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The Effects of Electromagnetic Fields on Human Health: Recent Advances and Future

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Abstract

The potential of electromagnetic fields (EMFs) for disease treatment and health enhancement has been actively pursued over the recent decades. This review first provides a general introduction about natural EMFs and related biological effects. Then the recent progress on the EMF treatment of some common diseases (such as cancer, diabetes, wound healing and neurological diseases, *etc.*) has been carefully reviewed and summarized. Yet, the blindness on the selection of therapeutic EMF parameters still hinders the broad ap-plication of EMF therapy. Moreover, the unclear mechanism of EMF function and poor reproducibility of experimental results also remain big challenges in the field of bioelectromagnetics. Bionics is a useful methodology that gains inspiration from nature to serve human life and industry. We have discussed the feasibility of applying bionic approach on the selection of therapeutic EMFs, which is based on the findings of natural EMFs. Finally, we advocate that the detailed information of EMFs and biological samples should be thoroughly rec-orded in future research and reported in publications. In addition, the publication of studies with negative results should also be allowed.

Keywords: electromagnetic fields, human health, disease treatment, health enhancement, bio-inspired electromagnetic fields

1. Introduction

The effects of electromagnetic fields (EMFs) on human health has gained extensive attentions over the recent decades. Although some cautious concerns exist for the safe use of EMFs[1], more research has been conducted to tap the therapeutic potential of EMFs for certain diseases. In fact, EMF treatment has achieved desirable therapeutic effects in many fields such as cancer, diabetes,

neural diseases, wound healing and so on. However, some challenges remain in the field of EMF therapy, which hinder the clinical application of EMFs. On one hand, the selection of EMFs is still a blind test without defined and widely accepted mechanism. On the other hand, some results of biological experiments with EMFs are conflicting to each other. Given the considerable amounts of researches and the controversial results on the effects of EMFs on health conditions of humans or animals, a general review with a broader coverage is needed to summarize the recent advances and to point out possible future directions.

From static magnetic field to visible light, non-ionizing radiation has a very broad spectrum. In the research field of bioelectromagnetics, the frequency of EMFs could be roughly divided into four categories[2] (Fig. 1): static (f = 0 Hz), Extremely Low Frequency (ELF, 0 Hz$<f\leq$ 300 Hz), Intermediate Frequency (IF, 300 Hz$<f\leq$ 10 kHz) and Radio Frequency (RF, 10 kHz$<f\leq$ 300 GHz). Based on the studies of EMF therapy we have analyzed, it is found that most of the EMF frequencies used in treatments are within the ELF range. Interestingly, many natural EMF frequencies also belong to the ELF range, such as: geomagnetic fluctuations[3], Schumann resonance[4], brain waves[5] and cell pulsations[6], *etc.* Such a coincidence raises an intriguing question whether the methodology of bionics could provide more guidance on the choice of therapeutic EMF parameters. Indeed, there are some studies to support this hypothesis[7, 8].

Herein, we first introduce some natural forms of EMFs, mainly focusing on earth electromagnetic envi-ronment and human electromagnetic emission. It is worth noting that human body can not only emit EMFs, but also be affected by external EMFs. Then, we have reviewed recent progress on the application of EMFs in the treatment of various diseases, including: cancer, diabetes, neural diseases, immune diseases, and so on. Two possible mechanisms of bioelectromagnetic effects, radical-pair theory and biochemical thermodynamic model, are also summarized in details. Finally, according to the scope of literatures discussed in this review, we have pointed out the main problems of EMF therapy and proposed the possible future directions, particularly of a bio-inspired approach.

2. Electromagnetic fields in nature

2.1 Earth electromagnetic environment

2.1.1 Geomagnetic field (GMF)

The earth is a huge magnet with the geomagnetic north pole near the geographic south pole and the geo-magnetic south pole near the geographic north pole. The intensity of the GMF on the Earth's surface varies from 20 μT to 70 μT[9] (Fig. 2). Creatures on the earth survive and evolve under the envelope of GMF, so some animals have developed GMF-dependent navigation[10–14] or orientation[15–19] systems. The disturbance of GMF, often caused by the solar wind, may yield adverse effects on the activity and health of animals on the earth[20,21]. It is found that geomagnetic

activity may suppress the secretion of melatonin *via* a possible mechanism of de-synchronized biological rhythms[22].

2.1.2 Schumann Resonance (SR)

Schumann Resonance (SR), first observed and proposed by Schumann, has been well investigated[23,24]. The atmosphere on the earth separates the land from the ionosphere, forming a huge natural resonant cavity. Schumann resonance is a global electromagnetic re-sonance generated in this cavity by tropical thunders-torms[25]. It consists of a fundamental frequency about 7.8 Hz and several resonant peaks typically at 14 Hz, 20 Hz, 26 Hz, 33 Hz, 39 Hz, 45 Hz, and 51 Hz[4]. It is commonly believed that Schumann resonance is beneficial to human health[4,8,22,26–28]. One study has demonstrated that a weak magnetic field mimicking Schumann resonance can protect the heart from oxida-tive stress and hypoxic conditions[8]. Another interesting finding is that the bands of Schumann resonance has a large overlap with human brain waves in frequency[5,29]. So Schumann resonance may function to maintain a stable biorhythm of human brain[27], which can pre-sumably be explained by the adaptation of human beings in evolution.

2.2 Human electromagnetic emission

Any accelerated motion of charged particles can generate EMFs according to Maxwell's equations. It is also true within human body. Some organs with active electrical transmission tend to produce detectable EMF signals, such as brain, heart and skeletal muscles[30]. Inside a cell, the movement of charged particles caused by the oscillation of cytoskeleton or cell membrane may also yield weak EMFs[31,32]. These EMFs generated by human body may be the medium through which external EMFs affect human health.

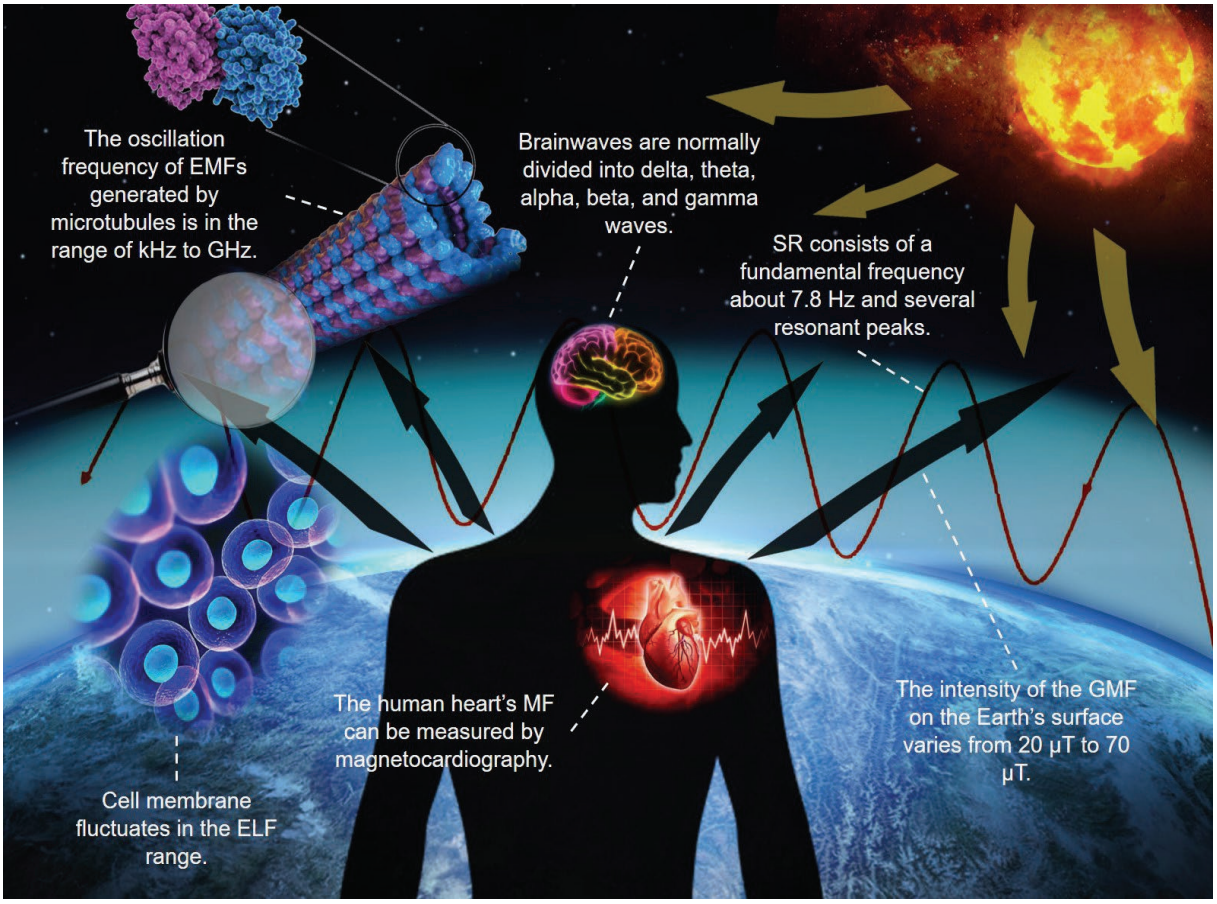

Fig.2 Illustration of the EMFs in nature, including earth electromagnetic environment and EMFs generated by human body.

