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Conductive Scaffolds for Heart Tissue Engineering: Current State and Future Outlook

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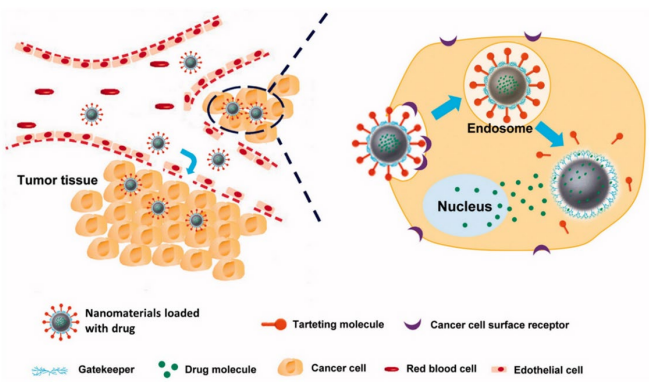
Graphical Abstract

The presence of electrical activity in body organs such as the nervous system, heart and bones has caused one of the most widely used treatment methods called electrotherapy to be widely used, especially in the relief of underlying pain. On the other hand, the progress of medical science in the field of nano stem cells and regenerative medicine has created many promises in treatment. Also, recently, treatments based on electric field have been widely used in cancer treatment. The main issues in regenerative medicine are the proliferation of nano stem cells to the required extent and directing them towards the differentiation of the target tissue. Electric field (EF) stimulation can play an important role in creating appropriate nano stem cell responses and directing nano stem cell differentiation towards osteogenesis/neuronogenesis/cardiomyogenesis. The electric field with nanosecond pulse as well as the electric field for tumor therapy have attracted a lot of attention for the treatment of cancer. Major signaling pathways and cellular responses elicited by electrical stimulation include reactive oxygen species and heat shock proteins, fluctuations in intracellular calcium ion concentration, ATP production, clustering or reaggregation of cell surface receptors., reconstruction of the cytoskeleton that affect the fate of the nano stem cell. Also, the lack of pain, ease and reasonable price have made cancer treatment with electric field more and more popular. In this research, an attempt has been made to briefly review the effects of electrical signals on the behavior of nano stem cells, as well as examples of their therapeutic effects in the treatment of tissue lesions and cancer.



Schematic of the inverse piezoelectric effect of synchrotron light source imaging of electrical stimulation on the fate of nano stem cells and its role and application in regenerative medicine and cancer treatment.

Keywords: Inverse piezoelectric effect; Synchrotron light source; Imaging; Electrical stimulation; Nano stem cells; Regenerative medicine; Cancer treatment

Introduction

Electricity is a basic need in our daily life. Electrotherapy, the use of electrical energy to treat medical disorders, dates back to 46 AD when Scribonius Largus, physician to Roman Emperor Claudius, discovered that standing on electric eels on the beach could relieve pain by inducing anesthesia [1–11]. For example, the early methods of medical electrical therapy to treat neurological and mental disorders, or paralysis, were more than administering electric shocks to patients [12–22]. In today's medicine, the use of low–level electrical energy is now accepted in a wide range of medical specialties, including neurology and psychiatry [23–34]. On the other hand, nano stem cells have a high potential in the application of tissue engineering and regenerative medicine due to their self–regeneration ability and high differentiation ability [35–46]. The two main goals pursued in the cultivation of these types of cells are their proliferation in the culture medium while maintaining their pluripotency and their differentiation into the required cell line [47–58]. With the growth and expansion of the science of biology and the greater understanding of cell biology, it became clear that biochemical factors are not the only factors involved in cell fate [59–70]. With the extensive research done in this field, they concluded that in order to imitate the cell membrane to achieve a specific goal, in addition to biochemical factors, it is also necessary to control biophysical factors such as mechanical, geometric and electrical factors [71–81]. The electrical properties of the field are a fundamental issue in cell–biomaterial interaction. Heidari et al. reported electric field generation during cellular activities such as cell division, proliferation, and migration [82–93]. After that, the idea was raised that it is possible to control cellular activities using electrical signals [94–105]. For example, due to the fact that nerve, muscle, fibroblast and osteoblast cells in the body are mostly under electrical stimulation, it is possible to use these electrical signals to direct the cells towards cardiac and vascular cells and differentiated nervously. On the other hand, the treatment of cancer as one of the main causes of death is highly regarded by scientists, and the use of electric field in its treatment is also expanding due to its advantages such as ease of use, reasonable price, and non–painfulness [106–114].

Results and Discussion

Effects of Electric Field on the Fate of Nano Stem Cells

Applying electrical stimulation to nano stem cells has several methods such as applying direct current, inductive coupling, capacitive coupling, quasi–capacitive coupling and concentration cell with agar salt bridge. Meanwhile, capacitive coupling is the most common method of applying an electric field to the cell culture medium and the cells in it. On the other hand, depending on the type of cell, the method of stimulation and its intensity, there is the possibility of major and very different changes in the fate of the nano stem cell. Especially, by choosing the right culture medium and the right intensity of the applied electric field and the right application method, even different cell lines can be obtained from the same cell source.

In general, the active electrical function of cells depends on the existence of ion channels in the cell membrane as well as polar molecules in the cell structure such as proteins and amino acids. In addition, the components of the cell skeleton, which are mainly made of protein, are affected by the electric field and electric current. Meanwhile, the effect of electric current and electric field of calcium and potassium ion channels on cell proliferation is well known. Figure (1) shows the effect of the electrical signal on the arrangement of the cell division spindle and its effects on the cell membrane. Also, the results show that the electric field caused cell polarization and migration due to the presence of ions in the cell environment. Figure (2) shows the effect of electric field on cell polarization and, accordingly, the migration of nano stem cells.

