Chapter 1
Parameters of Magnetic Fields and Their Differential Biological Effects

Abstract This chapter summarizes different parameters of the magnetic fields, including magnetic field types, intensity, homogeneousness, field direction and exposure time. Various factors that contribute to the differential effects of magnetic fields on biological samples, which lead to the seemingly lack of consistencies in literature will be discussed.

Keywords Static magnetic fields (SMF) • Pulsed magnetic field (PMF) • Magnetic field intensity • Gradient magnetic fields • Differential effects of magnetic fields

1.1 Introduction

The biological effects of magnetic fields can be directly influenced by different parameters. Depending on whether the magnetic intensity changes over time, magnetic fields can be divided into static magnetic field (SMF) or dynamic/time-varying magnetic field, which can be further divided into different categories according to their frequency. Depending on the magnetic field intensity, there are weak, moderate, strong (high) and ultra-strong (ultra-high) magnetic fields. Depending on the magnetic field spatial distribution, there are homogeneous or inhomogeneous magnetic fields. Here we will discuss the major variations in magnetic field parameters and their differential effects on biological objects.

1.1.1 Static Magnetic Field vs. Dynamic Magnetic Field

When the magnetic field intensity does not change over time, it is called "static magnetic field". In contrast, if the magnetic field strength changes over time, it is called "dynamic magnetic field" or "time-varying magnetic field". Pulsed magnetic fields (PMFs) are the most commonly seen dynamic magnetic fields, such as the 50 Hz or 60 Hz power frequency alternating current (AC) magnetic fields and radio-frequency magnetic fields. Over the past few decades, there are emerging concerns about the growing exposure to these electromagnetic fields, which also encouraged

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Fig. 1.1 The international EMF (electromagnetic fields) project. The international EMF project is to assess health and environmental effects of human body exposure to static and time-varying electric and magnetic fields. It includes the most commonly seen electromagnetic exposure (Figure and information were from the WHO website http://www.who.int/entity/peh-emf/project/en/)

a huge amount of epidemiological and laboratory studies. Accordingly, WHO (World Health Organization) has initiated the International EMF (electromagnetic fields) project to assess health and environmental effects of exposure to static and time-varying electric and magnetic fields in the frequency range 0–300 GHz (Fig. 1.1).

From the current research, it is obvious that cells respond very differently to magnetic fields with different types and intensities. For example, a 50-Hz, 1 mT PMF could increase rat pituitary GH3 cell proliferation (Grassi et al. 2004) but a 0.5 T static magnetic field obviously inhibited GH3 cell proliferation (Rosen and Chastney 2009). In addition, multiple evidences showed that different types of magnetic fields of the same magnetic field intensity could produce totally different effects on the same sample examined. For example, a 0.4 mT 50 Hz and a 2 μT 1.8 GHz PMFs both increased epidermal growth factor receptor (EGFR) phosphorylation, which were reversed by incoherent ("noise") magnetic fields of the same intensities (Wang et al. 2010; Li et al. 2012). Although the mechanism of how the incoherent magnetic field reversed the effect of PMF is still unknown, it is clear that the magnetic type can directly affect the field effects.

Since PMFs have variable parameters, such as field intensity and frequency, it is relatively difficult to study the biological mechanisms of magnetic effects comprehensively and systematically. For example, it was shown that PMFs with different frequencies can have diverse effects on cell proliferation. In comparison to the

time-varying/dynamic magnetic fields, SMFs are more suitable to study the fundamental biological mechanisms because they have less changeable parameters. The most commonly exposed SMFs are the permanent magnets, such as the magnets on household refrigerators, toys and accessories, which are usually not very strong (below 1 T). In addition, the core component of the MRI (Magnetic Resonance Imaging) machine in the hospital is a strong magnet, which generates a SMF with field intensities usually range between 0.5–3 T in most hospitals nowadays.

SMFs usually generate much milder effects on human beings compared to time-varying magnetic fields and many of the effects are actually beneficial. Therefore we are much more interested in SMFs, and this book will only focus on discussing the biological effects of SMFs. For people who are interested in dynamic electromagnetic fields from power lines, microwave ovens and cell phones, there are many other resources, including some books, such as *Biological effects of magnetic and electromagnetic fields* by Shoogo Ueno (1996), *Biomagnetics: Principles and Applications of Biomagnetic Stimulation and Imaging* by Shoogo Ueno and Masaki Sekino (2015), *Electromagnetic Fields in Biology and Medicine* by Marko S. Markov (2015) as well as some other reviews (Simko and Mattsson 2004; Funk et al. 2009). In addition to the published books and ICNIRP (International commission on non-ionizing radiation protection) guidance in 2014, recent works in 2016 also show that there are no detrimental effects of radiofrequency PMFs on research animal models at the levels that people are exposed to (Gao et al. 2016; McNamee et al. 2016). Overall, as far as we know, there is still not enough evidence to show that the dynamic magnetic fields that many people are concerned have definite adverse impacts on human health. However, more careful and long-term investigations in both epidemiology and laboratory research are certainly needed to draw an unambiguous conclusion.

1.1.2 Different Magnetic Field Intensities: Weak, Moderate, High and Ultra-high Magnetic Field

According to their magnetic flux intensity, SMFs used in the biological effect studies could be classified as weak (<1 mT), moderate (1 mT to 1 T), high (1–20 T) and ultra-high (20 T and above).

$$1\ \text{T (Tesla)} = 10{,}000\ \text{G (Gauss)}$$
$$1\ \text{G} = 100\ \mu T$$

It should be mentioned that the classification of magnetic fields varies between different research areas. Therefore people should always clearly label the magnetic field intensity that they use. Despite the classification, with the development of modern technology, people nowadays have much increased exposure to various SMFs. Figure 1.2 shows some examples of different SMF intensities, including the