2.2.1 Brainwaves

Brainwaves are rhythmic or repetitive electrical activities in the Central Neural System (CNS), first discovered and recorded by German neurologist Hans Berger[33]. Brainwaves are normally categorized into five types according to the frequency, which include delta waves (0.5 Hz – 4 Hz), theta waves (4 Hz – 8 Hz), alpha waves (8 Hz – 13 Hz), beta waves (13 Hz – 32 Hz) and gamma waves (25 Hz – 140 Hz)[5]. Although several types of waves may be coursing through the brain at any given time, there are some correlations between a certain dominant type of brain waves and a particular beha-vior[5]. Delta waves are often associated with deep, dreamless sleep. Theta waves are seen in children and adults in a drowsy, meditative or pathological state. Alpha waves are related to awake rest with closed eyes. Beta waves are associated with normal waking con-sciousness and concentration, and are suppressed during exercise. Gamma waves are linked to normal visual consciousness and rapid-eye-movement sleep. Specific electromagnetic and sonic stimuli within the range of brainwave frequency are believed to induce better sleep, to enhance memory and to treat neural disease. Fur-thermore, based on brain waves, electroencephalogram (EEG)[34] and magnetoencephalography (MEG)[35] [30,36–39] have been invented for brain function research and diagnosis of neurological diseases[5,40].

2.2.2 Cell pulsation

Microtubules, actin filaments and intermediate fi-laments constitute the cytoskeleton that provides the structural support for eukaryotic cells. Microtubules are formed by α/β tubulin dimers, which have positive and negative charges at the ends[41]. Hence, a microtubule filament can be considered as a series of tiny batteries that are stacked end-to-end. Microtubules vibrate these charged dimers constantly and thus a weak EMF will be produced[42–45]. The oscillation frequency of EMFs generated by microtubules is in the range of kHz to GHz[44]. This type of cell EMF could be essential for cell migration and mitosis.

Cell membrane is a fluctuating lipid bilayer based on the widely accepted fluid mosaic model proposed by Singer and Nicolson[46]. With the development of mi-croscopic technology, the pulsation of some types of cells have been directly observed and recorded in live cells in real time. One study has demonstrated the os-cillatory shape of suspended Swiss-3T3 fibroblast cells by a Spot-RT CCD camera. Its oscillation frequency spectrum shows a base frequency of 0.028 Hz and mul-tiple harmonic peaks within 1 Hz[47]. Another study has reported the 3D characteristics of membrane waves for fibroblasts by using an optical technique named nonin-terferometric wide-field optical profilometry (NIWOP). The amplitudes of these waves are between 130 nm to 300 nm[48]. More recently, a noninvasive cell membrane fluctuation monitoring system based on quartz nanopi-pettes has been developed. The vibrations of cervical cancer cells (Hela) and breast cancer cells (MCF-7) consist of a high frequency and a low one. The fre-quencies of Hela cells are 1 Hz and 10 Hz, and those for MCF-7 are 1 Hz and 9

Hz. The high frequency is con-sidered to represent the local membrane vibration driven by the nanopipettes electroosmotic flow, whereas the low frequency represents the natural pulsation frequency of the entire cell[6]. In line with these findings, our pre-vious work has shown that EMF of 0.5 Hz selected em-pirically can effectively inhibit the proliferation of low-density Hela cells[49]. It is probably because the frequency used in our experiment coincides with or close to the natural pulsation frequency of Hela cells and such a resonance may cause rupture or some other damages on the membrane, which requires further in-vestigation.

2.2.3 Other human electromagnetic emission

In fact, all the organs of human body can generate EMFs, such as the heart and lungs. Inside the cells, or-ganelles such as mitochondria and nucleus[50,51] may also produce EMFs, although these EMFs may be hard to be detected. In the future, the detection technology for weak electromagnetic activity in living organisms should be vigorously developed, which will promote the deep understanding of bioelectromagnetics and the ap-plication of EMF therapy.

3. Application of EMF therapy

Various applications of EMF therapy have been reported to date, which have been summarized in Fig. 3 and Table 1 – 7. Specific discussion of these applications categorized by disease or symptoms are followings.

3.1 Cancer

Cancer is one of the most common causes of death. Traditional treatments for cancer include surgical resec-tion, chemotherapy and radiation therapy. Each method has been employed in clinical applications with some level of success. However, they all have obvious limita-tions and side effects. Hence, people have been conti-nuously developing new approaches for cancer treat-ment. Among them, EMFs have long been proved to be safe and effective in treating tumors[52].

In recent years, the influence of EMFs on cancer has become a hot topic in the field of bioelectromag-netics. An early study has found that breast cancer cells (MCF-7) exhibits signs of cell damage after 3 d of daily 60 min exposure to 3 mT pulsed electromagnetic field (PEMF) at the frequency of 20 Hz, whereas normal breast cells (MCF-10) remain intact under the same EMF radiation regime. The cell damage is manifested more significantly over time[53]. In another study, a 10 min exposure to 20 mT EMF at 120 Hz given as twice per day is shown to inhibit tumor growth and reduce tumor volume in C3H/HeJ mice bearing mammary adenocarcinoma. Moreover, it is also found in this work that the angiogenesis of mammary adenocarcinoma can be inhibited by the treatment of EMF at 120 Hz[54]. Ghadirian *et al.* have reported ELF-EMF of 100 Hz and 1 mT alters the expression of proteins in breast cancer cells (BT-474) to induce apoptosis[55]. Consistently, an *in vivo* study has discovered that 4 mT EMF at 50 Hz can reduce the tumor volume of breast cancer transplanted into mice, induce apoptosis, and decrease the number of blood vessels[56].

Beside the above investigations on the effect of EMFs on breast cancer, a clinical assessment (Phase I/II study) of the efficiency and safety for very low levels of amplitude-modulated EMF treatment on advanced hepatocellular carcinoma (HCC) has been reported by Costa *et al.* [52]

Table 1 Summary of the EMF treatment on cancer

EMF form	Frequency	Intensity	Exposure protocol	Effects	Ref.
Square wave ELF-PEMF	0.5 Hz	35 μT – 70 μT	Repeated cycles of 20 min on and 20 min off for 6 d	Inhibits cell proliferation and induces apoptosis of Hela cells	[49]
EMF	7.83 Hz	0.3 mT	48 h	Inhibits the growth of B16F10 cancer cells	[7]
PEMF	20 Hz	3 mT	60 min per day for 3 d	MCF7 cells damage, but without damage for normal MCF-10 cells	[53]
EMF	6 Hz – 25 Hz		1 h one day for 5 d	Suppresses the proliferation of B16-BL6 mouse melanoma, MDA-MB-231, MDA-MB-468, BT-20, MCF-7 breast cancer, and HeLa cervical by 30-40%	[64]
SMF combined with a sine wave EMF	(1) 6 Hz (2) 16 Hz	SMF: 45 μT, EMF: 100 μT	4 d 90 min per day for 2 weeks 24 h and 72 h	Inhibits cell growth and decreases cells in the S phase (1) Breast cancer cells MDA-MB-231 (2) Biphasic pleural mesothelioma MSTO-211H cell lines Tumor volume and the number of blood vessels decreases in mice. Increases early apoptosis of cancer cells	[58]
EMF	50 Hz	4 mT	2 h per day for 3 d	Decreases cell proliferation and induces apoptosis of nephroblastoma and neuroblastoma	[56]
EMF	50 Hz	10 mT	2 h per day for 3 d	Induces DNA damage and apoptosis and inhibits of tumor growth	[175]
SMF combined with an EMF	50 Hz	5.1 mT	12 h	Enhances the antiproliferative effect of 5-FU in breast cancer cell	[174]
SMF combined with an EMF	50 Hz	5.1 mT	2 h 72 h	Enhances the killing of A2780 ovarian cancer cells by cisplatin Hela and PC-12 cells proliferation rate reduction	[173]
EMF	50 Hz	1 mT	24 h 114 h	Increases the anti-tumor effect regulated by A3ARs Heightens the killing effect of TMZ on human Glioblastoma U87 Cells	[60]
EMF	50 Hz	200 G	24 h	Decreases cell viability and Cyclin-D1 expression of human Glioblastoma Multiforme (GBM)	[61]
EMF	60 Hz	1.2 mT ± 0.1 mT			[176]
PEMF	75 Hz	1.5 mT			[188]
PEMF	100 Hz	100 G			[59]
PEMF	100 Hz	100 G ± 15 G			[57]
Semi sine wave pulse EMF	120 Hz	(1) 20 mT (2) 15 mT	(1) 10 min twice a day for 12 d (2) 10 min a day for 12 d 8 h per day for 2 d	(1) Most effective tumor growth (murine 16/C mammary adenocarcinoma cells) (2) Maximum anti-angiogenesis	[54]
SMF combined with EMF	10 MHz	SMF: 45 μT, EMF: 10 μT		Decrease the total number of fibrosarcoma HT1080 cells	[62]