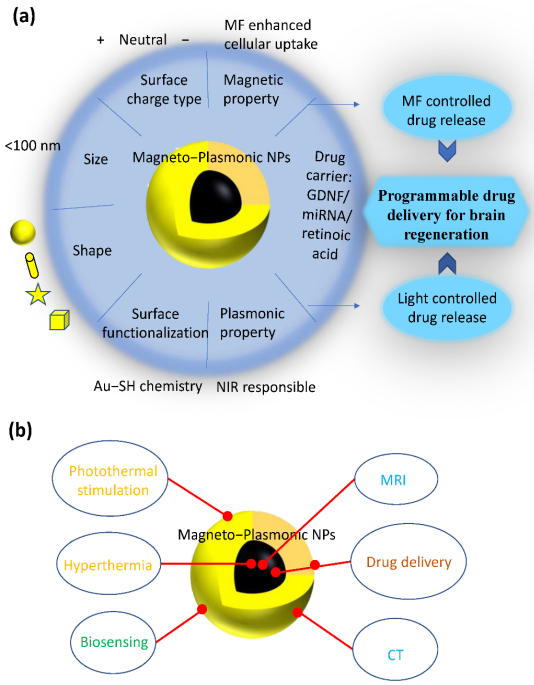


Figure (1): Inverse piezoelectric effect of synchrotron light source imaging of electrical stimulation on the fate of nano stem cells and its role and application in regenerative medicine and cancer treatment.

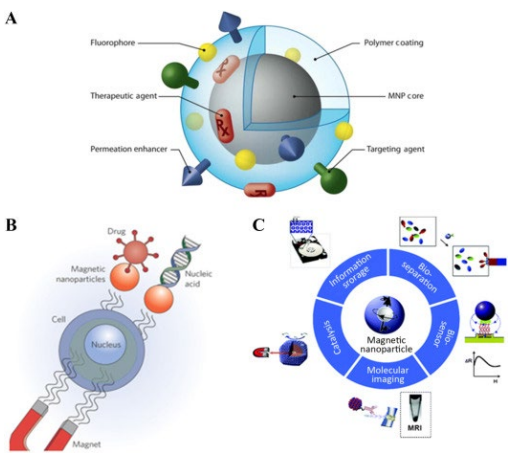


Figure (2): Effects of electric field on the fate of nano stem cells.

It should also be noted that the change in ion content and cell polarization can cause a cascade of intracellular signaling pathways and cause cell differentiation. Figure (3) shows the effect of the pulsed electrical signal on the differentiation of mesenchymal nano stem cells into cardiac muscle cells. In addition, the results of some investigations have shown that the electrical signal has caused dedifferentiation and morphological changes in the cell, which is related to the calcium channel mechanisms, and it can become a new point of hope for the production of inducible cells in a simpler way. In addition, it should be noted that the use of conductive scaffolds is very effective in order to improve the effect of the electrical signal, and today several studies have focused on the use of this type of scaffolds in various fields, and the promising effects in the regeneration of biological tissues with electrical activity such as orthopedics, nervous and cardiac have been observed (Figures 1–3).

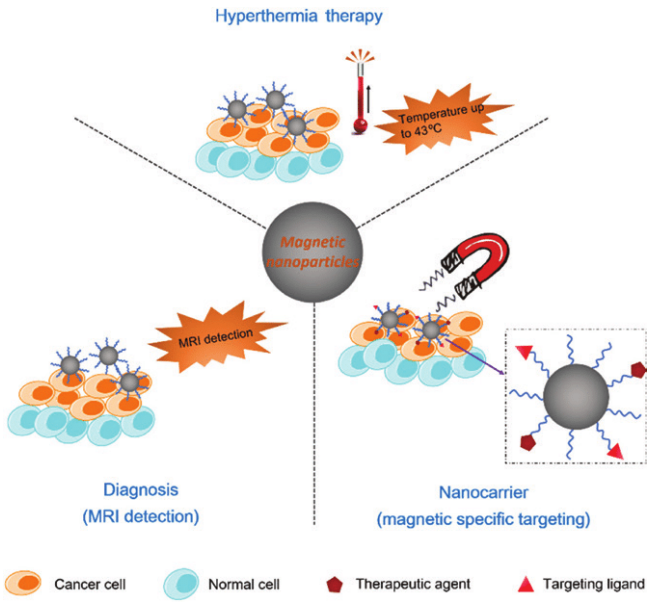


Figure (3): Therapeutic effects of electric signal on tissue repair.