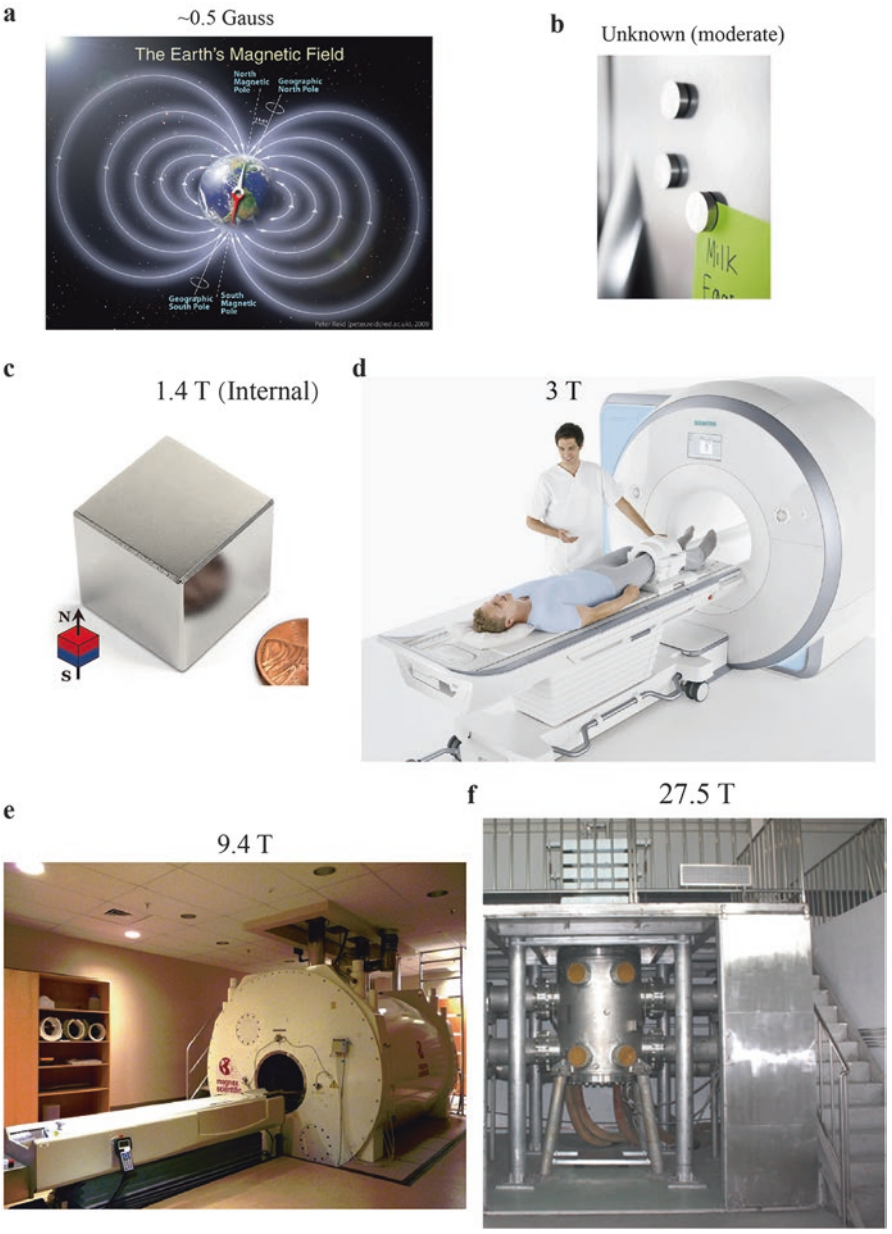

Fig. 1.2 Static magnetic fields of different intensities. (**a**) Earth magnetic field (~0.5 Gauss, 50 μT). The picture was from NASA website. **(b)** Small permanent magnets for household uses. The picture was from amazon.com, by MapMagnets. It shows a few small permanent magnets (22 × 6 mm) with unidentified magnetic field intensities. They are frequently used on whiteboards, refrigerators, and office cabinets. **(c)** A square shaped permanent magnet (Grade N50 with 14,200 internal Gauss=1.4 T). Its relative dimension can be compared to the penny by its side. The picture was also from amazon.com, by CMS Magnetics. **(d)** A 3 T MRI from SIEMENS. The picture was from SIEMENS website. **(e)** A 9.4 T MRI at University of Minnesota Medical School with 65 cm bore size that can be used on human head. **(f)** A water-cooled magnet in the Chinese High Magnetic Field Laboratory. It can provide up to 27.5 T ultra-high SMF

ubiquitous earth magnetic field of weak intensity, permanent magnets of various intensities (usually moderate intensity), MRI machines in hospitals and research institutes with high SMFs, as well as ultra-high magnets currently mainly used for research purposes (Fig. 1.2). It should be mentioned that the use of high and ultra-high magnetic fields is expanding quickly in recent years, which is no longer limited to the conventional investigation of condensed matter physics and material science, but expanded to diamagnetic materials, such as the majority components of our human bodies.

Because of the public sensitivity, the question of the possible effects of SMFs of 0.5–7 T, the range of the MRI machines in current hospitals as well as in preclinical researches (Fig. 1.2d), on human health is of paramount interest. The MRI process involves a combination of non-ionizing SMFs, gradient magnetic fields and pulsed radiofrequency fields. Currently the MRI scanners are considered to be safe and studies show that 7 T high field MRI is well tolerated by humans without excessive discomfort (Miyakoshi 2006; Simko 2007; Heilmaier et al. 2011), DNA damage (Fatahi et al. 2016) or other cellular abnormalities (Sakurai et al. 1999). At the same time, since stronger magnets could give better resolution and more detection possibilities, the researchers and engineers are currently investigating on building MRI machines with stronger magnetic fields. In fact, there are currently 9.4 T MRI machines (Fig. 1.2e) not only used on animal studies in research but also on healthy human volunteers at preclinical stage (Adair 2000; Miyakoshi 2005; Zhang et al. 2015). Moreover, 21.1 T MRI has already been developed and applied on samples such as mouse brain (Schweitzer et al. 2010; Schepkin et al. 2014; Nagel et al. 2016) (see Chap 2, Fig. 2.3).

Although FDA increases the limit of SMF field intensity with no significant risk to 8 T, whether longer time exposure to SMFs of this intensity is safe on human body is still not clear. In addition, whether higher fields above 8 T are safe on human is unclear either. There will be increasing safety concerns along with the development of ultra-high MRI machines. So far there are very limited studies that have investigated on high SMFs around 9 T on animal and human cells. In 2011, Zhao et al. studied human-hamster hybrid (*A*L) cells and found that 8.5 T SMF decreased cellular ATP level and increased ROS level (Zhao et al. 2011). Nakahara et al. found that 10 T SMF alone did not affect CHO (Chinese Hamster Ovary) cells for the cell cycle distribution or proliferation unless they were combined with X-ray treatment (Nakahara et al. 2002). Recently, we found that although 9 T SMF did not affect CHO cells, they could inhibit some human cancer cell growth, such as colon cancer HCT116 cells and nasopharyngeal cancer CNE-2Z cells (Zhang et al. 2016b). In addition, human glioblastoma A172 cells embedded in collagen gels, but not A172 cells alone, oriented perpendicular to the field direction of 10 T SMF (Hirose et al. 2003), which is largely due to the diamagnetic anisotropy of collagen fibers. Zhao et al. investigated the effects of 13 T SMF on immortalized hamster cells and human primary fibroblasts cells and found that both cell cycle and cell viability were not affected (Zhao et al. 2010). A high SMF of 14 T affected the morphology of smooth muscle cell assemblies, as well as cell colony shapes, which extended along the direction of the magnetic field (Iwasaka et al. 2003). Moreover, Rat2 rat

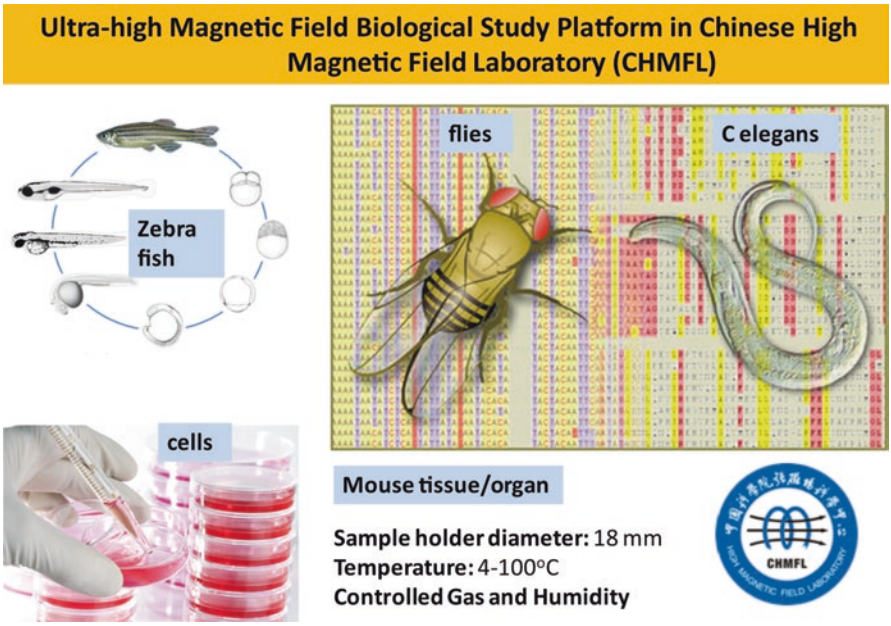

Fig. 1.3 Ultra-high magnetic field biological study platform in Chinese High Magnetic Field Laboratory (CHMFL). The biological study platform with 18 mm culture plates is suitable to study various cell cultures, including human and animal cells, eukaryotes and prokaryotes, as well as small animal models, such as fruit flies, *C elegans* and zebra fish