Table 2 Summary of the EMF treatment on diabetes

EMF form	Frequency	Intensity	Exposure protocol	Effects	Ref.
Quasi-triangular wave PEMF	1 Hz, 10 Hz, 20 Hz, and 40 Hz	1.5 mT	1 h per day for 4 weeks	Decreases glucose levels of diabetic rats and improves hyperalgesia and ectopic pain	[92]
PEMF	15 Hz	1.46 mT	30 min per day for 6 weeks	Blood glucose levels decrease in diabetic rats	[86]
Square wave PEMF	15 Hz	2.4 mT	8 weeks	Repairs bone damage in diabetic rats	[87]
PEMF	15 Hz	Peak value: 2.0 mT, Effective value: 0.7 mT	19 d	Accelerates diabetic wound healing and improve tissue repair ability	[89]
PEMF	20 Hz	8 mT	1 h per day for 10 d	Improve the wound healing and wound tensile strength of diabetic rats Promotes proliferation of myofibroblast and wound healing in diabetic mice	[90]
Sinusoidal PEMF	25 Hz	5 mT	1 h per day for 14 d	Increases the total thickness of diabetic wound tissue	[84]
PEMF	25 Hz	10 mT	1 h per day for 14 d	Reduces blood glucose level of diabetic rats Ameliorates impairments in the relaxation response of these rings of diabetic rats Increases proliferation of pancreatic cells and insulin production	[85]
Alternating MF	50 Hz	5/8 mT	Exposure for 165 min per days for 3 weeks	Lowers blood glucose levels in mice	[77]
PEMF	50 Hz	5 mT	4 times per day for 30 min for 30 d	Reduces the glucose level of mice	[177]
Sinusoidal EMF	60 Hz	5 mT	5 d		[78]
SMF combined direct EF or alternating EF	16 kHz	100 mT	1 h per day for 28 d		[80]
2 phase square wave EMF	110 kHz	700 mG ± 20 mG	30 min one time		[79]

Table 3 Summary of the EMF treatment on neural diseases

EMF form	Frequency	Intensity	Exposure protocol	Effects	Ref.
Sinusoidal PEMF	2 Hz	0.3 mT	1 h a day, 5 d a week, for 4 weeks 30	Promotes nerve regeneration and repairs sciatic nerve injury in rats	[100]
Rectangular PEMF	10 Hz	4 mT – 5 mT	min each time	Relieves Refractory Migraine(RM)	[105]
Square wave PEMF	15 Hz	1.6 mT	8 h per day for 7 weeks	Improves diabetic peripheral neuropathy (DPN),	[99]
PEMF	20 Hz	10 mT	2 h per day for 10 d	Improves the memory and learning ability in dementia rats Promote	[104]
EMF	40 Hz	7 mT	15 min per day for 4 weeks	recovery in poststroke patients	[189]
Sinusoidal PEMF	50 Hz	1/100/500/2000 μT	2 h per day for 60 d	Improves memory retention in the adult male rats	[103]
PEMF	50 Hz	0.6 mT	5 d a week for 3 weeks	Improves the neck pain, disability, depression, anxiety, and quality of life in cervical disc herniation	[178]
				Induces hBM-MSCs nerve differentiation	
Sinusoidal EMF	50 Hz	1 mT	12 d	Promotes functional recovery following SCI	[93,94]
PEMF	50 Hz	2.5 mT	1 h per day for 14 d	Promotes the neuronal differentiation of hBM-MSCs	[144]
Sinusoidal EMF	50 Hz	1 mT	6 d	Enhances the survival of new neurons	[95]
EMF	50 Hz	1 mT	3.5 h per day for 6 d	Induces the differentiation of BMCS into nerve cells	[102]
Sinusoidal EMF	50 Hz	5 mT	1 h per day for 12 d	Promotes the neurogenesis of ischemic NPCs	[96]
				Protects the nerve of mice with ischemic stroke	
EMF	50 Hz	0.4 mT	7 d	Reduces oxidative damage and neuron loss in rats induced by 3NP	[97]
PEMF	60 Hz	10 mT	6 h per day for 14 d		[101]
Sinusoidal EMF	60 Hz	0.7 mT	2 h in the morning and 2 h in the afternoon for 21 d		[98]

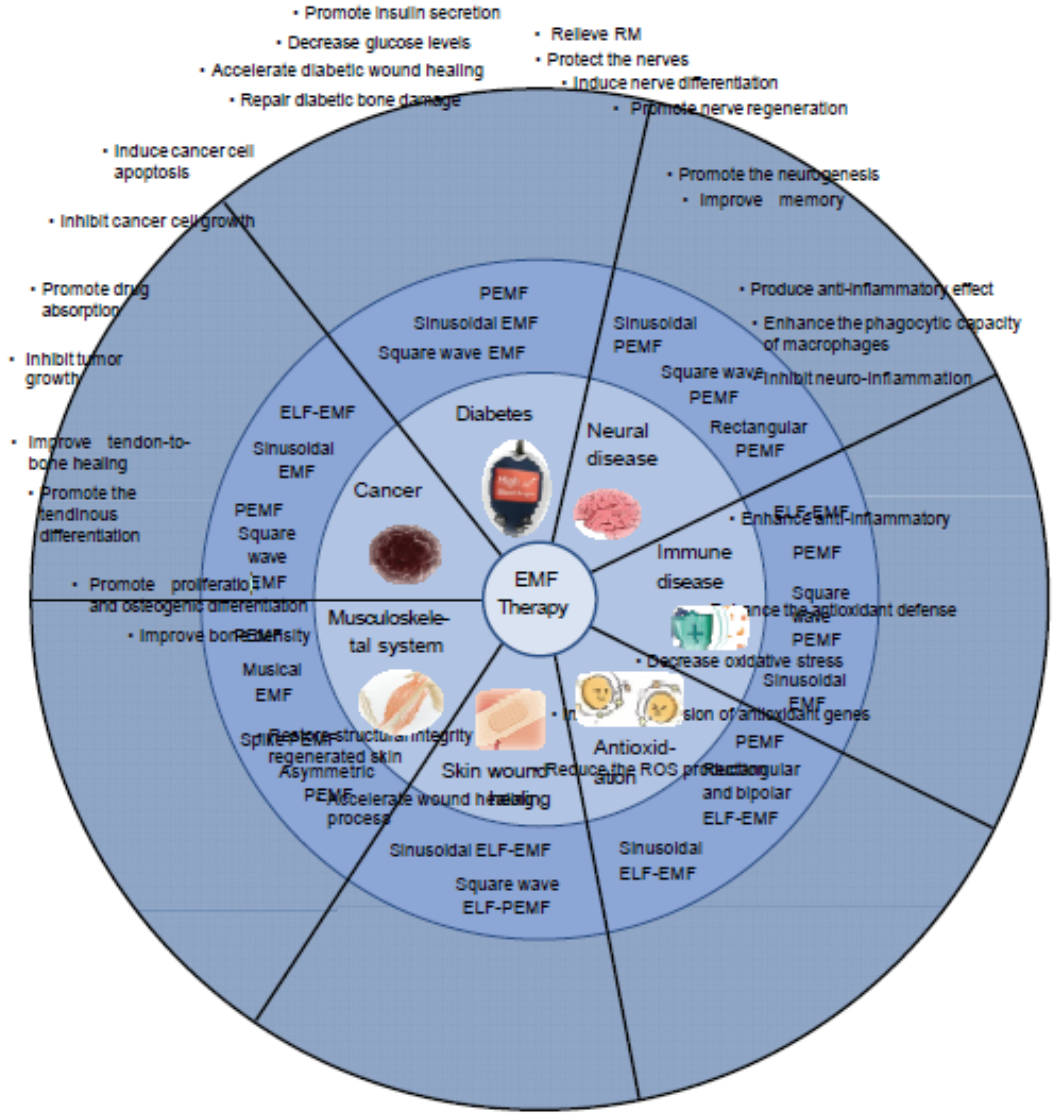

Fig. 3 Summary of applications of EMFs therapy on different diseases.