Therapeutic Effects of Electric Signal on Tissue Repair

The first field of interest in regenerative medicine is wound healing, especially chronic wounds such as diabetic wounds. In general, the wound healing process includes inflammatory stages, cell proliferation and extracellular matrix rearrangement. If the healing process does not progress properly and the wound continues for more than a month, it may be described as a chronic wound. Electrical stimulation in wound healing mainly involves the application of electric current through electrodes that are placed directly on the skin. The use of this special type of electrode dressing has had a significant effect on the treatment of chronic wounds such as bedsores in patients. Figures (4–7) show the image of this type of dressings. It has been shown in human studies that electrical stimulation accelerates wound healing and increases skin repair and is an adjunctive treatment method in plastic surgery and can improve the survival of vascularized implants (flap) and grafts (implants without vascularization). and accelerate postoperative recovery as well as reduce necrosis after reconstruction. Also, previous studies have shown that electrical stimulation (ES) causes angiogenesis in all types of tissues and cells. Therefore, it can reduce the problems caused by the death of fat tissues used in autologous fat transfer (a cosmetic surgery technique) and increase tissue survival, which is a result of stimulating fat nano stem cells in the tissue. Many years have passed since the successful use of external electrical stimulation at the bedside to improve bone healing. Research has shown that this success has a significant effect, especially in irreparable bone defects, and in recent years, it has been suggested as an aid to bone tissue engineering treatments to optimize their therapeutic potential. This idea is due to the positive effects of electrical stimulation on the migration of nano stem cells, their proliferation, differentiation and adhesion to the scaffold, that all the aforementioned cell behaviors are beneficial for bone tissue engineering (BTE). The voltage used in these studies was in the range of 100 mV/mm. Another important tissue in the movement system is cartilage, whose repair is very significant today. A review of animal and clinical data has shown that electrical stimulation may increase cell proliferation and stimulate the synthesis of molecules related to the extracellular matrix of articular cartilage, such as type II collagen, aggrecan, and glycosaminoglycan. Nerve tissue is the most known tissue with electrical activity. Usually, in peripheral nerve damage, recovery is incomplete. Brunton's studies have shown that electrical stimulation directs axon growth and causes directional cell migration. A clinical study by applying a pulsed field with a frequency of 20 Hz for 100 milliseconds at a field of 200 mV/mm to human neural nano stem cells showed that the repair observed in the defect filled with nano stem cells and the use of stimulation electrical has been comparable with the autologous transplant group. The presence of a conductive substrate has had a significant effect on improving the differentiation of nano stem cells into nerves. One of the most interesting materials in this field is graphene, whose findings have shown that its presence in the scaffold improves the synaptic activity of nerve cells. Also, a review of studies has shown that the use of hair cells and spiral ganglion neurons (SGN) along with electrical stimulation can create new hopes in the treatment of deafness. In addition, investigating the electrical stimulation of MSCs on polycaprolactone/carbon nanotube conductive scaffolds has shown that the expression levels of rhodopsin (RHO) and pyriferin genes as markers of differentiation into eye

photoreceptor cells were significantly higher in electrically stimulated cells. Skeletal muscle tissues as well as cardiac muscle constitute another group of tissues with electrical function, and the use of electrical stimulation can be an effective step in compensating for their damage. Skeletal muscle is an electrochemical tissue that relies heavily on interaction with its extracellular matrix for internal organization and mechanical function. The combination of coating with laminin and electrical stimulation caused thicker myotubes compared to non–stimulated and non–coated samples. Therefore, through a combination of biochemical and electrical stimuli, it has created a new way to develop mature muscle tissue in 3D soft scaffolds. It has also been observed that the combination of electrical and mechanical stimulation has improved muscle contraction force through the rearrangement of extracellular matrix fibers. Also, the investigation of the effect of electrical stimulation on the differentiation of human induced pluripotent cells has shown that electrical stimulation in combination with mechanical stimulation has increased the differentiation efficiency of nano stem cells into cardiomyocytes, which can be a suitable method for the clinical treatment of heart attack in the future. Diabetes is one of the common non–communicable diseases that have very harmful effects on health. Pancreatic β cells play an important role in glucose homeostasis by secreting insulin (the only hormone capable of reducing blood glucose concentration). Disturbance in insulin secretion causes a chronic increase in blood sugar, which is characteristic of type 2 diabetes (T2DM). In recent years, research has shown that although the origin of these cells is endodermal, β cells share many characteristics with nerve cells, including electrical excitability. A group of researchers have shown that the combined treatment of thermal shock and mild electrical stimulation may preserve pancreatic cell volume and improve glucose homeostasis in diabetes. Also, animal studies have shown that intestinal electrical stimulation (IES) causes weight loss. However, it is not yet clear whether this method is a cure for diabetes. Although it reduced the apoptosis of pancreatic β cells, it had no effect on their proliferation (Figures 4–7).

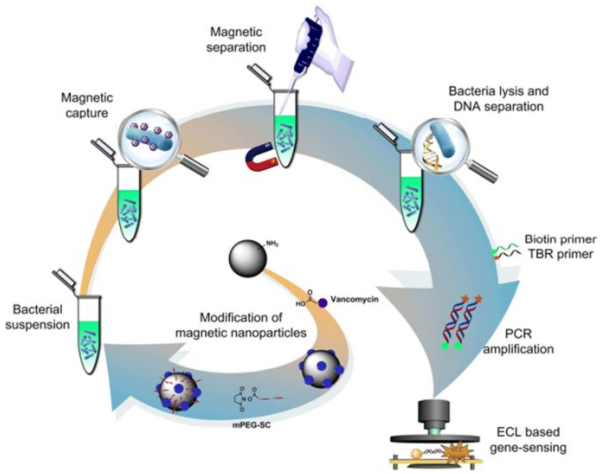


Figure (4): Combined treatment of thermal shock and mild electrical stimulation may preserve pancreatic cell volume and improve glucose homeostasis in diabetes.

