curr Alzheimer Res 3:229-235.
Murdoch C, Finn A (2000) Chemokine receptors and their role in inflammation and infectious diseases. Blood 95:3032-3043.
Onodera H, Jin Z, Chida S, Suzuki Y, Tago H, Itoyama Y (2003) Effects of 10-T static magnetic field on human peripheral blood immune cells. Radiat Res 159:775-779.
Panagopoulos DJ, Margaritis LH (2010) The identification of an intensity 'window' on the bioeffects of mobile telephony radiation. Int J Radiat Biol 86:358-366.
Parmentier S, Bohme GA, Lerouet D, Damour D, Stutzmann JM, Margaill I, Plotkine M (1999) Selective inhibition of inducible nitric oxide synthase prevents ischaemic brain injury. Br J Pharmacol 127:546-552.
Pessina GP, Aldinucci C (1998) Pulsed electromagnetic fields enhance the induction of cytokines by peripheral blood mononuclear cells challenged with phytohemagglutinin. Bioelectromagnetics 19:445-451.
Petrini M, Polidori R, Ambrogi F (1990) Effects of different low-frequency electro-magnetic fields on lymphocyte activation: at which cellular level? J Bioelectr 9:159-166.
Polla BS, Kantengwa S, Francois D, Salvioli S, Franceschi C, Marsac C, Cossarizza A (1996) Mitochondria are selective targets for the protective effects of heat shock against oxidative injury. Proc Natl Acad Sci U S A 93:6458-6463.
Ren RF, Hawver DB, Kim RS, Flanders KC (1997) Transforming growth factor-beta protects human hNT cells from degeneration induced by beta-amyloid peptide: involvement of the TGF-beta type II receptor. Brain Res Mol Brain Res 48:315-322.
Rhodin JA, Thomas T (2001) A vascular connection to Alzheimer's disease. Microcirculation 8:207-220.
Richards TL, Lappin MS, Lawrie FW, Stegbauer KC (1998) Bioelectromagnetic applications for multiple sclerosis. Phys Med Rehabil Clin N Am 9:659-674.
Ridding MC, Rothwell JC (2007) Is there a future for therapeutic use of transcranial magnetic stimulation? Nat Rev Neurosci 8:559-567.
Rollwitz J, Lupke M, Simko M (2004) Fifty-hertz magnetic fields induce free radical formation in mouse bone marrow-derived promonocytes and macrophages. Biochim Biophys Acta 1674:231-238.
Rosen AD (1992) Magnetic field influence on acetylcholine release at the neuromuscular junction. Am J Physiol 262:C1418-1422.
Sahin E, Gumuslu S (2007) Immobilization stress in rat tissues: alterations in protein oxidation, lipid peroxidation and antioxidant defense system. Comp Biochem Physiol C Toxicol Pharmacol 144:342-347.
Sandyk R (1992) Successful treatment of multiple sclerosis with magnetic fields. Int J Neurosci 66:237-250.
Sandyk R (1995a) Long term beneficial effects of weak electromagnetic fields in multiple sclerosis. Int J Neurosci 83:45-57.
Sandyk R (1995b) Chronic relapsing multiple sclerosis: a case of rapid recovery by application of weak electromagnetic fields. Int J Neurosci 82:223-242.
Sandyk R (1997) Treatment with electromagnetic fields reverses the long-term clinical course of a patient with chronic progressive multiple sclerosis. Int J Neurosci 90:177-185.
Sandyk R, Iacono RP (1993) Resolution of longstanding symptoms of multiple sclerosis by application of picoTesla range magnetic fields. Int J Neurosci 70:255-269.
Sandyk R, Iacono RP (1994) Multiple sclerosis: improvement of visuoperceptive functions by picoTesla range magnetic fields. Int J Neurosci 74:177-189.
Sandyk R, Dann LC (1995) Resolution of Lhermitte's sign in multiple sclerosis by treatment with weak electromagnetic fields. Int J Neurosci 81:215-224.