Table 5 Summary of the EMF treatment onmusculoskeletal system

EMF form	Frequency	Intensity	Exposure protocol	Effects	Ref.
Asymmetric PEMF	8 Hz	3.82 mT	40 min per day for 180 d	Improving bone density, vitamin D status, muscle strength and balance	[121]
Spike PEMF	(1) 33 Hz,	0.25 μT – 3.16 μT	10 min of 33 Hz, 20 min of 7.8 Hz for once every 2 d for three times	Promote cell proliferation accelerating closure of the wounds	[130]
PEMF	(2) 7.8 Hz 15 Hz 15 Hz 20	2 mT	2 h per day for 3 d	Enhances the repair efficiency and quality of pTi in bone defect	[129]
Rectangular wave PEMF	Hz 50 Hz 50	5 mT	2 h	Affects osteoblast proliferation and differentiation	[123]
PEMF	Hz 50 Hz 50	2 mT	6 h per day for12 d	Promote the directional osteogenic differentiation of BMSCs	[193]
PEMF	Hz 75 Hz 100	0.6 mT	90 min per day for 3 d	Promotes the proliferation and osteogenic differentiation of skull osteoblasts	[126]
PEMF	Hz 100 Hz 3.85 kHz	0.6 mT	60 min per day for 12 d	Stimulates osteogenic differentiation and maturation of rat calvarial osteoblasts	[127]
Sinusoidal EMF		1.8/3.6 mT	30 min per day for 15 d	Promotes differentiation and mineralization of osteoblasts	[194]
EMF		20 mT	30 min per day for 21 d	Promotes ADSCs osteogenesis differentiation in the presence of $ZnSO_4$	[195]
PEMF		1.5 mT	8 h per day for 21 d	Promotes the tendinous differentiation of UC-MSCs	[133]
Musical mod-ulated EMF		A few gauss	30 min per day for 2 weeks	Promotes cell proliferation and increase cell activity	[119]
PEMF		1 mT	4 h per day for 4 d	Promotes C2C12 myoblast proliferation	[134]
PEMF		0.5 mT	3 h per day for 16 weeks	Improves early tendon-to-bone healing	[132]

Table 6 Summary of the EMF treatment on skin wound healing

EMF form	Frequency	Intensity	Exposure protocol	Effects	Ref.
Sinusoidal EMF	12 Hz	1 mT	8 h	Speeds wound-healing process	[141]
PEMF	12 Hz	12 G	60 min for 14 times within 3 weeks	Accelerates wound healing and improve microcirculation	[196]
Sinusoidal EMF	50 Hz	1 mT	24 h	Accelerates wound healing	[140]
Square wave PEMF	50 Hz	1 mT	18 h	Speeds wound-healing process	[141]
Sinusoidal EMF	50 Hz	1 mT	72 h	Increases in keratinocyte growth Decreases proinflammatory cytokine secretion	[197]
PEMF	50 Hz	2.25 mT	15 min on days 7, 8 and 9 of cell culture	Accelerates wound healing of ESC transplantation, and restore structural integrity of regenerated skin	[198]
EMF	50 Hz	5 mT	60 min per day for 20 d	Accelerates wound repair	[137]
PEMF	75 Hz ± 2 Hz	2 mT ± 0.2 mT	10 min per day for 21 d		[199]

Table 7 Summary of the EMF treatment on antioxidative function enhancement

EMF form	Frequency	Intensity	Exposure protocol	Effects	Ref.
PEMF	16 Hz	6 μT – 282 μT	7 min per day for 5 d	Induces antioxidative defense mechanisms in hOBs	[152]
EMF	40 Hz	7 mT	15 min per day for 4 weeks (5 d a week)	Increases enzymatic antioxidant activity	[149]
Rectangular and bipolar wave EMF	40 Hz	5 mT	15 min per day for 14 d	Enhances the antioxidant defence of the body Decreases oxidative stress induced by global cerebral ischemia	[150]
EMF	50 Hz	0.5 mT	7 d	Increases expression of antioxidant genes in McF-7 cells Protects cells against oxidative damage	[147]
Sinusoidal EMF	50 Hz	0.5 mT	15 min on/15 min off for 2 h	Reduces inflammation and oxidative stress to promote functional recovery following SCI	[151]
PEMF	50 Hz	2 mT	8 h per day for 90 d 1 h per day for 14 d	Enhances antioxidant	[143]
PEMF	50 Hz	2.5 mT	2 h in the morning and 2 h in the afternoon for 8 d	Increases the MnSOD-based antioxidant protec-tion and reduced the ROS production	[144]
Sinusoidal EMF	60 Hz	0.7 mT	15 min each, repeated 3 times over 5 d	Inhibit production of ROS and protect cardiac cells	[145, 146]
Square wave PEMF	75 Hz	2 mT	44 min		[148]
EMF	0.08 Hz – 195 Hz	4560 μT			[153]

[52]

This work has demonstrated that the amplitude-modulated EMF is safe and possesses a posi-tive anticancer effect on patients with advanced HCC. Also to this end, our previous study has demonstrated that an ELF-EMF mimicking the frequency of cell pulsation has an inhibitory effect on the proliferation of Hela cells, but without observable adverse side effects on normal cells[49].

It is worth pointing out that the inhibitory effect of EMFs on malignant cells is probably frequency-dependent[57,58]. Such a frequency dependence could also be cell line specific. It has been shown that 6 Hz EMF has a better inhibitory effect on breast cancer cells (MDA-MB-231), but 16 Hz EMF is more potent for biphasic pleural mesothelioma cells (MSTO-211H)[58]. Furthermore, Tang *et al.* [7] have found that the EMFs within Schumann resonance frequency can effectively inhibit the growth of melanoma cells (B16F10).

In addition, several lines of evidence have shown that EMFs can also promote the uptake of drugs by tumor cells and enhance the efficacy of chemotherapy[59–61]. For instance, the combination of low-dose Temozolomide (TMZ), an anti-cancer agent, and 100 Hz, 100 G ELF-EMF can significantly boost the killing effect of TMZ on human glioblastoma cells (U87) and inhibit the development of tumors[59]. In another study, it has been demonstrated that 50 Hz ELF-EMF can not only make ovarian cancer cells (A2780) more sensitive to cisplatin by activating p53 pathway, but also improve drug uptake by tumor cells[61]. This implies that EMFs combined with oncology drugs may be a new approach to treat cancer in the future, lowering the re-quired dosage of therapeutic agents and thus considera-bly reducing side effects.

Moreover, combining EMF with static magnetic field (SMF) may be another option for new cancer treatment. It has been reported that fibrosarcoma cells HT1080 subjected to a 45 μT SMF combined with a 10 μT 10 MHz EMF suffers a 30% reduction in the total cell number after 2 d, compared to those with SMF alone[62].

Although it is commonly accepted that EMFs can restrain tumor development, the mechanism of its action is still elusive and has been extensively discussed. Some studies have intended to explain it by the induction of apoptosis. One work has reported that for glioblastoma cells (U87) exposed to 100 Hz 100 ± 15 G ELF-PEMF for 24 h, cell viability and cyclin-D1 expression have been decreased by 29% and 31%, respectively, with elevated p53 and caspase-3 levels[57]. Some investiga-tions try to connect EMFs with the arrest of cell cycle. For examples, there are a few reports showing that ELF-EMFs reduce cells at the S-phase of mitosis, and its inhibition is mediated by calcium flux[58,63]. However, a contradictory result exists, demonstrating that breast cancer cells (MCF-7) exposed to 50 Hz EMF for 12 h can promote cell entry into S phase and enhance the cytotoxicity of 5-fluorouracil (5-FU)[60]. Others have attempted to find particular signaling pathways for EMFs action. Buckner *et al*. have reported Thomas-EMF, a low-intensity, frequency-modulated (25 Hz – 6 Hz) EMF, can

regulate adenosine 30, 50-cyclic monophosphate (cAMP) and MAP kinase to suppress the proliferation of mouse melanoma cells (B16-BL6)[64]. Yet, another study shows that EMFs can inhibit the phosphorylation of Epidermal Growth Factor Receptor (EGFR) in cancer cells, thereby altering the actin cytoskeleton and key processes involved in cell movement[65]. Overall, a clear mechanism by which EMFs act on cancer cells remains unclear and hypothetical.

Nevertheless, some groups have managed to achieve clinical applications of EMFs in the field of cancer treatment. A group in US has developed FDA-approved devices with tumor-treating fields (TTFields), which use alternating Electric Fields (EFs) to reduce tumor growth. Since 2004, a series of clinical trials have proved the effectiveness and safety of TTFields in the treatment of glioblastoma multiforme (GBM)[66–71]. Related mechanism research indicates that TTFields can interfere the formation of mitotic spindles[72], increase the sensitivity of cancer cells to chemotherapy drugs[68], and inhibit the metastasis of tumors[73,74]. The work by this group suggests that EMFs may inhibit cancer cell proliferation through multiple pathways.

In summary, ample studies have shown that EMFs of a certain intensity and frequency can play an anti-cancer role. So EMF therapy is a justifiable option for cancer treatment, either standing alone or in combination with other therapies. However, the mechanism of action still needs to be explored and elucidated, which may help to reconcile the contradictory results reported. Meanwhile, it is also important and effort-worthy to identify specific EMF parameters effective for various types of cancers and apply them to clinical treatments.

3.2 Diabetes

Diabetes is a public health problem with rising concerns, which may caumay cause multiple complications and se multiple complications and impair life quality of patients. Currently, the treatment of diabetes mainly relies on the methods of changing lifestyle, using hypoglycemic drugs, and supplementing exogenous insulin to control or reduce blood glucose levels. As a common form of physical therapy, EMFs have long been known to have metabolic effects, and there are more and more reports on the effects of EMFs and more reports on the effects of EMFs on diabetes and glucose metabolism.