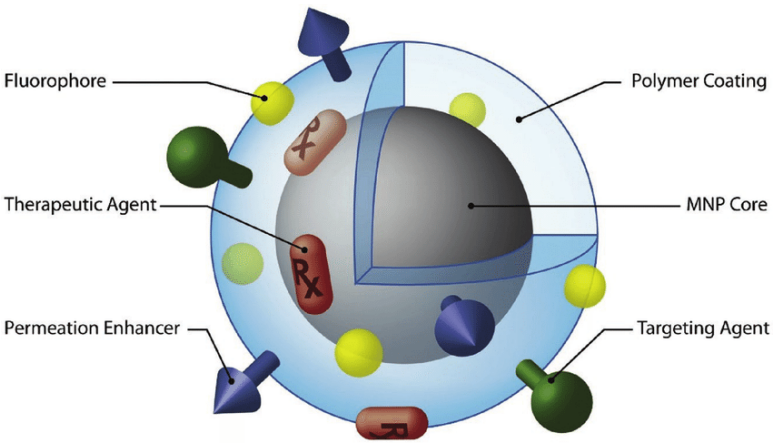


Figure (5): effect of the electrical signal on the arrangement of the cell division spindle and its effects on the cell membrane.

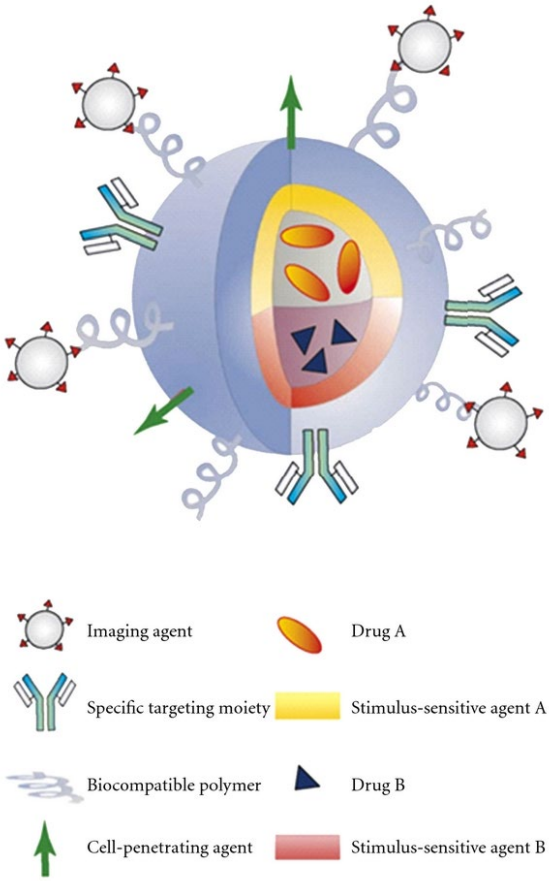


Figure (6): Effect of the pulsed electrical signal on the differentiation of mesenchymal nano stem cells into cardiac muscle cells.

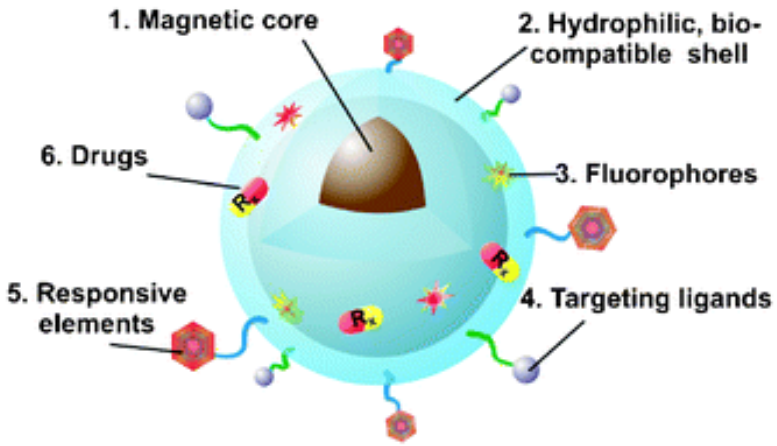


Figure (7): Therapeutic use of electric signal in cancer treatment.

The use of electrotherapy in oncology is less clear and is mainly based on animal studies. In 1959, Swiss researchers hypothesized that the application of electric current would inhibit or reduce the growth of growing cells. Low intensity electric current can inhibit ribonucleotide reductase involved in DNA synthesis. Austrian physician and electrical engineer Rudolf Pekar investigated the effect of galvanic current on cancer cells in the 1970s and developed electrical therapy to combat solid tumors. Cancer treatment based on low–intensity electric current is highly developed in China due to its advantages such as cheap price and effectiveness. Although limitations such as limitations in applied current intensity, penetration depth and damage to nearby tissues will limit its use in the bedside, nowadays the tendency is towards using electric field instead of electric current due to higher penetration depth and also Its better selective performance was observed. Unlike the direct and continuous electric field which has the effects of cell proliferation, the Nanosecond Pulsed Electric Field (nsPEF) and the electric field resulting from the alternating current, which is better known as the tumor therapeutic field (TTF), have the effects of apoptosis and as a result, are used in cancer treatment (Figure 8–10).