fibroblast cells, NIH-3T3 mouse cells, HeLa human cervical cancer cells and murine hippocampal cells were exposed to 7–17 T ultra-high SMFs, which affected Rat2, NIH-3T3 and HeLa cell attachment and neuron cell differentiation. Immunostaining analysis revealed that the actin cytoskeleton was affected by ultra-high SMFs (Valiron et al. 2005). A great deal of researches must be conducted to demonstrate the safety of ultra-high MRI before it can be fully applied on human bodies.

Due to technical limitations, the biological effects of strong field of ≥20 T on human cells have never been investigated until recently. Although the ultra-high field NMR (nuclear magnetic resonance) machines currently available can generate around 20 T SMFs, they have very narrow bore size that is impractical to accommodate cell culture plates. In addition, the animal and human cells need to be cultured with accurate temperature, humidity and gas control, which make the NMR machines unsuitable to do these experiments. For large bore SMF equipment, there are currently only very few magnets that can generate ≥20 T ultra-high SMFs, which are mostly used for material science and physical science studies. People need to construct special sample holders to make these magnets appropriate to study biological samples such as animal and human cells, as well as small animal models. We recently constructed a cell incubation system matching the large bore ultra-high magnet (Figs. 1.2f, 1.3). It can provide accurate temperature and gas control for cell cultures and some small

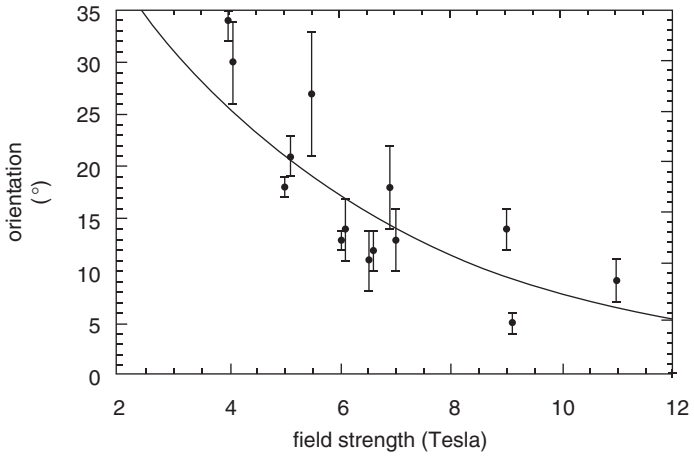

Fig. 1.4 Differential biological effects in different magnetic field intensities. Degree of orientation for microtubules assembled in the presence of SMFs as a function of magnetic field strength (The figure was reprint with permission from (Bras et al. (1998). Copyright © 1998 The Biophysical Society. Published by Elsevier Inc)

animal models. Recently we used a human nasopharyngeal carcinoma CNE-2Z cell line to study the effect of the 27 T ultra-strong SMF on its cell number, viability, cell cycle, and microtubule cytoskeleton. We found that the 27 T SMF did not have an immediate cytotoxic effect. However, it affected the spindle orientation and morphology (Zhang et al. 2017a).

There are many studies show that the magnetic field intensity is one of the key factors that cause the bio-effects differences. For example, Okano et al. found that moderate intensity gradient SMF of 0.7 T (Bmax) significantly reduced the nerve conduction velocity of frog nerve C fibers but gradient SMF of 0.21 T (Bmax) did not (Okano et al. 2012). Our recent findings showed that 0.4–9 T moderate and strong magnetic fields can affect EGFR orientation to inhibit its activity and cancer cell growth while weaker SMFs cannot (Zhang et al. 2016b). *In vitro* kinase assays using purified EGFR proteins showed that its kinase activity was inhibited by SMFs in an intensity-dependent manner (Zhang et al. 2016b). In addition, we recently found that 27 T ultra-strong SMF can affect spindle orientations in cells while moderate intensity SMFs cannot (Zhang et al. 2017a).

The magnetic field intensity and their effects on biological samples need to be examined case by case. Multiple studies show that some biological effects are directly correlated with the SMF intensity and the higher magnetic field intensities are frequently associated with stronger phenotypes (Bras et al. 1998; Takashima et al. 2004; Glade and Tabony 2005; Guevorkian and Valles 2006; Zhang et al. 2016b). For example, the microtubules can be aligned by SMFs and the alignment is increased in higher magnetic field intensity (Bras et al. 1998) (Fig. 1.4). Takashima et al. studied the DNA integrity of fruit fly in strong SMFs of 0.5–14 T and found that although an increase linearly dependent on the magnetic

flux density was observed between 0.5 T and 2 T, but it was saturated at exposure levels over 2 T and did not further increase at 5 or 14 T stronger SMFs (Takashima et al. 2004). However, higher magnetic field intensity may have different or even opposite biological effects compared to lower intensities. For example, Morris et al. showed that application of a 10 or 70 mT, but not a 400 mT, SMF for 15 or 30 min immediately following histamine-induced edema resulted in a significant reduction in edema formation (Morris and Skalak 2008). In addition, study in Shang's group demonstrated that 500 nT and 0.2 T SMFs promoted osteoclast differentiation, formation and resorption, while 16 T had an inhibitory effect (Zhang et al. 2016a).

1.1.3 Homogeneous vs. Inhomogeneous Magnetic Field

Depending on the spatial distribution of magnetic fields, SMFs can be classified as homogeneous SMF and inhomogeneous SMF, in which the field strength can be spatially constant (homogeneous) or different (inhomogeneous). Both homogeneous and inhomogeneous magnetic fields are present in many cases. For the electromagnets designed for SMFs, the center of the magnet provides a homogeneous magnetic field, as long as the samples are placed within a certain range. For example, Nakahara et al. showed the magnetic field intensity distribution as well as gradient distribution within a 10 T superconducting magnet (Nakahara et al. 2002). "0" indicates the center of the magnet, where the magnetic flux density is maximum and the field gradient is "0". However, if the samples are placed far away from the center, the magnetic field usually becomes inhomogeneous. For example, if the sample is placed around 20 cm from the center of their magnet, the magnetic field density becomes around 5 T and the field gradient is maximum. Figure 1.5 shows the magnetic field intensity distribution as well as gradient distribution within a 27 T water-cooled magnet (Fig. 1.5). At the center of the magnet, the magnetic field flux density is maximum and the field gradient is 0. In contrast, at around 7 cm away from the center, the field gradient is maximum while the magnetic field intensity decreases to < 20 T. Similarly, although the center of the MRI machine has a homogeneous magnetic field, MRI workers who stand step away from the MRI machines receive a gradient (inhomogeneous) magnetic field.