Some studies have demonstrated that certain forms of EMFs can lower blood glucose level. One group has investigated the influence of EMFs on insulin level in animals showing that EMFs can lower the glycemic activity of type I diabetic mice[75]. Another study suggests that modulated alternating Magnetic Field (MF) of 5 mT and 8 mT at 50 Hz can reduce blood glucose, total cholesterol and triglyceriOKde levels in the plasma of diabetic ratsrats[76,77]. Sakura et al. have shown that ELF-EMF at 5 mT not only increases activity and proliferation of pancreatic cells, but also promotes insulin production at high glucose concentration (100 mg·dl−1) [78]. In another study, a 700 mG 110 kHz EMF could reduce the blood glucose level of diabetic rats. Moreover, when EMF is combined with insulin, the blood glucose level can be reduced to the normal level[79]. In addition, the combination of SMF, alternating electric field and infrared irradiation can change the characteristics of cell

membrane to reduce the blood glucose level in diabetic rats[80]. So EMF therapy may be an effective approach to treat diabetes in the future.

However, the anti-diabetic mechanism of EMFs remains unclear. One work has demonstrated that ELF-EMFs can enhance insulin secretion by increasing the number of pancreatic cells[78,81]. Other studies have shown that insulin secretion of cells can be boosted when the frequency of EMFs is consistent with the inherent frequency[82,83]. Another study has reported that EMFs can lower blood glucose level by affecting the endocrine system[77]. Yet, the underlying molecular mechanism by which EMFs lower blood glucose still needs further exploration.

EMFs can also serve as adjuvant therapy for some complications caused by diabetes. For example, some earlier studies have demonstrated that PEMF (25 Hz) can promote the proliferation of myofibroblast to accelerate the early stage wound healing in diabetic rats[84,85]. A more recent study has reported that PEMF (15 Hz, 1.46 mT) can not only reduce blood glucose level of diabetic rats, but also improve the muscle strength of rats with diabetic muscle atrophy by promoting protein synthesis and inhibiting protein degradation[86]. Another study indicates that PEMF treatment can partially repair diabetes-induced bone damage and improve mechanical properties of bones in diabetic rabbits[87,88]. PEMFs can also act against osteoporosis caused by diabetes[87]. Impaired wound healing is another prominent complication of diabetic patients[89]. PEMFs have been found to accelerate wound healing and improve the mechanical properties of soft tissue in diabetic rats[89,90]. Furthermore, it has been demonstrated that PEMFs can restore the normal anti-oxidative stress function in diabetic rats by reducing oxidant levels and increasing antioxidant levels[91]. Interestingly, it has also been reported that 1.5 mT PEMF at 1 Hz, 10 Hz, 20 Hz and 40 Hz can relieve other symptoms related to diabetes, such as hyperalgesia and allodynia[92].

In brief, EMFs can not only regulate the blood glucose level of diabetic patients, but also exert a positive effect on the treatment of complications caused by diabetes. Actually, the effects on these complications are not surprising as EMFs have been shown to interfere with various biological activities as discussed below. These recent works have laid the foundation for the future clinical application of EMFs in treating diabetes and related complications.

3.3 Neural diseases

There are many kinds of neural diseases in human, which are difficult to cure due to the nature of these diseases. Fortunately, numerous studies have shown that EMFs can play a beneficial role in the treatment of neural diseases.

Alzheimer's Disease (AD) is a common neurodegenerative disease for senior people. Neural differentiation of human bone marrow-derived mesenchymal stem cells (hBM-MSCs) may provide an opportunity to restore neural function in AD patients. Some literatures have demonstrated that EMFs can induce hBM-MSCs to differentiate into neural stem cells[93–96]. One research shows that EMFs combined with drugs may enhance the repair of some brain injuries, and promote the *in vivo* differentiation of transplanted hBM-MSCs derived from *in vitro* culture[94]. Further mechanism research has found that ELF-EMFs can induce the neural differentiation of hBM-MSCs by regulating

intracellular level of Zn-metallothionein[93]. In another study, ELF-EMF (50 Hz, 0.4 mT) has been reported to effectively promote the proliferation and differentiation of neural progenitor cells (NPCs) by increasing the level of phosphorylated Akt[97]. These reports above indicate that EMFs may hold a promising measure for AD treatment by stimulating neuronal differentiation.

EMFs can also contribute to the regeneration of nerves for other neural diseases and injuries. For example, one study shows that the exposure to EMF (60 Hz, 0.7 mT) for 21 d can not only elevate the neurotrophic level and prevent the loss of striatum neurons, but also repair brain damage and improve the behavior of rats with 3-nitropropionic acid (3NP)-induced Huntington's disease[98]. Another research demonstrates that Diabetic Peripheral Neuropathy (DPN) can be repaired by PEMF therapy (15 Hz) in an animal model, suggesting that EMF may be adopted in the clinical treatment of DPN[99]. ELF-PEMF has also been reported to show regenerative effect on comminuted sciatic nerve injury[100], and protect the nerves during the recovery of ischemic stroke mice[101].

Moreover, EMFs have been used to improve memory and learning ability, the key functions of brain. A study has found an interesting phenomenon that ELF-EMF exposure can increase the survival of newborn neurons in mice by decreasing pro-apoptotic protein Bax and improving anti-apoptotic protein Bcl-2. Therefore, the memory and spatial learning ability of mice are boosted[102]. A recent report has also revealed that the exposure to ELF-EMF has a positive effect on memory[103]. Another work suggests that PEMF (20 Hz, 10 mT) exposure can improve memory and learning ability of rats with streptozotocin (STZ)-induced dementia, possibly *via* Insulin Growth Factors (IGF) signaling[104]. These reports indicate that EMFs have great potential in enhancing brain function and treating cognitive disorders.

Last but not least, EMFs have also been used to treat some less common neurological diseases. It has been reported that PEMF (10 Hz, 4 mT – 5 mT) can significantly relieve headaches in patients with Refractory Migraine (RM)[105]. Through clinical trials, Paolucciet *et al.* have found that ELF-EMF in combination with specifically designed dietary supplements can effectively improve the symptoms of carpal tunnel syndrome[106].

In short, EMFs have the potential to treat a variety of neural diseases. Actually, it is not surprising given the bioelectromagnetic nature of neural system, which has abundant rhythmic electrical signals. Current researches have provided experimental basis for the application of EMFs in boosting neural differentiation and regeneration as well as in enhancing memory and learning capabilities. Yet, more in-depth understanding of the interaction between EMFs and signaling pathways within neural system is still necessary.

3.4 Immune system

The effects of EMFs on immune system is more complicated, since both positive and negative responses of immune system subjected to EMF radiation have been reported.

Rheumatoid Arthritis (RA) is a chronic autoimmune disease that primarily affects joints, and currently there is no ideal treatment. It has been known that PEMFs can improve RA symptoms by playing an anti-inflammatory role. For example, an early study has found that PEMF can help to restore normal Ca^{2+} ion flux and Na^{+}/K^{+} balance. Hence the cell can begin the process of down-regulating inflammatory cytokines, Heat-Shock Proteins (HSPs), and proangiogenic molecules such as Vascular Endothelial Growth Factor (VEGF), making it possible for the body to rebuild healthy cartilage[107]. Another report has demonstrated that an exposure to PEMF of 5 Hz and 4 μT for 90 min could produce significant anti-exudative effect in arthritic rats and change the symptoms back to normal. Its anti-inflammatory effects may be mediated, at least in part, by stabilizing cell membrane and by restoring Ca^{2+} ATPase (PMCA) and Ca^{2+} levels on plasma membrane in lymphocytes, thereby inhibiting the biosynthesis of prostaglandin E2 (PGE2)[108]. A recent study has proved that, compared with the clinically favored immunosuppressive methods, the measure of using PEMF to regulate inflammation and immune function is relatively safer[109]. As a promising new strategy, the progress on the use of PEMFs to treat RA has been well reviewed in a recent article[110]. To sum up, PEMFs have a significant therapeutic effect on RA by down-regulating immune responses and may supplement the traditional treatments of RA in the future.

EMFs have also shown the ability to affect immune cells and factors beyond the scenario of RA. For example, one study shows that 1 mT ELF-EMF at 50 Hz can enhance the response and phagocytosis of phagocytes to infectious pathogens by up-regulating multiple factors such as Nitric Oxide (NO), cyclic guanosine monophosphate (cGMP) and HSP70[111]. Another study has found that continuous exposure to 5 Hz PEMF can reverse the downregulation of inflammatory markers, such as tumor necrosis factor (TNF-α) and nuclear factor kappa B (NFκB), and yield a trend of down-regulating TNF-α-induced protein 3 (A20) in an inflamed-cell model challenged by lipopolysaccharide. The authors suggest that the regulation of TNF-NFκB activity by PEMF may be a suitable therapy for patients with sepsis[112]. Moreover, it has been demonstrated that PEMFs are probably effective in treating chronic inflammation by mediating the expression of genes that play important anti-inflammatory roles[113]. It has also been shown that PEMFs can inhibit neuro-inflammation in N9 microglial cells by activating, at least partially, the JNK-MAPK signaling pathway[114]. Some other studies have shown the regulation of inflammation cytokines by ELF-EMFs in post-stroke patients[115,116]. The effects of ELF-EMFs on the expression and release of cytokines of innate and adaptive immune responses have been summarized in another review paper. This review has exhibited that short-term exposure to strong ELF-EMF (2 to 24 hours/day for one week) may increase the innate immune response, while long-term exposure to low-density ELF-EMF (2 to 24 hours/day for 8 years) may reduce the adaptive immune response, especially for T helper 1 (Th1) subtypes[117].