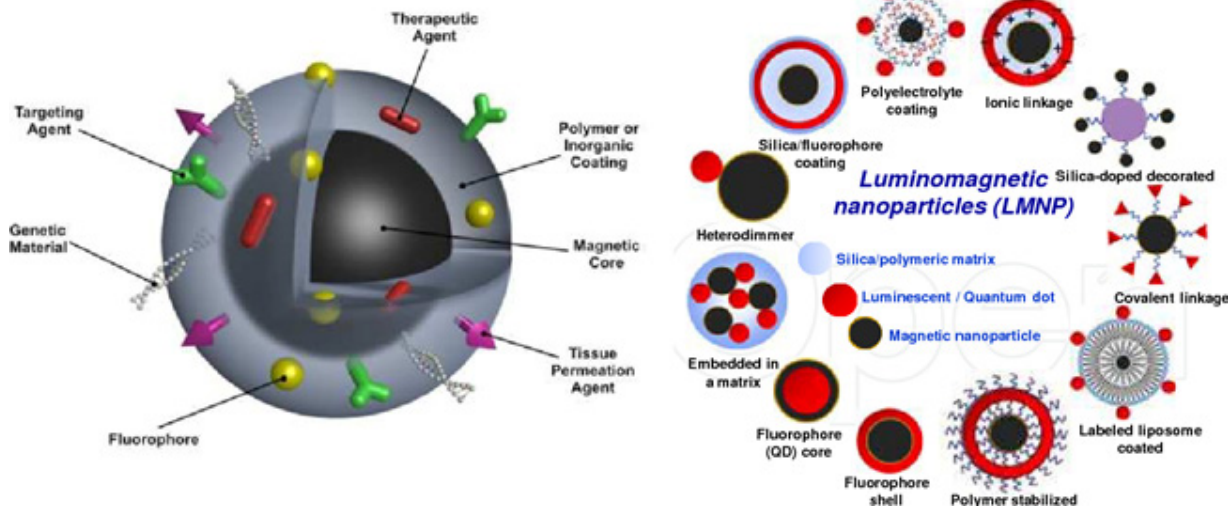


Figure (8): Effects of cell proliferation, Nanosecond Pulsed Electric Field (nsPEF) and electric field as the tumor therapeutic field (TTF).

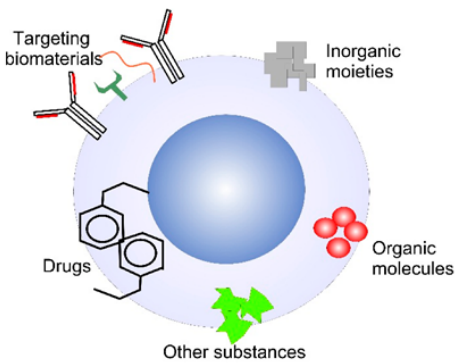


Figure (9): Effects of apoptosis in cancer treatment.

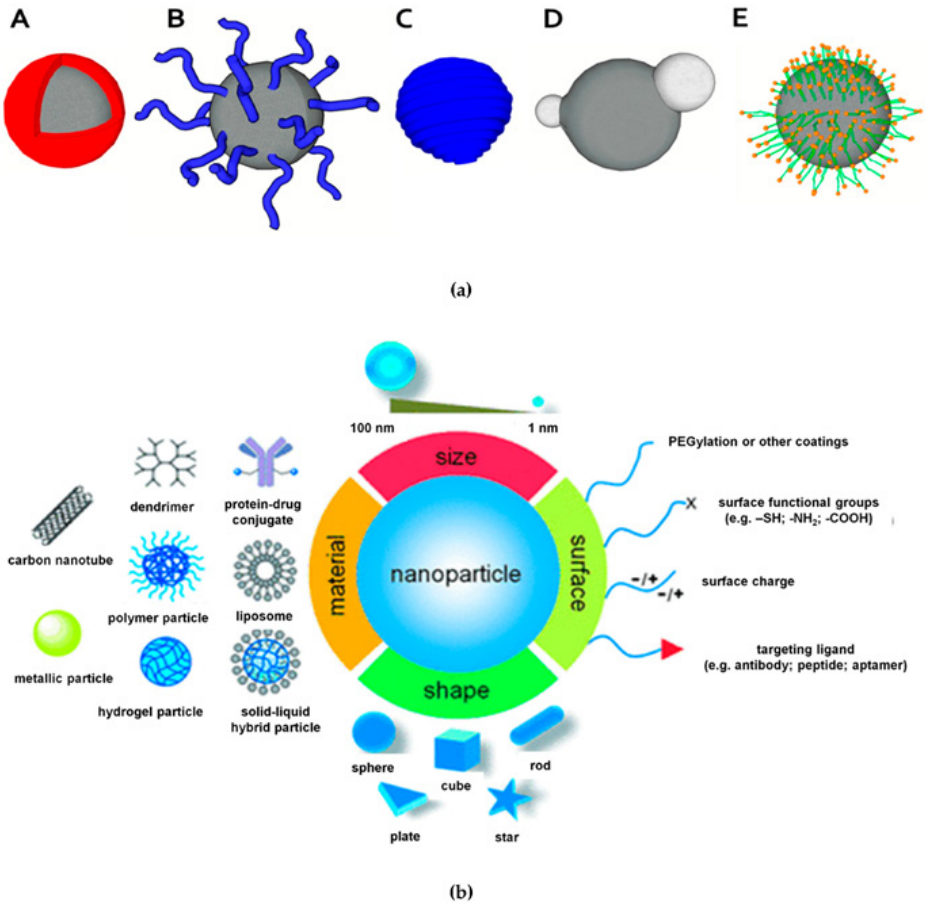


Figure (10): Pulsed electric field in cancer treatment.