To help evaluate exposure to gradient magnetic fields (GMFs) of staff working with 1.5 and 3 T MRI machines, Iachininoto et al. used an exposure system reproducing measured signals of the 1.5 T and 3 T MRI (1.5 T-protocol and 3 T-protocol) and investigated their effects on hematopoietic stem cells. They exposed CD34+ cells obtained from six blood donors to 1.5 T-protocol and 3 T-protocol for 3 days and then cultured for 4 weeks. Results showed that *in vitro* GMF exposure did not affect cell proliferation but instead induced expansion of erythroid and monocytes progenitors soon after exposure and for the subsequent 3 weeks. However, CD34+ cells isolated from MRI workers behaved similarly to sham-exposed CD34+ cells, suggesting that other cells and/or microenvironment factors might prevent GMF

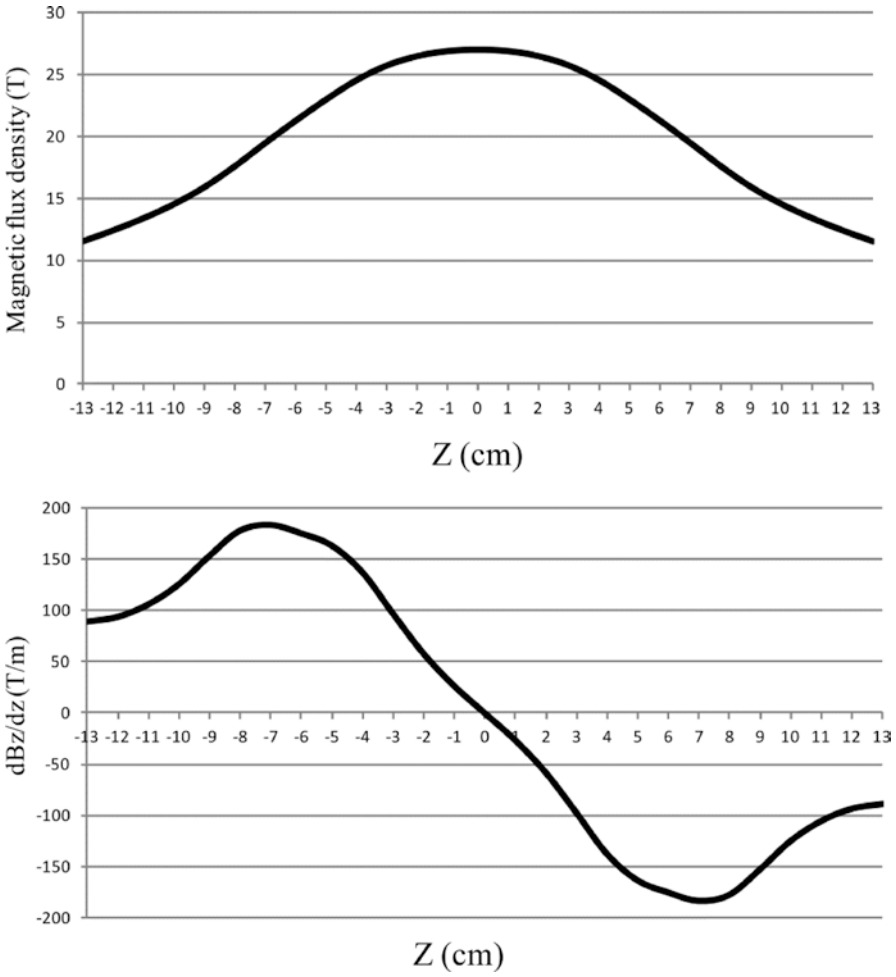

Fig. 1.5 Magnetic field intensity and gradient distribution within an ultra-high magnet that provides 27 T SMF at the center. This is based on the water-cooled magnet #4 in the Chinese Academy of Sciences, Hefei, China. *Upper panel* shows the magnetic flux density and the *lower panel* shows the magnetic field gradient. The *X axis* indicates distance from the center (Figure was provided by Lei Zhang)

effects on hematopoietic stem cells in human bodies (Iachininoto et al. 2016). So far there are no detrimental effects of MRI on regular MRI staff members have been reported.

The magnetic forces used in magnetic levitation belong to the inhomogeneous SMFs. The magnetic field intensity decreases along the upward direction away from the center so that the forces can point to the upward direction to balance gravity. The magnetic force acting on diamagnetic object is repulsive and if it is stronger than gravity, the object will be levitated. The famous "flying frog" used a 16 T supercon-

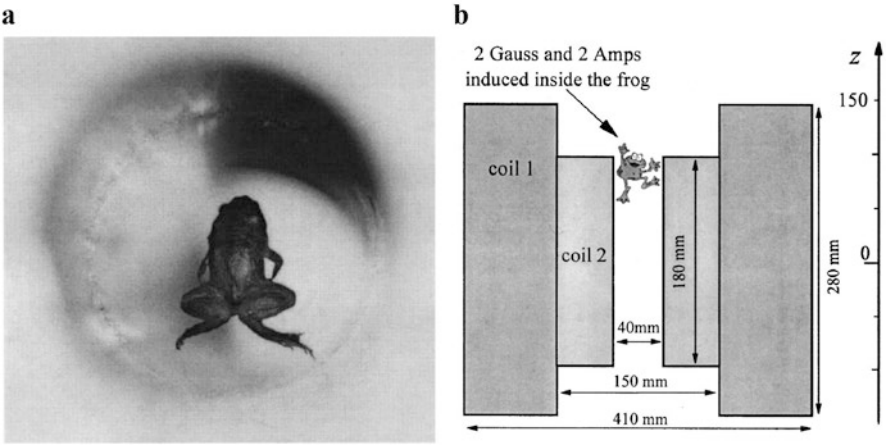

Fig. 1.6 The flying frog. (**a**) A small frog levitated in the stable zone within a 16 T magnet. (**b**) Illustration of the position of the frog within the magnet (The figures were adapted with permission from Simon and Geim (2000). Copyright © AIP Publishing LLC)

ducting magnet that provided a SMF with a gradient that is large enough to balance the gravity of the frog when it was placed at the upper part of the magnet, away from the center (Fig. 1.6). Apparently, magnetic levitation can only be achieved in static magnetic fields, but not in pulsed magnetic fields.

Besides the flying frog, there is another excellent example of using magnetic levitation to "fly" much smaller living objects, single cells. In 2015, Durmus et al. made a small magnetic levitation platform (Fig. 1.7a). This is based on the principle that each cell has a unique cellular magnetic signature, predominantly owing to the formation of intracellular paramagnetic reactive oxygen species. For example, cancer cells, white blood cells (WBC) and red blood cells (RBC) are all different from each other (Fig. 1.7b). Apparently this platform is much smaller than the one that is needed to fly a frog (Fig. 1.7c) and the magnetic field strength is also much weaker (Fig. 1.7d) because cells are much smaller and lighter than frogs. They actually used permanent magnets of moderate intensity (hundreds of militesla) in this platform (Fig. 1.7d). This relative simple set up actually can give ultrasensitive density measurements because each cell has a unique levitation profile (Fig. 1.7e) (Durmus et al. 2015). They proposed that this technique could be used in label-free identification and monitor of heterogeneous biological changes in various physiological conditions, including drug screening in personalized medicine.