Overall, the effect of EMFs on RA is better established, whereas the influence of EMFs on the immune system in other scenarios depends on the specific EMFs used. Due to their diverse forms,

EMFs can induce distinct immune responses. Therefore, it is critical to identify EMFs with desirable therapeutic effects to guide clinical application. In the future, EMFs may afford an ideal treatment for certain immune diseases.

3.5 Musculoskeletal system

Osteoarthritis (OA) is one of the most common joint diseases. An earlier study has demonstrated that PEMF therapy is safe and effective in improving the symptoms of knee osteoarthritis in clinical trials and is more efficacious in relieving the pain in patients than placebo[118]. In another study, human OA chondrocytes have been exposed to ELF-EMF and Therapeutic Application of Musically Modulated Electromagnetic Field (TAMMEF) with variable frequencies, intensities, and waveforms for 30 min per day for 2 weeks. The results show that TAMMEF promotes cell proliferation more significantly than ELF-EMF. Furthermore, TAMMEF increases cell activity and decreases Heavily Vacuolized (HV) cell density and clustering[119]. The positive intervention of TAMMEF on OA chondrocytes provides a physical approach to the treatment of OA.

Similarly, EMF treatment of osteoporosis has also been explored. It has been demonstrated that PEMF can facilitate osteoblastogenesis, inhibit osteoclastogenesis, and enhance the activity of Bone Marrow Stem Cells (BMSCs) and osteocytes, ultimately resulting in the retention of bone mass and strength[120]. Meanwhile, another study has shown that an exposure to PEMF of 8 Hz and 3.82 mT for 40 min per day for 180 d can improve bone density, vitamin D level, muscle strength and balance in postmenopausal osteoporosis patients[121,122]. Moreover, the effect of PEMF treatment on osteoporosis is comparable to that of alendronate, a common drug used to prevent and treat osteoporosis, and can be maintained for 19 weeks after treatment[121,122]. Furthermore, several studies have shown that PEMFs can promote the proliferation and differentiation of osteoblasts, thus promoting osteogenesis[123–125]. PEMF with an amplitude of 0.6 mT at 50 Hz can significantly accelerate osteogenic differentiation and maturation of rat cranial osteoblasts by activating BMP-Smad1/5/8 pathways. The activation of these pathways is probably due to the increase of the expression level of bone morphogenetic protein receptor II (BMPRII). In other words, upregulation of BMPRII expression may magnify the effects of PEMF on osteoblast differentiation and maturation[126, 127].

The implantation of porous titanium alloys (pTi) is often used to treat osseous defects in clinical practice, but there is a risk of inadequate osseointegration[128]. It has been shown that PEMF can enhance the proliferation and pTi attachment of osteoblasts benefiting the formation of skeleton. Moreover, PEMF can promote skeletal anabolic activity through a Wnt/β-catenin signaling-involved mechanism, thereby improving osteogenesis and osseointegration of pTi[129]. So PEMF exposure combined with implanted pTi may be an effective way to treat bone defects and injuries in the future.

EMFs can not only be employed as a therapy for bone defect, but also be used as a physical treatment of muscular injuries. It has been shown that ELF-PEMFs can significantly promote cell proliferation of patellar fibroblasts and thus improve *in vitro* wound healing[130]. Another report has demonstrated that EMFs can accelerate the repair of injured tendons and ligaments in a horse model[131]. Tucker *et al.* have reported that PEMFs can enhance early tendon-to-bone healing in acute supraspinatus muscle disconnection in rats[132]. So PEMFs may be used in the clinical application of rotator cuff repairing. In another study, the authors have investigated the effect of ELF-PEMF on *in vitro* tenogenic differentiation of Mesenchymal Stem Cells (MSCs) isolated from the human umbilical cord (UC-MSCs). The results have shown that 1.5 mT PEMF at 75 Hz can elevate the tendinous differentiation of UC-MSCs[133]. PEMFs in combination with allogeneic UC-MSCs may be considered as a future therapeutic option for tendon tissue repair. Xu *et al.* have demonstrated that PEMF (100 Hz, 1 mT) is able to enhance the proliferation of myoblasts (C2C12), which may be mediated by the activation of MAPK/ERK pathway[134].

In summary, several lines of evidence have proved a positive role of EMFs on the regeneration of bone and muscular tissues. So it is widely believed that EMFs have a bright prospect in the treatment of musculoskeletal injuries and diseases.

3.6 Skin wound healing

Skin wound healing is a sophisticated process involving a series of coordinated responses including immune responses, cell migration and proliferation, angiogenesis and neuroregeneration[135]. EMFs have been proposed as a promising adjuvant therapy for skin would healing with multiple evidences from published literature.

Pesceet *et al.* have reviewed experimental studies on the role of EMFs in the expression and regulation of cytokines associated with wound healing. Although EMFs are found to increase the initial inflammatory responses, the overall effects of EMFs during the entire wound healing process is anti-inflammatory. In particular, it has been shown that EMFs can alter the cytokine production in macrophages and drive the transition from the pro-inflammatory state to anti-inflammatory state, contributing to wound healing[136]. More recently, Bai *et al.* have investigated the effects of EMF exposure on Epidermal Stem Cells (ESC) seeded in collagen scaffold in a mouse model of skin wound healing. The results show that an exposure to 5 mT EMF at 50 Hz for 60 min per day for 20 days can accelerate wound healing and restore the structural integrity of the regenerated skin[137].

Several different pathways have been proposed as the mechanisms by which EMFs promote wound healing. For instance, it has been indicated that PEMFs can reduce inflammation by regulating the calcium/calmodulin/NO pathways, stimulating the production of growth factors and affecting angiogenesis, thus accelerating wound healing[138]. Similarly, in another study, it has been hypothesized that EMFs may affect NO signal transduction, cytokine profiles, expression of growth

factors, cell migration and proliferation, regulation of MAPK/extracellular signal-regulated kinases and inflammation, thus favoring wound healing[135]. In clinical trials, Guerriero *et al.* have reported an innovative PEMF therapy, Emysimmetric Bilateral Stimulation (EBS), for the successful treatment of refractory skin ulcers in two elderly and fragile patients[139]. Moreover, Patruno *et al.* have found that the beneficial effect of ELF-EMFs on wound healing may be mediated by Akt/ERK pathway, and EMFs are able to regulate the expression of the matrix metalloproteinase 9 (MMP-9) through Akt/ERK pathway to accelerate wound healing[140]. They also discover that the positive role of ELF-EMFs in wound repair depends on the ability to regulate inflammatory mediators and to promote the proliferation and migration of keratinocytes. Costantiniet *et al.* have investigated the effects of an ELF sinusoidal electromagnetic field (ELF-SEMF) and an ELF-PEMF with an intensity of 1 mT on an oral healing model based on gingival fibroblasts. The results show that the exposure to both EMFs can promote the transition from inflammatory stage to proliferative stage of wound healing, which probably correlates with the induction of metalloproteinase 2 (MMP-2), monocyte chemoattractant protein 1 (MCP-1), and heme oxygenase 1 (HO-1)[141].

In brief, EMFs have demonstrated anti-inflammatory effects by promoting the resolution of inflammation, which can accelerate the transition to proliferative stage and wound healing. Hence, EMFs have a potential to speed up wound healing. Yet, a better-defined mechanism regarding the function of EMFs in wound healing needs further investigation.

3.7 Antioxidative function enhancement

Antioxidative defense is important for various cell functions(*i.e.* proliferation, differentiation, and apoptosis)[142]. Several groups are working to find new, non-invasive ways to elevate antioxidant levels in cells. In this context, many literatures have reported the antioxidative effects of EMFs.

The antioxidative effects of PEMFs in mice have been investigated. One study has revealed that long-term use of PEMFs can protect cells against oxidative damage compared to the group with limited exposure[143]. Similarly, a more recent study has demonstrated that ELF-PEMF (50 Hz and 2.5 mT) can accelerate functional recovery from Spinal Cord Injury (SCI) in rats by reducing inflammation and oxidative stress, and enhancing HSP70 levels[144].

Moreover, EMFs can also protect the brain and nerve cells from oxidative damage. Earlier studies have shown that ELF-EMFs can increase cytoplasm and nuclear NF-E2-related factor 2 (Nrf2) levels to mitigate the oxidative damage of nerves induced by

3-nitropropionic acid (3-NP) in an animal model of Huntington's disease[145,146]. Another recent study has suggested that the exposure to ELF-EMF can reduce oxidative stress induced by global cerebral ischemia and alleviate the possible negative effects that free radical species can cause in the brain[147]. PEMF with specific parameters (75 Hz, 2 mT and 15 min each, repeated three times over 5 d) has been

found to enhance the resistance of human neuroblastoma cells (SK-N-BE(2)) against a pro-oxidant stimulus. In this study, PEMF increases antioxidative protection and reduces the production of Reactive Oxygen Species (ROS) in response to the pro-oxidant stimulation. Such an effect appears to be associated with increased mitochondrial antioxidative function against superoxide anions[148].