Pulsed Electric Field in Cancer Treatment

Based on the pulse length, this technology is classified into millisecond, microsecond, nanosecond and picosecond pulses. The predominant use of pulsed electric fields is to modify the permeability of cell membranes, which is sometimes called electroporation and has been used in various ways to treat cancer. In this method, by applying an electric field to the cells, the permeability of the cell membrane increases. This allows the transfer of chemicals, drugs or DNA to the cell (also called electrotransfer). These include introducing genes to tumor cells to activate the immune response, introducing compounds with cytotoxicity to tumor cells, initiating necrosis using irreversible electroporation, and initiating immunological death and apoptosis of cancer cells with nanosecond nanopulse stimulation. In the meantime, nanosecond electric pulse as a developed technology of electroporation has been increasingly used in cancer treatment. This technology has been used first for military applications and also for use in the food industry and water purification. There are two main properties that distinguish it from microsecond pulses: intracellular penetration and large electric field amplitude. Pulses with nanosecond range due to their very short range and intracellular penetration can show unique effects inside the cell, also since the total energy provided is proportional to the product of pulse duration, current and voltage, duration Shorter pulse increases the voltage applied by this factor 0001 (relative to electroporation), so the voltage and current applied to cells and tissue can be much higher, while much less heat is generated. Possible mechanisms for the death of cancer and tumor cells include Nanosecond Pulsed Electric Field (nsPEF)–induced permeability of the plasma membrane and consequent influx of calcium ions, loss of mitochondrial membrane potential, which is probably due to events beyond the permeability of the inner mitochondrial membrane such as the release of cytochrome C or even Caspase activation. Figures (11–13) show the mechanisms of cell death caused by Nanosecond Pulsed Electric Field (nsPEF) in cells in the acute lymphoblastic leukemia cell line. One of the important advantages of nanosecond electric pulse is its ability to be used in combined treatment with various conventional treatments such as surgery, chemotherapy, photothermal and gene therapy. It has also been shown that the nanosecond electrical pulse has improved the function of the immune system and increased the sensitivity of neutrophil immune cells to cancer cells. So far, this technology has been used in the treatment of colon, liver and breast cancers and acceptable results have been obtained. The electric pulse with picosecond range is also a kind of development of the electric pulse with nanosecond scale, which has a pulse duration 1000 times shorter. The therapeutic effect of this technology has also been observed by preventing angiogenesis and removing cancer cells in cervical cancer (Figures 11–13).

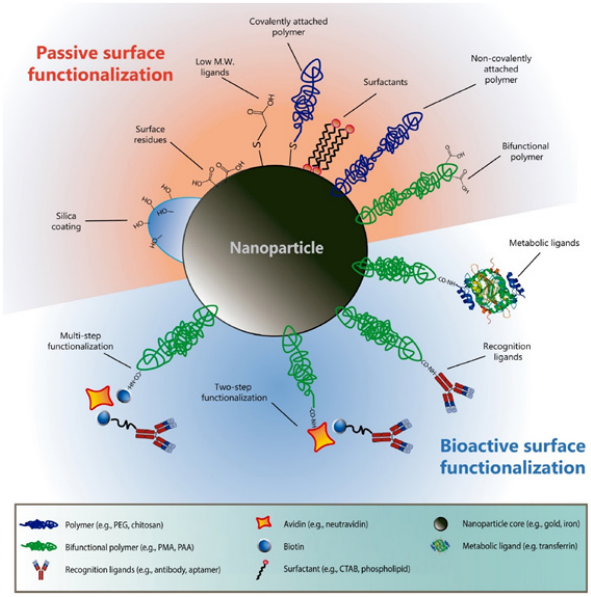


Figure (11): Therapeutic effect of preventing angiogenesis and removing cancer cells in cervical cancer.

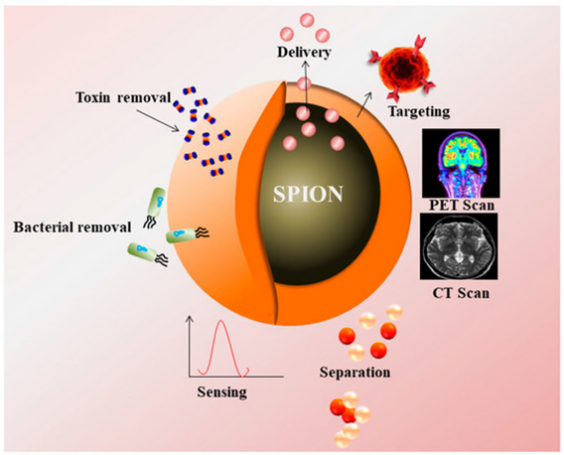


Figure (12): Electric pulse with picosecond range as a kind of development of the electric pulse with nanosecond scale.

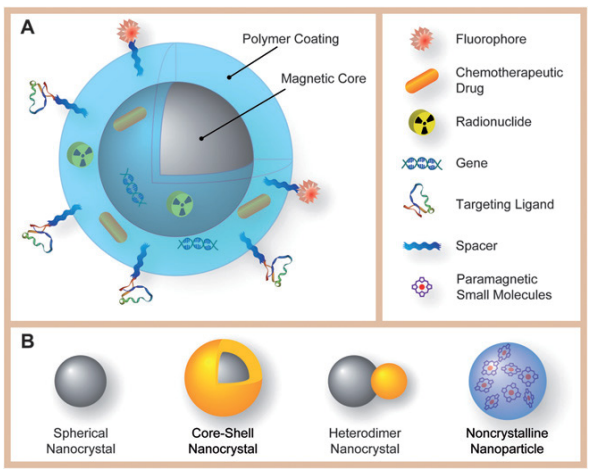


Figure (13): Application of tumor therapy field in cancer treatment.