In fact, multiple groups have utilized magnetic levitation technique to mimic the "weightless" condition and study its effects on cells. For example, the Shang group did a series of studies to investigate the effects of SMF with a vertical gradient using a large gradient strong magnet (Qian et al. 2009; Di et al. 2012; Qian et al. 2013). They compared the samples when they were placed at 0 gradient (1 g, indicate that the gravity is normal), or at above or down the magnet center, where the magnetic force is upward (0 g) or downward (2 g), respectively. The "0 g" position mimics the weightless condition and the "2 g" position has the double gravity forces

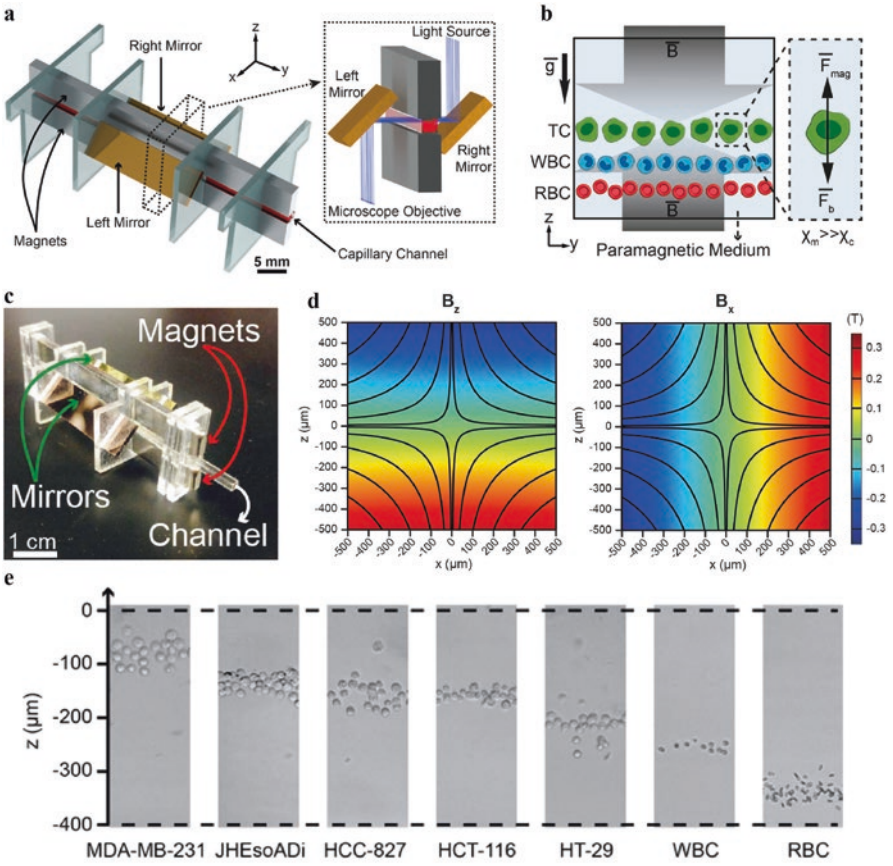

Fig. 1.7 Magnetic levitation of single cells using a densitometry platform, the MagDense cell density meter. (**a**) Illustration of the platform. (**b**) Final equilibrium height of cells in MagDense. Owing to the magnetic induction (B) and gravity (g), cells are levitated in the channel and are focused in an equilibrium plane where magnetic forces (Fmag) and buoyancy forces (Fb) equilibrate each other. Magnetic susceptibility of the medium (χm) is chosen to be bigger than the cells' magnetic susceptibility (χc). Different cell types with different densities, such as cancer cells (TC), WBC, and RBC, are separated from each other. (**c**) Photograph of densitometry platform. Capillary channel is introduced between two permanent neodymium magnets whose same poles are facing each other ("N" to "N" and "S" to "S"). Mirrors are used to image samples along the side of the channel. (**d**) FEM simulation results showing z and x component of magnetic induction (Bz, Bx) inside the channel. Total magnetic induction (Bz+Bx) is also presented as streamlines on the images. (E) Distribution of cancer and blood cells in the MagDense along the channel (HCC827, nonsmall cell lung adenocarcinoma cells; HCT116, colorectal carcinoma cells; HT29, colorectal adenocarcinoma cells; JHesoAD1, esophageal adenocarcinoma cells; MDA-MB-231, breast adenocarcinoma cells) (The figures were adapted from Durmus et al. (2015) (open access))

in the downward direction. Since "0 g" and "2 g" have identical magnetic field intensity of around 12.5 T and the magnetic field direction (B) is upward at both positions, their only difference is the direction of magnetic force. At "0 g" position, the magnetic force that is equivalent to the gravity in the opposite direction so that

"0 g" can be used to investigate the effect of weightless condition. At "2 g" the magnetic force is the same as the gravity so that it mimics the double weight condition. In the meantime, the "1 g" position provides homogenous SMF with no gradient so that it can be used to investigate the effect of magnetic field itself. Their results showed that the magnetic field and the reduced gravity worked together to affect integrin protein expression in osteoblast-like cells. Moreover, MTT assays also revealed that the 12–16 T SMFs could increase the cell number/viability of MG-63 and MC3T3-E1 cells since all three positions increased the MTT assay reading. However, they observed the difference between "1 g" of 16 T to "0 g" and "2 g" of 12 T, which is more likely due to the 4 T difference in magnetic field intensity.

There are some other studies indicate that the SMF homogeneousness have impacts on the biological effects. This is not surprising because the magnetic force acting on any particular object is proportional to the magnetic field intensity, field gradient, and the magnetic susceptibility of the object. Magnetic fields with low or no field gradients can be used to induce a magnetic torque, rather than a magnetic force, which acts on magnetic objects to move them along magnetic gradients. For example, Kiss et al. compared the homogeneous and inhomogeneous SMFs generated by permanent magnets and found that although both homogenous and inhomogenous SMFs of moderate intensity can significantly reduce pain in mice, the spatial SMF gradient might be responsible for the pain relief rather than the exposure to the SMF itself (Kiss et al. 2013). In addition, the SMFs with high gradient have been applied in red blood cell separation as well as malaria-infected red blood cell separation and diagnosis (Owen 1978; Paul et al. 1981; Nam et al. 2013), which will be further discussed in Chap. 4.

However, there is also some evidence shows that the magnetic intensity, rather than the gradient, is the key factor. For example, Denegre et al. found that the cleavage plane of frog eggs can be reoriented by SMF of 16.7 T and they did not observe differences when they placed the sample in the center (with homogeneous magnetic field) or away from the center (with inhomogeneous magnetic field) (Denegre et al. 1998). They thought that the magnetic field intensity, but not the gradient, generates effects on the samples. However, based on experimental and theoretical studies, we think their observation could because the cell division can be affected by both homogeneous and inhomogeneous SMFs as long as the magnetic field is strong enough. Whether the homogeneous and inhomogeneous field produce different phenotypes on other biological samples still needs more systematic investigations. At least one obvious difference is that the gradient field (inhomogeneous) with an upward direction could lift a frog, but a homogeneous field with no gradient could not.