In addition, it has been proven that EMFs can benefit post-stroke patients by enhancing the activity of antioxidant enzymes. For example, one clinical trial shows that ELF-EMF can significantly increase the antioxidative activity of the enzymes in stroke patients, improve the patients' functional and psychological state, and enhance the overall therapeutic effect after stroke[149]. Similarly, another study has demonstrated that after ELF-EMFs treatment, mRNA expression of catalase, superoxide dismutase, and glutathione peroxidase are obviously elevated in stroke patients, which increases the antioxidative defense of the body. So it is believed that ELF-EMF therapy can enhance the endogenous antioxidative function by increasing the expression of antioxidant enzymes at transcriptional level[150].

Indeed, there are multiple studies that are in line with the above findings. Mahmoudinasab *et al.* have investigated the effects of ELF-EMFs on the expression levels of antioxidant genes in human MCF-7 cells. Their work has found that 0.5 mT ELF-EMF at 50 Hz may promote the expression of antioxidant genes, thus improving the antioxidative defense in cells[151]. Interestingly, another study has found that single-dose exposure to ELF-PEMF can enhance the level of ROS in human osteoblast (hOBs). However, such an increase of ROS would not harm hOBs.

Instead, it would stimulate the intracellular antioxidative stress defense as a protective mechanism. As a result, repeated ELF-PEMF exposures can reduce the formation of ROS in hOBs, induce the expression of oxidative defense-related genes and up-regulate the level of antioxidant enzymes, such as superoxide dismutases (SODs), catalase (CAT), glutathione peroxidases (GPXs) and glutathione-disulfide reductase (GSR)[152]. Besides, EMF exposure can also function against oxidative stress in the scenarios of injuries. For example, EMFs can yield a protective effect on myocardial cells suffering ischemia reperfusion injury[153].

To sum up, EMFs can enhance the antioxidative capability of a body and repair the oxidative damage through a series of intracellular reactions. Therefore, it may open up a new way for clinical treatment of diseases related to oxidative damage and supplement conventional therapies to restore normal functions under oxidative stress.

4 Mechanism of bioelectromagnetic effects

The effect of EMF on a living organism, as discussed above, is often called bioelectromagnetic effect. Such an effect is normally divided into two aspects, thermal effect and nonthermal effect. Herein, we only focus on the discussion of nonthermal bioelectromagnetic effect. Several

mechanisms have been proposed to explain the nonthermal bioelectromagnetic effect, such as radical-pair mechanism[154], biochemical thermodynamic model[58], biogenic magnet mechanism[10,155] and ion oscillation model[156,157]. Among these possible mechanisms, the theories based on radical-pair and biochemical thermodynamics are more widely accepted as the explanations for the health effects of EMFs.

4.1 Radical-pair mechanism

The radical-pair mechanism, proposed in 1978, has been first used to explain the phenomena of geomagnetic navigation in animals[158]. Now, it is also used to explain the impact of EMFs on animal health. To understand the magnetoreception mechanism based on radical-pair theory, some basic concepts must be clarified first:

(1) A radical: a molecule which contains an odd number of electrons.

(2) A radical pair: two radicals produced simultaneously (usually by a chemical reaction).

(3) Spin (*S*, spin angular momentum): a property of electrons, protons and neutrons that makes them magnetic. When the spins of two unpaired electrons in a radical pair are parallel to each other, $S = 1$; and when antiparallel, $S = 0$.The two states of the radical pair are called triplet ($S = 1$) and singlet ($S = 0$), respectively. It is believed that the formation of radical pairs is spin-selective. In the organic chemical reaction: $A + B \rightarrow [A^{\bullet +}\ B^{\bullet -}]$, the radical pair$[A^{\bullet +}\ B^{\bullet -}]$ can only be generated in a singlet state. Similarly, the reverse reaction that produces the reactants cannot proceed in the triplet state.

(4) Hyperfine interactions: the interaction between the spin of the nucleus and the unpaired electron in an atom. A nucleus containing an odd number of protons or neutrons has a magnetic moment. Among the organic radical pairs, the two most important magnetic nuclides are ^{1}H (1 proton) and ^{14}N (7 protons and 7 neutrons). Hyperfine interaction causes dynamic transformation between the singlet and triplet states of radical pairs[159]. The proportion of singlet radical pairs oscillates in a complex manner, and its frequency (usually a few megahertz) depends on the strength of the hyperfine interaction. If there is no hyperfine interaction, the radical pairs will remain in a singlet state and will not be affected by external magnetic fields[160].

(4) Zeeman interaction: The interaction between an external magnetic field and an isolated electron spin. The Zeeman interaction causes oscillations in the direction of the electronic magnetic moments, the frequency of which is called Larmor frequency. The anisotropy of the hyperfine interaction determines the anisotropy of Zeeman interaction, which enables the radical pair to function as the basis of a magnetic-direction sensor.

The theory of radical pairs for magnetic reception is based on the above basic concepts and characteristics of free radical pairs. The singlet radical pairs $^{S}[A^{\bullet +}\ B^{\bullet -}]$ generated by the reactants can

proceed by three competing pathways (Fig. 4). The first one is the reverse reaction to revert to the reactants A and B. The second is the forward reaction to yield product C. Finally, the third is the conversion of singlet radical pairs to triplet radical pairs, which can also be reversed. The external magnetic field affects the ratio of singlet and triplet radical pairs through Zeeman interaction, and further determines the amount of reactant A/B and product C. Therefore, the parameters of external magnetic fields, such as intensity and direction, may change the final yield of product C.

The radical-pair mechanism and its application in animal geomagnetic navigation have been well summarized in a previous review[154]. In addition to the geomagnetic navigation of animals, the radical-pair mechanism has also been used to explain the effects of magnetic fields on ATP synthesis[161–163] and DNA synthesis[164]. The hypothesis of radical-pair mechanism seems to be a perfect theory at molecular level. However, it is still a grand challenge to correlate such a molecular change with the effects at cellular and organism levels. Thus, future work should focus on finding solid connections to prove it is indeed the magnetoreception mechanism in organisms.

4.2 Biochemical thermodynamic model

In the last decade, thermodynamic methods, normally used in engineering, have been creatively applied to the analysis of cancer cells[165–167]. To this end, a frequency-selective EMF therapy for cancer and a new biochemical thermodynamic model have been developed[58, 168].

The model is based on two theoretical understandings:

(1) According to thermodynamic theory, a cell is modelled as an open system, which maintains a non-equilibrium thermodynamic state with the environment through flux control[169, 170]. Each cell is a small system that constantly consumes energy and matter, and then emits heat and waste to maintain its entropy and survival. Inside the system, energy conversion coupled with metabolism and chemical reactions afford entropy and energy to the cell. Therefore, the activities in the cell depend on its energy conversion.

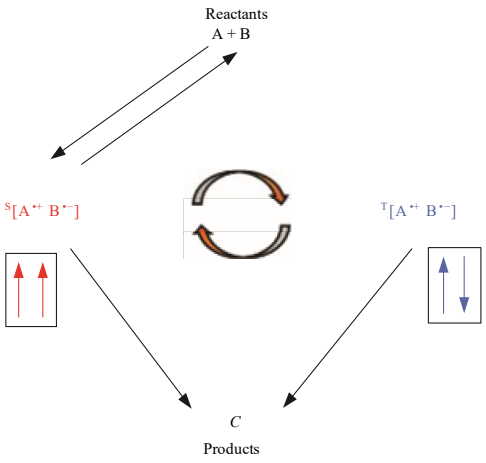

Fig. 4 Scheme of the radical-pair mechanism. Singlet $^{S}[A^{\bullet+}\ B^{\bullet-}]$ can produce both reactant A/B and product C, while triplet $^{T}[A^{\bullet+}\ B^{\bullet-}]$ can only yield product C. So the amount of product C depends on the ratio of singlet $^{S}[A^{\bullet+}\ B^{\bullet-}]$ to triplet $^{T}[A^{\bullet+}\ B^{\bullet-}]$. The external magnetic field affects the ratio of the singlet state $^{S}[A^{\bullet+}\ B^{\bullet-}]$ to the triplet state $^{T}[A^{\bullet+}\ B^{\bullet-}]$ through Zeeman interaction, which in turn determines the yield of product C.

(2) In physics, resonance is a phenomenon in which a vibration system or external force drives another system to oscillate at a specific frequency with a greater amplitude. The researchers have demonstrated that natural oscillation frequencies exist in living systems, and resonance effects can be achieved by electromagnetic or mechanical stimulation[168].

(3) By combining these two principles, some researchers believe that the energy and mass flux can be changed by the resonance, which will alter cell behaviors consequently. Considering the heat exchange between the cell and the surrounding environment, the following equation can be obtained according to the first law of thermodynamics[58]:

$$\rho c V \frac{\mathrm{d}T}{\mathrm{d}t} = \alpha A(T - T_0). \quad (1)$$

The resonance frequency is[58]:

$$f = \frac{\alpha A}{\rho c V}, \quad (2)$$

where ρ is the density, c is the specific heat capacity, V is the cell volume, T is the temperature, t is time, α is the coefficient of convection between the blood and the cell membrane, A is the area of the cell surface, and 0 in T_0 is the mean reference (the environment of the cell system).