Application of Tumor Therapy Field in Cancer Treatment

Tumor field therapy technology is a non–invasive therapy technology based on the alternating electric field and the biophysical phenomenon of dielectrophoresis (DEP), and is involved in the treatment of solid tumors. Also, its therapeutic basis is to prevent cell division by disrupting the replication of hereditary material by creating Disturbance in its polymerization, as well as disruption of the division spindle, and on the other hand, creating a heterogeneous electric field in the cell, and as a result, causing its dysfunction in the case of cancer cells. In addition, this heterogeneous electric field can disrupt the enzymatic function of the cell, which is inherited in the synthesis phase, and even induce apoptosis in the abnormal cell. Figure (14) shows the cellular mechanism of this technology and Figure (15) shows a sample of its equipment on the patient's body. Another positive point of this treatment is that it can work in a completely specific way and only target abnormal cells in terms of metabolism and transcription and does not harm healthy cells, and therefore it has been approved by the FDA. In addition to the mentioned cases, the tumor treatment field improves the function of the immune system and induces immunogenesis in such a way that it leads to the improvement of the function of the dendritic cells that express antigens (dendritic cells) and also increases the sensitivity and action. Therefore, T cells become cytotoxic (cytotoxic T cells) and both of these cells play an important role in facing cancer. Another important point is that this technology can be used as monotherapy or combined treatment with other treatments. Until now, the mentioned technology has been mostly used in glioblastoma cancer and has been able to play a very important role in improving the survival of patients. Figure (16) shows the effect of the simultaneous use of this technology together with the anticancer drug temozolomide (TMZ) in the survival of patients with glioblastoma cancer has been shown. Also, apart from glioblastoma cancer, this technology has also been used in the treatment of lung cancer (Figures 14–16).

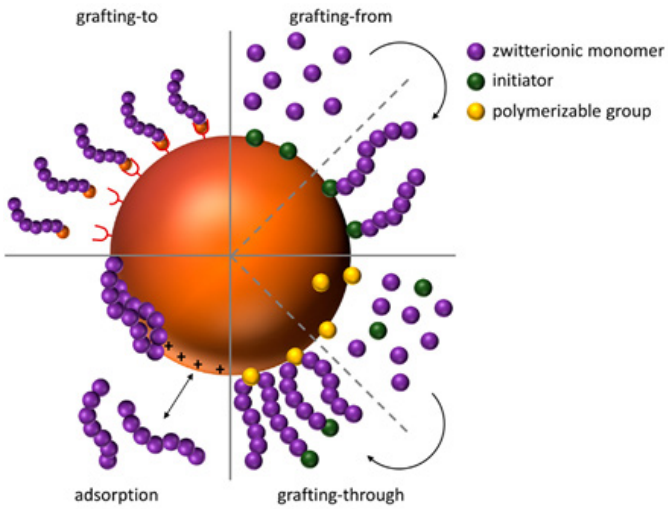


Figure (14): Effect of the simultaneous use of this technology together with the anticancer drug temozolomide (TMZ) in the survival of patients with glioblastoma cancer.

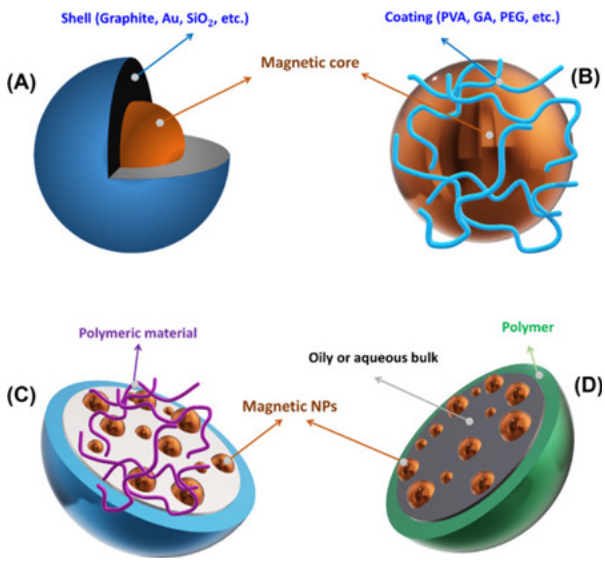


Figure (15): Application of tumor therapy field in cancer treatment.

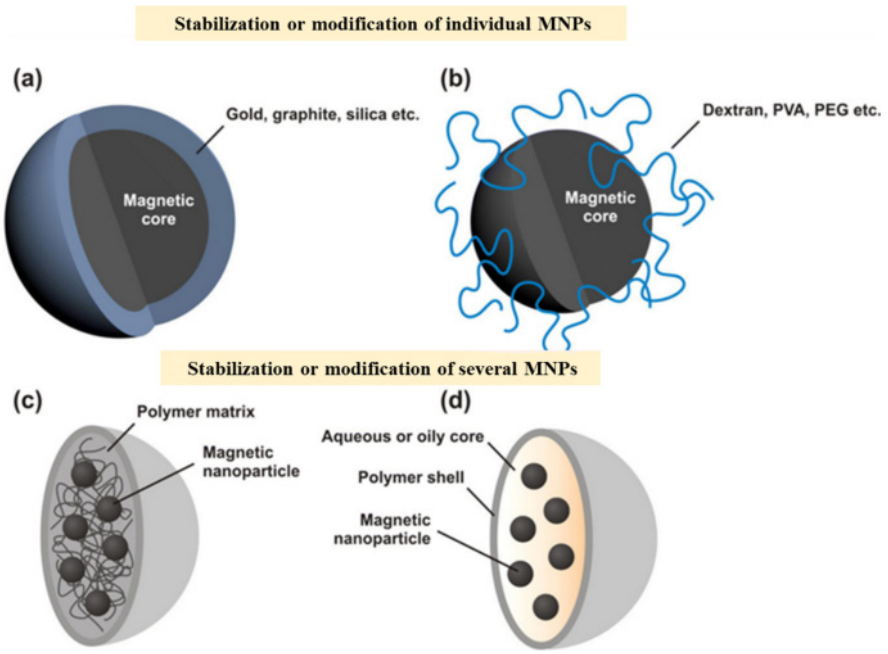


Figure (16): Electrical stimulation and helping to reduce the side effects of cancer.