1.1.4 Exposure Time

People are exposed to more and more electromagnetic radiation such as mobile phones and power lines, whose effects on human health are still debated. One of the constricting factors is that long-term exposure effects are still lacking. In contrast, the human exposure to most SMFs, other than earth magnetic fields, is only for a limited time. For example, the duration of the MRI examinations in hospitals is usually a few minutes to a couple of hours. Even for people who work with MRI, the exposure time is relative limited. So far there are no known detrimental effects of repetitive MRI exposure on human bodies, as long as they follow the MRI instructions.

It has been shown that exposure time is a key factor that contributes to the differential effects of magnetic fields on biological samples. Different exposure time will have variable effects to many aspects. For example, in 2003 Chionna et al. found that U937 cells exposed to 6 mT SMF showed cell surface microvilli shape change after 24 h exposure but they have distorted cell shape after longer exposure (Chionna et al. 2003). In 2005, Chionna et al. found that cytoskeleton was also modified in a time dependent manner in Hep G2 cells exposed to 6 mT SMF (Chionna et al. 2005). In 2008, Strieth et al. found that prolongation of the exposure time from 1 min to up to 3 h increased the 587 mT SMF-induced reduction effects on red blood cell velocity (vRBC) and functional vessel density (Strieth et al. 2008). In 2009, Rosen and Chastney exposed GH3 (rat pituitary tumor) cells to 0.5 T SMF for different time points and found that the effects on cell growth is time dependent. After 1-week 0.5 T SMF exposure, the cell growth of GH3 cells was reduced by 22% but returned to control level in a week after magnetic field retrieval. After 4-week 0.5 T SMF exposure, the cell growth of GH3 cells was reduced to 51% and returned back to control level after 4 weeks after magnetic field retrieval (Rosen and Chastney 2009). In 2011, Sullivan et al. found that ROS in fetal human lung fibroblast WI-38 cells was significantly increased by 18 h of moderate intensity SMF exposure but not 5 days of exposure (Sullivan et al. 2011) although the underlying mechanism is still unknown. Also in 2011, Tatarov et al. tested the effect of 100 mT SMF on mice bearing metastatic breast tumor EpH4-MEK-Bcl2 cells. They found that exposure of the mice to magnetic fields for 3 h or 6 h, but not 1 h, daily for as long as 4 weeks suppressed tumor growth (Tatarov et al. 2011). In 2014, Gellrich et al. found that although both SMF single exposure and repeated exposure increased the blood vessel leakiness and reduced functional tumor microvessels, the repeated SMF exposure had stronger effects (Gellrich et al. 2014). Recently, we tested the effect of 1 T SMF on human skin cancer A431 cells and also observed the time-dependent ROS changes (Fig. 1.8). All these studies show that the SMF exposure time is a key factor for their effects on biological systems and people should keep the exposure time in mind when they design their own experiments or analyze the literature.

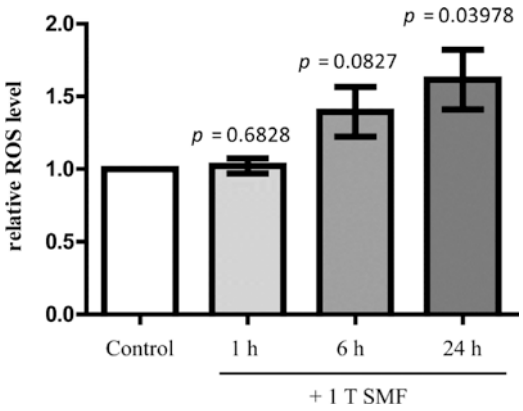

Fig. 1.8 1 T SMF increased ROS level in human skin cancer A431 cells in a time-dependent manner. 4–5 × 10^5 cells/ml of A431 cells were plated one night ahead and exposed to a 1 T SMF for different time points before the ROS levels were measured. The 1 T SMF was provided by placing the cell plate on the top center of a 5 cm × 5 cm × 5 cm neodymium permanent magnet, with the North pole up. The control group was placed with at least 30–40 cm away from the magnet with a measured magnetic field intensity background of 0.9 Gs, which was 10,000-fold lower than the 1 T experimental groups (Our lab unpublished data) (Figure was provided by Huizhen Wang)

1.1.5 Magnetic Poles and Different Field Directions

Although the scientific explanation is apparently missing, there are some reports saying that the different poles of a permanent magnet would have different effects on living organisms. Most of these points were brought up by people in the magnetic therapy field and the most famous claim was brought up by Dr. Albert Roy Davis and Walter C. Rawls. In 1974, Dr. Albert Roy Davis and Walter C. Rawls, Jr. wrote a very interesting book "*Magnetism and its effects on the living systems*". They claimed that the N pole and S pole of the magnet could have dramatically different effects on living systems. The original finding was actually from an "earthworm incident" in 1936, in which the earthworms had eaten through one side of the cardboard container near the S pole while the earthworms in the other container near N pole did not have obvious effects. The magnetic strength was around 3000 Gauss (0.3 T) in this "earthworm incident". Further analysis revealed that the earthworms near the South pole were "one- third larger, longer in length and larger in diameter and were extremely active". In this book, they also described many interesting findings about the differential effects of North vs. South magnetic pole on biological processes, such as the ripen speed of green tomatoes, radish seed germination, small animals, as well as cancers. Overall, they think the North pole is the "negative energy pole" which arrests life growth and/or development while and the South pole is the "positive energy pole" that increases life, growth and development. Although their claims have not been scientifically proven, there are many other non-scientific reports supporting the Davis and Rawls's claims. However, since no illustration or picture was provided in their book about these experiments, the relative

location of the earthworms or other samples they tested near the magnets is unclear. Moreover, there are many remaining questions. For example, whether the North or South pole magnets could generate the same effects when they were placed on the top vs. bottom, or at the side of the samples are completely unknown. Therefore, I think it is necessary for scientists to perform carefully designed and well controlled studies to test their claims. From my point of view, it is very likely that the magnetic field direction, but not the magnetic pole itself, could generate some differences on biological samples. More researches are needed to draw an explicit conclusion.

There are actually two studies have indicated that SMFs of different orientations could generate differential results in mice and cells. Milovanovich et al. found that 128 mT static magnetic fields affected various organs in mice (Milovanovich et al. 2016) (Fig. 1.9). They compared the SMFs with two opposite directions, the upward field direction (field direction was opposite to the gravity) and downward direction (field direction was the same to the gravity). In the mice serum, the HDL level was increased by both upward and downward SMFs. In addition, SMFs of both directions can decrease the amount of total white blood cell and lymphocytes in serum, granulocytes in spleen and inflammation in kidney (Fig. 1.9a) (Milovanovich et al. 2016). However, it is interesting that the upward SMF caused increased spleen cells but the downward SMF did not (Fig. 1.9b), while the downward SMF decreased the granulocytes number in serum but the upward SMF did not have as significant effect (Fig. 1.9a) (Milovanovich et al. 2016).

In addition, recently, a separate study by De Luka et al. also suggested that the moderate intensity magnetic fields with different orientations may have differential effects on copper level in mice brain (De Luka et al. 2016). They measured the zinc and copper levels in different organs in mice that were exposed to SMFs (98 mT max) of upward or downward directions. They found that SMF could change the zinc and copper levels differentially in different organs. More interesting, the SMF of downward direction seemed to have more obvious effects (De Luka et al. 2016). The difference was small but statistically significant.