Selvam R, Ganesan K, Narayana Raju KV, Gangadharan AC, Manohar BM, Puvanakrishnan R (2007) Low frequency and low intensity pulsed electromagnetic field exerts its antiinflammatory effect through restoration of plasma membrane calcium ATPase activity. Life Sci 80:2403-2410.
Simko M, Mattsson MO (2004) Extremely low frequency electromagnetic fields as effectors of cellular responses in vitro: possible immune cell activation. J Cell Biochem 93:83-92.
Sotsios Y, Whittaker GC, Westwick J, Ward SG (1999) The CXC chemokine stromal cell-derived factor activates a Gi-coupled phosphoinositide 3-kinase in T lymphocytes. J Immunol 163:5954-5963.
Tasset I, Medina FJ, Jimena I, Aguera E, Gascon F, Feijoo M, Sanchez-Lopez F, Luque E, Pena J, Drucker-Colin R, Tunez I (2012) Neuroprotective effects of extremely low-frequency electromagnetic fields on a Huntington's disease rat model: effects on neurotrophic factors and neuronal density. Neuroscience 209:54-63.
Tasset I, Perez-De La Cruz V, Elinos-Calderon D, Carrillo-Mora P, Gonzalez-Herrera IG, Luna-Lopez A, Konigsberg M, Pedraza-Chaverri J, Maldonado PD, Ali SF, Tunez I, Santamaria A (2010) Protective effect of tert-butylhydroquinone on the quinolinic-acid-induced toxicity in rat striatal slices: role of the Nrf2-antioxidant response element pathway. Neurosignals 18:24-31.
Tenuzzo B, Chionna A, Panzarini E, Lanubile R, Tarantino P, Di Jeso B, Dwikat M, Dini L (2006) Biological effects of 6 mT static magnetic fields: a comparative study in different cell types. Bioelectromagnetics 27:560-577.
Thomas T, Thomas G, McLendon C, Sutton T, Mullan M (1996) beta-Amyloid-mediated vasoactivity and vascular endothelial damage. Nature 380:168-171.
Tintut Y, Patel J, Territo M, Saini T, Parhami F, Demer LL (2002) Monocyte/macrophage regulation of vascular calcification in vitro. Circulation 105:650-655.
Tokalov SV, Gutzeit HO (2004) Weak electromagnetic fields (50 Hz) elicit a stress response in human cells. Environ Res 94:145-151.
Tunez I, Santamaria A (2009) Model of Huntington's disease induced with 3-nitropropionic acid. Rev Neurol 48:430-434.
Tunez I, Drucker-Colin R, Jimena I, Medina FJ, Munoz Mdel C, Pena J, Montilla P (2006) Transcranial magnetic stimulation attenuates cell loss and oxidative damage in the striatum induced in the 3-nitropropionic model of Huntington's disease. J Neurochem 97:619-630.
Tweedie D, Sambamurti K, Greig NH (2007) TNF-alpha inhibition as a treatment strategy for neurodegenerative disorders: new drug candidates and targets. Curr Alzheimer Res 4:378-385.
Vianale G, Reale M, Amerio P, Stefanachi M, Di Luzio S, Muraro R (2008) Extremely low frequency electromagnetic field enhances human keratinocyte cell growth and decreases proinflammatory chemokine production. Br J Dermatol 158:1189-1196.
von Bernhardi R, Eugenin J (2012) Alzheimer's disease: redox dysregulation as a common denominator for diverse pathogenic mechanisms. Antioxid Redox Signal 16:974-1031.
Wardlaw JM, Sandercock PA, Dennis MS, Starr J (2003) Is breakdown of the blood-brain barrier responsible for lacunar stroke, leukoaraiosis, and dementia? Stroke 34:806-812.
Zhao M, Song B, Pu J, Wada T, Reid B, Tai G, Wang F, Guo A, Walczysko P, Gu Y, Sasaki T, Suzuki A, Forrester JV, Bourne HR, Devreotes PN, McCaig CD, Penninger JM (2006) Electrical signals control wound healing through phosphatidylinositol-3-OH kinase-gamma and PTEN. Nature 442:457-460.
Zlotnik A, Yoshie O (2000) Chemokines: a new classification system and their role in immunity. Immunity 12:121-127.