Electrical Stimulation and Helping to Reduce the Side Effects of Cancer

One of the difficulties of cancer treatment, which has caused a severe decrease in the quality of cancer patients, is the side effects caused by its drugs, as well as the disabilities caused by the disease itself or its treatment strategies such as surgery. Studies have shown that electrical stimulation is an effective method not only in the treatment of cancer, but also in reducing the complications caused by the drugs used or the disabilities caused by its treatment (Figures 17 and 18).

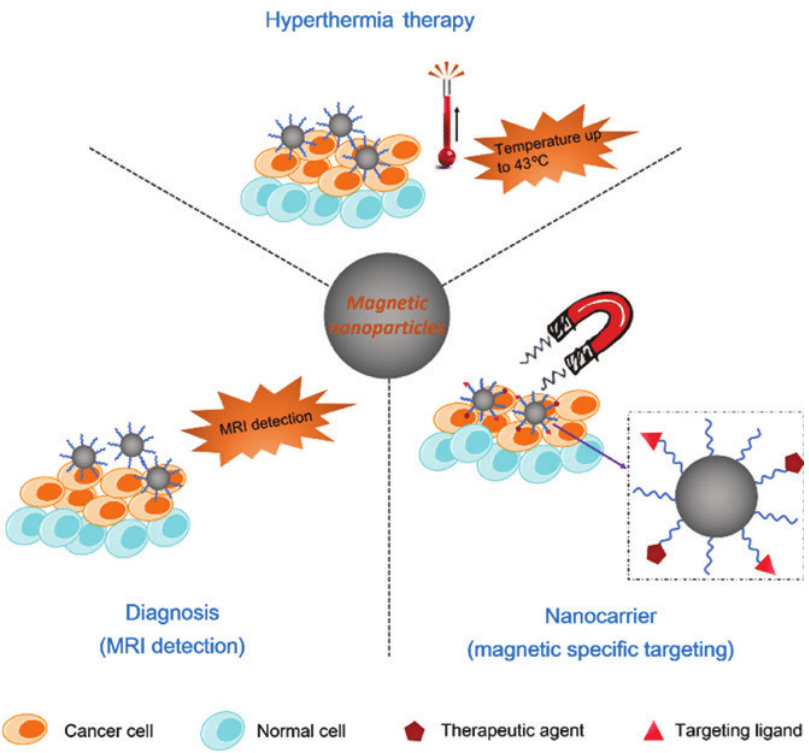


Figure (17): Electrical stimulation is an effective method not only in the treatment of cancer.

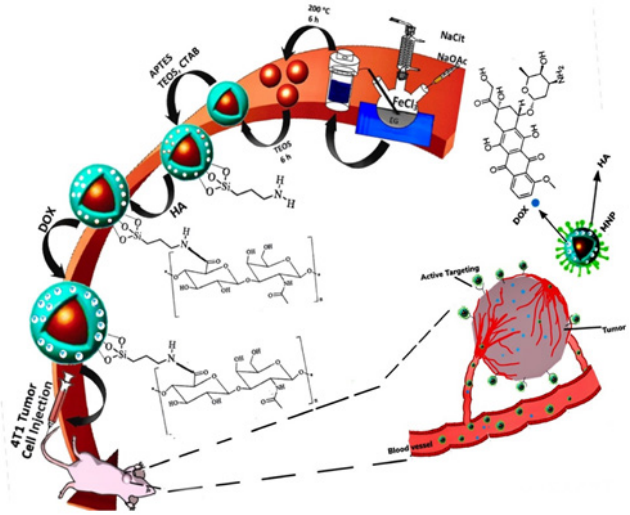


Figure (18): Reducing the complications caused by the drugs used or the disabilities caused by its treatment.

Conclusion

Electrical stimulation can induce growth, differentiation or even migration in nano stem cells, which are of particular importance in regenerative medicine for tissue regeneration. Also, electrical stimulation caused angiogenesis and improved adhesion of cells to the scaffold. The most important issue in improving the efficiency of electrical stimulation is the use of conductive scaffolds. The use of electrical stimulation alone or together with other chemical and physical signals has created many hopes for the reconstruction of many organs. On the other hand, the pulsed electric field, especially the nanopulse electric field, effectively induces apoptosis and death of cancer cells through the activation of intracellular mechanisms. Also, the electric field resulting from the alternating current effectively interfered with the proliferation of cancer cells and induced apoptosis in them. The common benefits of the mentioned treatments are improving the functioning of the immune system, the possibility of using them in combination with other treatments, ease of use, non–invasiveness, and their reasonable price. Also, studies show that electrical treatments not only help to treat cancer, but also reduce the side effects caused by the treatment and significantly improve the quality of life of patients. As a result, it can be said that the use of electrical stimulation and the application of bioelectrical principles could cause huge progress in regenerative medicine, cancer treatment, and as a result, improve the life span and quality of life of patients.

Acknowledgement

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