At the same time, there was also evidence showing that the magnetic field direction or magnet pole does not make a difference. In 2011, Sullivan et al. examined fetal human lung fibroblast WI-38 cells for their response to magnetic fields that were generated by pairs of "N" vs. "S" magnetic pole facing each other but with different orientations (Fig. 1.10). In this way, the cells placing between the magnets were exposed to magnetic fields of different orientation, and they were also relative closer to either "N" pole or "S" pole. They examined cell attachment and cell growth curves and found that the different exposure methods both could decrease cell attachment and cell growth but there was no difference between them (Sullivan et al. 2011). I think the different observations in these studies are likely due to the differences in biological samples examined. It is interesting that not only both Milovanovich et al. (2016) and De Luka et al. (2016) observed differential responses of mice when they were exposed to magnetic fields of different directions, they also showed that different organs responded differently. Based on results from their studies, the magnetic field direction can make difference in some organs or on some types of cells while have no difference in other organs or cell types. Therefore it is

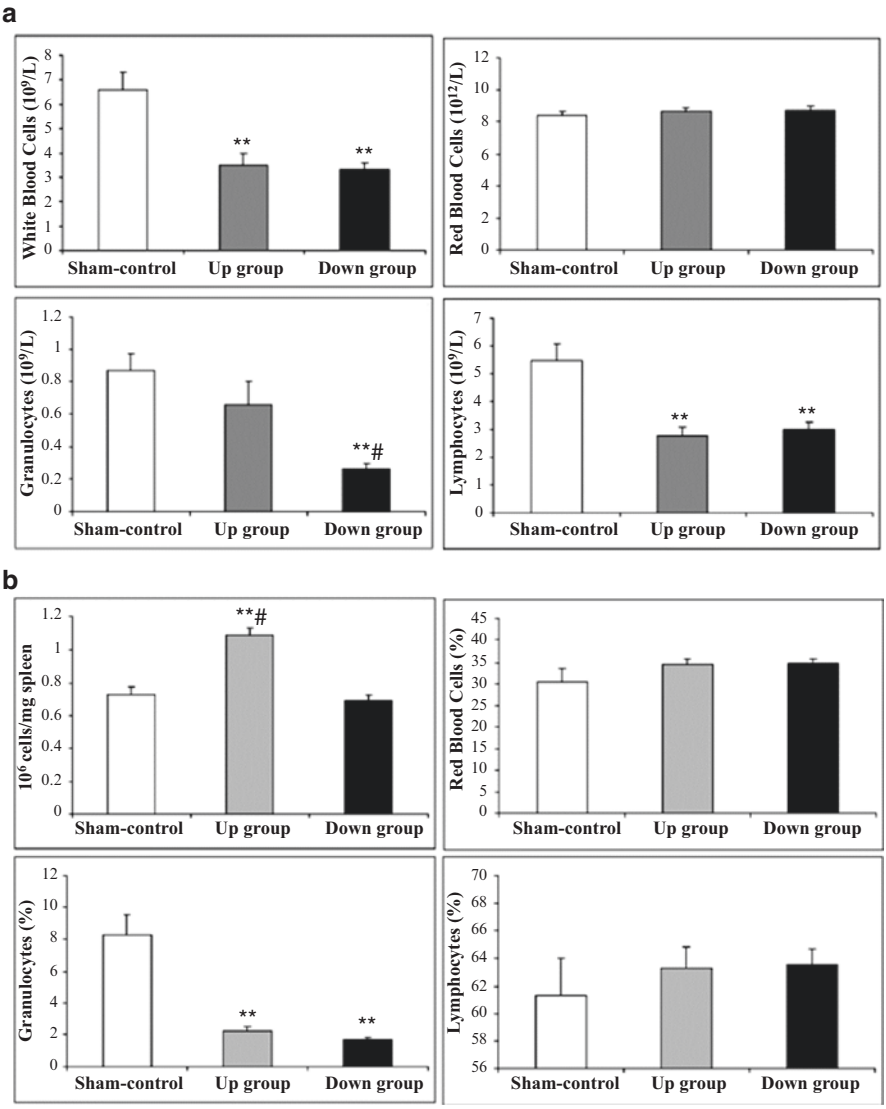

Fig. 1.9 Magnetic field direction influences the SMF effect on mice. "up group" means the group of mice that were exposed to SMF with the upward field direction. "down group" means the group of mice that were exposed to SMF with the downward field direction. Magnetic flux density is 128 mT. (**a**) Cell count of blood in mice exposed to SMFs of different direction, including total serum white blood cells, serum red blood cells, serum granulocytes and serum lymphocytes. **p<0.01 compared to control. # p<0.05 compared to up group. (**b**) Cell count in spleen of mice exposed to SMFs of different direction, including the total spleen cells, spleen red blood cells, spleen granulocytes as well as spleen lymphocytes. **p<0.01 compared to control. # p<0.01 compared to down group (The figures were adapted with permission from Milovanovich et al. (2016). Copyright © 2015, Springer-Verlag Berlin Heidelberg)

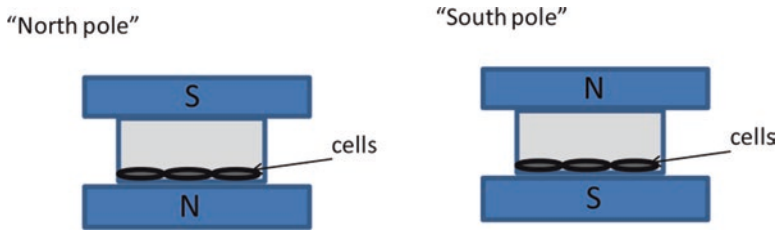

Fig. 1.10 Field direction did not make differences on human lung fibroblast WI-38 cell attachment or proliferation. In 2011, Sullivan et al. compared the different exposure methods on WI-38 cells attachment and proliferation but did not observe obvious difference (Figures are based on results from Sullivan et al. (2011))

not too surprising that Sullivan et al. examined only one cell type, fetal human lung fibroblast WI-38 cells, and did not observe any field direction-induced differences.

Overall the magnetic field direction or magnetic pole-induced bio-effects differences are not well supported yet. Scientific investigations are still lacking and mechanistic explanations are also missing. If the "N" vs. "S" magnetic pole induced dramatic differences in living systems proposed by Dr. Albert Roy Davis and Walter C. Rawls are real, it would help to explain some inconsistencies in current literature because most people did not pay attention to the magnetic poles in their studies, including us in our earlier experiments. However, based on our knowledge, the effects are likely not as simple and clear-cut as claimed by Dr. Albert Roy Davis and Walter C. Rawls. Our lab is currently investigating this issue systematically by comparing different magnetic poles and field directions on different types of cells for their effects on multiple aspects. Our initial data suggest that the effects seem to be cell type- and cellular activity-dependent (our unpublished data). Since most studies so far did not provide information about the magnetic pole information, we strongly recommend that people should pay attention to the magnets they use and keep a clear record about the magnetic field direction and/or the magnetic poles in their studies. This is actually crucial because the results could be totally different.