It has been demonstrated that the proliferation of cancer cells can be inhibited by a certain frequency of EMF selectively[168,170]. It is through the biochemical thermodynamic model that a method to calculate the specific frequency of EMF that inhibits cancer cell proliferation was proposed for the first time. However, the fundamental mechanism of how EMF affects cellular heat exchange needs further investigation.

There are other magnetoreception mechanisms reported. Biogenic magnet mechanism, which believes that bio-ferromagnetite[155] or magnetic protein[10] is the primary magnetic receptor, is usually used to explain geomagnetic navigation of animals. In contrast, ion oscillation model is based on the forced-vibration of all free ions on the surface of cell plasma membrane caused by an external oscillating field[156]. Then this coherent vibration of electric charge is able to irregularly gate electrosensitive channels on the plasma membrane and thus disrupt the electrochemical balance and function in cells[157].

5 Discussion

5.1 Evaluation of published research

Over the recent decades, the number of publications on applying EMFs in disease treatments has been rapidly growing. Most of the obtained results have confirmed the therapeutic effectiveness of EMFs on some diseases. Yet, among these studies, the investigations on the treatment with natural

EMFs and artificial EMFs mimicking natural EMFs are still rare. The earth's electromagnetic environment has accompanied the entire evolution of mankind. Hence, human beings have adapted to the existence of GMF and SR. It means that the absence or disturbance of the earth's magnetic environment, like hypomagnetic field in space[171] and planetary magnetic storms[172], will induce adverse health effects on humans. In modern society, people are often in a chaotic EMF environment, such as the households with EMFs generated by alternating currents and the metal-shielded environment in cars and airplanes, which may affect human health. Therefore, it is important to study the impact of the absence or disturbance of natural electromagnetic fields on human health.

In the research of EMF therapy, one key step is to choose the appropriate EMF parameters, including frequency, intensity, waveform, *etc.* However, most studies can only select EMF frequencies arbitrarily, which may cause lower EMF therapy efficiency and/or inconsistent results. The application of 50/60 Hz ELF-EMFs in the treatment of diseases is a good example. As known, 50 Hz and 60 Hz are the frequencies of household alternating currents. This has led to many studies on the health effects of 50/60 Hz ELF-EMFs. After careful examination of the published works, it is quite surprising to find that 50/60 Hz ELF-EMFs seem to have the potential to treat almost all kinds of diseases, such as cancer[56,61,173–176], diabetes complications[77,78,177], neurological diseases[96,101,102,178], wound healing[137,140,141], musculoskeletal recovery[126,127], and many more. In a sense, this is a good phenomenon, indicating that EMF has a promising future in the treatment of many diseases. However, this also raises big concerns, because it means we have not yet found the best form of EMFs to treat various diseases. 50/60 Hz are unlikely to be the best EMF frequencies to treat all diseases judged by the frequency ''window'' in bioelectromagnetics. Even in the field of cancer treatment, distinct types of cancer cells often correspond to different inherent frequencies[58,179]. A study, supporting the above view, has found that the viability of GBM cancer cell is decreased by PEMF of 100 Hz, but increased by PEMF of 50 Hz[57]. Therefore, it is highly desirable to establish a method or principle that can guide the choice of therapeutic EMF parameters.

Researchers have never stopped investigating the biophysical mechanism of bioelectromagnetic reception. Some possible bioelectromagnetic mechanisms have been proposed, such as radical-pair mechanism[154], ionic oscillation model[156], biochemical thermodynamic model[58] and biogenic magnets[10,155], *etc.* However, most of these mechanisms are hard to prove, except for the biogenic magnet mechanism, which is usually referred to by geomagnetic navigation studies. The uncertainty of the biophysical mechanism of EMFs has caused some suspicions, and therefore hindered the application of EMF therapy.

Another problem in bioelectromagnetics is that some experiments are difficult to reproduce and sometimes can even yield contradictory results[180–182]. There are various possible factors leading to this outcome, such as inconsistent EMF emission, different EMF background, ignoring EMF direction,

and other unknown reasons. To make it worse, the lack of a definite mechanism renders it difficult to analyze the reason of contradictory results.

5.2 Perspectives for the future

Some studies have directly or indirectly proved the importance of natural EMFs on human health. For example, an interesting study has found that spending at least 120 min in nature every week brings health and happiness[183]. In addition to the fresh air, sounds and colors in nature, the natural electromagnetic environment is also considered important. More convincing experimental studies have shown that hypogeomagnetic field could induce disorder in tubulin[184] and actin[185] organization. Similarly, Jia *et al.* have demonstrated that hypomagnetic field (< 300 nT) can exacerbate the loss of bone mineral and alter the biomechanical characteristics of femurs in hindlimb-unloaded rats[171]. Besides GMF, EMFs with frequencies corresponding to SR, brain waves, and cell membrane pulsation have also been found to exhibit positive effects on human health. Therefore, the potential therapeutic effects of EMFs mimicking natural EMFs need to be further explored.

In the absence of a clear mechanism, the approach of bionics can be used to select appropriate EMF parameters. Bionics is a methodology that applies the inspiration gained from nature to serve human life and industry. Natural electromagnetic activities, such as GMF, SR, brain waves, heart waves and cell pulsations, *etc.*, can provide us with ample bionic inspirations. Our previous research has proved that bio-inspired EMF (0.5 Hz, 35 μT – 70 μT) can reduce the ATP synthesis of certain cancer cells and inhibit the proliferation of cervical cancer cells (Hela)[49]. It is noteworthy that the intensity of this bio-inspired EMF is equivalent to GMF, which means higher safety. One recent study has shown that the artificial EMF (7.8 Hz, 90 nT) in the Schumann resonance band can protect rat hearts from oxidative stress and hypoxic conditions[8]. Similarly, Tang *et al.* have found that a SR frequency of 7.83 Hz (0.3 mT ± 0.05 mT) can inhibit the growth of cancer cells[7]. As mentioned before, the FDA-approved TTFields (100 kHz – 300 kHz) with a low-intensity can selectively slow down the proliferation of tumor cells by inhibiting cell division[72]. Mechanistic studies have shown that TTFields can cause cell death by disrupting microtubule spindle formation and localization during metaphase, which leads to mitotic catastrophe[72,186]. It is worth noting that the frequency of TTFields is located in the oscillation frequencies of microtubules[44]. It suggests that the assembly of microtubules can be inhibited by its own frequency. These studies have demonstrated that the bionic approach is effective in the selection of EMF parameters for disease treatments. Therefore, in future research, the bionic method based on natural EMFs may afford good guidance to the selection of proper EMF parameters for disease treatments.

The complexity of living organisms as well as the huge gap between biology and physics is still limiting the elucidation of magnetoreception mechanisms. The searching and discussion of these mechanisms will probably last for a long time until sufficient progress has been made in biophysics

and related technologies. Nevertheless, recent attempts *via* molecular biology approaches have yielded some understanding on the mechanism of the biological effects of EMFs. Indeed, distinct signaling pathways have been investigated based on different disease scenarios and some possible hypotheses have been proposed, such as Akt pathway and Bcl-2 upregulation for neural degeneration[97,102], Wnt/β-catenin signaling for osteogenesis[129], elevated p53 and caspase-3 levels for cancer cell inhibition [57], Akt pathway activation for cell migration[65], regulation of TNF-NFκBactivity for sepsis[112], calcium/calmodulin/NO pathway for angiogenesis[138], *etc*. At present, we should consider these existing mechanistic hypotheses in a more inclusive manner. Due to the complexity of living systems, one form of EMF may cause multiple responses at the same time[187]. A representative case is that GMF could guide the navigation and affect health simultaneously. Hence, it appears that EMFs can target multiple signaling pathways in cells, which may depend on the frequency and/or intensity of the EMFs applied. Future researches probably need to focus on several key aspects of cell biology, such as apoptosis, cell cycle progression, and ATP metabolism, to reveal the molecular mechanisms for the action of EMFs in cells.

In order to avoid more conflicting studies, some effective measures must be taken. First, both the experimental EMF and background EMF should be well noted in future publications with as many details as possible, including frequency, waveform, intensity, and direction. Among them, the direction of the EMF and the background EMF are more often ignored. Then, information on biological samples (cells, mice, patients, *etc.*) should also be recorded in details. The factors that lead to different results are probably hidden in these details. Finally, repetitive verification experiments should be encouraged and the publication of studies with negative results should be allowed to avoid unnecessary repetitive work and to make a better-informed decision in the selection of parameters for therapeutic EMFs. Only in this way can we get a knowledge closer to the truth.

6 Conclusion

In conclusion, EMF therapy is a promising treatment for various diseases. Yet, there are still some unsolved problems, such as the blindness in the selection of EMF parameters, the lack of defined mechanism and the conflicting experimental results. In future research, more attention should be focused on the impact of natural EMFs on human health. Then, the methodology of bionics should be applied to guide the selection of parameters of therapeutic EMFs. To this end, the natural EMFs of earth electromagnetic environment and human electromagnetic activity will provide more inspiration for EMF treatment. The status of unclear magnetoreception mechanism may last for a long time. Meanwhile, to make a better informed-decision, the details of EMF settings and biological samples should also be carefully recorded in future research and thoroughly reported in publications. Last but not least, studies with negative results should be published.

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