1.1.6 Factors Contributing to the Lack of Consistencies in Bioeffects Studies of Magnetic Fields

As mentioned above, despite the numerous scientific research and non-scientific case reports about the magnetic effects on living organisms, the magnetic field effects on biological systems are still looked upon with doubts and suspicions by many scientists outside of the field, as well as by the mainstream medical community. This is largely due to a lack of consensus on the biological effects in general that are backed up by solid scientific evidences and explanations. We have to admit that the countless scientific researches or non-scientific case reports are enriched with many seemingly contradictory results, which make many people confused and

hence become suspicious, including myself a few years ago. Then we carefully analyzed the evidence in the literature about the biological effects of magnetic fields to try to view them collectively in a scientific way. We found that most of these inconsistencies can be explained by the different parameters of either the magnetic fields or the biological samples people used in individual studies. For example, the magnetic field parameters mentioned above in this chapter all contribute to the differential effects, such as the types of magnetic fields, the field intensities and frequencies of magnetic fields, the homogeneity and directions of the fields, the magnetic poles and the exposure time. More importantly, we found that the biological samples people examined directly affect the magnetic effects. For example, we recently found that both cell types and cell densities have direct impact on the effects of 1 T SMF on cells (Zhang et al. 2017b). The cancer vs. non-cancer cells from the same tissue responded completely differently to the same magnetic field. Unexpectedly, the same cell line responded totally different when they were seeded at different cell density and we found that the EGFR-mTOR-Akt cell signaling pathway is likely involved in this regulation (Zhang et al. 2017b). In fact, even normal (non-cancer) cells from the same tissue have different responses to the magnetic field. The Shang group compared the effects of 500 nt, 0.2 T, 16 T on osteoblast MC3T3-E1 cells (Zhang et al. 2014b), as well as pre-osteoclast Raw264.7 cells (Zhang et al. 2016a) and found that the osteoblast and osteoclast cells responded totally opposite to these SMFs. Both hypo and moderate magnetic fields reduced osteoblast differentiation but promoted osteoclast differentiation, formation and resorption. In contrast, 16 T SMF increased osteoblast differentiation inhibited osteoclast differentiation. They also wrote a particular review to systematically summarize the effects of SMFs on bone that is worth to look into (Zhang et al. 2014a). More surprisingly, some people (including ourselves) found that even cell passage number could affect the experimental results, which will be further discussed in Chap. 4.

In 2009, Colbert et al. wrote a comprehensive review "Static Magnetic Field Therapy: A Critical Review of Treatment Parameters" (Colbert et al. 2009). Their purpose was to summarize SMF studies involving the application of permanent magnets in humans. In this review, they critically evaluated the reporting quality of ten essential SMF dosing and treatment parameters and proposed a set of criteria for reporting SMF treatment parameters in future clinical trials (Fig. 1.11). They reviewed 56 studies about magnetic therapy, in which 42 studies were done in patient populations and 14 studies were done in healthy volunteers. As we have discussed in earlier part of this Chapter, the magnetic field parameters greatly influence their effects on biological systems. However, by analyzing ten magnetic field related parameters in these studies, including the magnet materials, magnet dimensions, pole configuration, measure field strength, frequency of application, duration of application, site of application, magnet support device, target tissue, distance from magnet surface, and found that 61% of the studies failed to provide enough

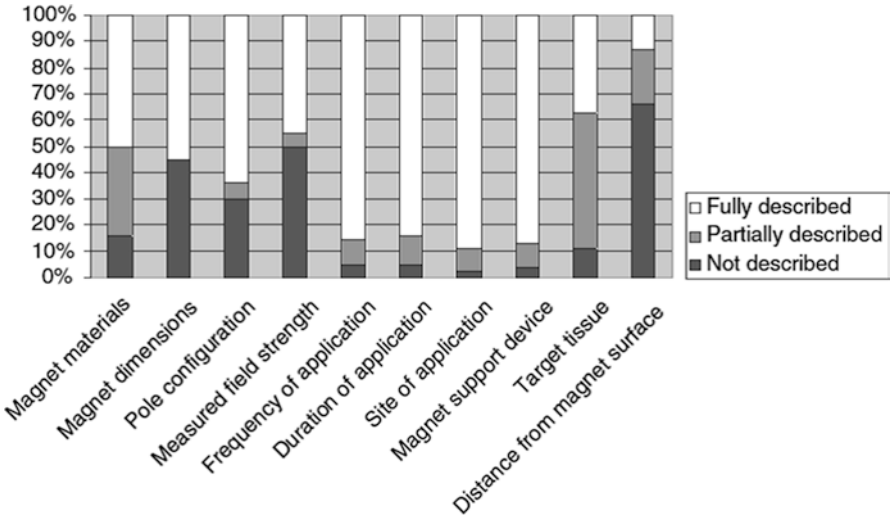

Fig. 1.11 Quality of reporting ten static magnetic field (SMF) dosage and treatment parameters was assessed in 56 human studies (The figure was from Colbert et al. (2009). Copyright © 2007 The Authors (open access))

experimental details about the SMF parameters to permit protocol replication by other investigators. Apparently, the lack of sufficiently detailed description of SMF parameters greatly prevented people from getting consensus conclusions from these studies. We strongly encourage people in the field of magnetic field studies to clearly label their parameters, such as the ten parameters listed in the Colbert paper, in their own research.

Last but not the least, there are also some other factors contributing to these differences, such as instrument and technical sensitivities, which have been greatly improved in the past few decades. Nowadays people have much advanced instruments and techniques, which should enable more findings that were not detectable before. The absence of magnetic field effects in some studies may simply due to the technical limitations and/or inadequate control of experimental conditions. We should take advantage of the modern technologies to answer related questions. For example, we recently used liquid-phase STM to get high resolution single molecular images of proteins (Wang et al. 2016) and combined with biochemistry, cell biology as well as molecular dynamics simulation to reveal that moderate and strong SMFs could change EGFR orientation to inhibit its activation and some cancer cell growth (Zhang et al. 2016b). At the same time, we should keep all relevant factors in mind, such as magnetic field type and intensity, cell type and density when we do our own research and analyze the relevant literature. This will help us reduce the diversity and contradictions in this field and also help us to correctly understand the mechanism of the biological effects caused by the magnetic field.

1.2 Conclusion

Since the human body itself is an electromagnetic object, it is not surprising that the magnetic fields could produce some effects on them. There are indeed many convincing experimental evidences as well as theoretical explanations about the effects of magnetic field on some biomolecules, such as the cytoskeleton microtubules, membrane, as well as some proteins (will be discussed in Chapter 3). In the meantime, most studies in the literature on the biological and health effects of magnetic fields had been inconclusive or contradictory, which was largely due to the various parameters used in individual studies, including the magnet fields themselves, samples examined, as well as the experimental set up. It seems that there is a large gap between atom/molecular level and cell/tissue/organism level that people need to fill in to correctly and scientifically understand the biological effects of magnetic field. For now, experimental and theoretical studies are both at a very preliminary stage. To help us get a more complete understanding of the biological effects of magnetic fields and their underlying mechanisms, more systematic, well controlled studies with fully described experimental details are strongly encouraged. Furthermore, increased collaborations between scientists in physics, biology and chemists are necessary to make substantial progresses in this emerging field.

Ethics The frog research studies in this chapter had their ethics approved. For Okano et al. 2012, it was stated that "the animal experiments were carried out with the approval of the Animal Ethics Committee of Chiba University (Chiba, Japan)".

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