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Electric field-responsive nanoparticles and electric fields: physical, chemical, biological mechanisms and therapeutic prospects

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ABSTRACT

Electric fields are among physical stimuli that have revolutionized therapy. Occurring endogenously or exogenously, the electric field can be used as a trigger for controlled drug release from electroresponsive drug delivery systems, can stimulate wound healing and cell proliferation, may enhance endocytosis or guide stem cell differentiation. Electric field pulses may be applied to induce cell fusion, can increase the penetration of therapeutic agents into cells, or can be applied as a standalone therapy to ablate tumors. This review describes the main therapeutic trends and overviews the main physical, chemical and biological mechanisms underlying the actions of electric fields. Overall, the electric field can be used in therapeutic approaches in several ways. The electric field can act on drug carriers, cells and tissues. Understanding the multiple effects of this powerful tool will help harnessing its full therapeutic potential in an efficient and safe way.

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1. Introduction

Electric fields are among physical triggers that have revolutionized therapy. Occurring endogenously or exogenously, the electric fields can be used in a variety of therapeutic approaches.

Among the wide variety of applications, electric fields may serve as a trigger for drug release from drug delivery systems. In such cases, electro-responsive systems (including electro-responsive nanosystems) are used as stimuli-responsive drug carriers, that can enable (distal) spatially and temporally controlled drug release [1,2]. The active ingredient can thus be released in a sustained or pulsed manner, on demand, *via* the application of a low intensity external electric field. Apart being a trigger for release from drug carriers, electric fields act on cells (Fig. 1). Exogenous electric fields of higher intensities can directly influence the permeability of cellular membranes [3], and can be used as a stimulus for drug delivery [4] or serve as a therapeutic tool to ameliorate/induce (wound) healing and restore tissue integrity [5].

Electric field pulses parameters can be adapted and optimized for different applications, including intracellular delivery of chemicals [6] and genes [7–9], as well as tissue ablation [10]. The enhancement of transdermal delivery of charged compounds is known as iontophoresis [11,12]. Chemicals and genes can be delivered to bacteria, yeasts, cells and tissues, in the process denominated as "reversible electroporation" (or electropermeabilization) [13,14]. In this technique, pulsed electric fields induce a transient membrane permeabilization that allows the entry of compounds into cells [15,16]. Chemotherapy, where antitumor drugs are combined with electric field pulses, is called electrochemotherapy [17].

Moreover, microorganisms can be killed and cancer cells can be ablated after permanent permeabilization of the cell's membrane, without addition of chemical agents, but with the application of stronger electric fields. This process is known as "irreversible electroporation" [18].

In addition, when used *in vivo*, the electric field can induce local transient blood flow modifications [19].

Interestingly, studies also demonstrate that injured tissues generate endogenous electric fields [20,21], which are much more intense that the ones generated by uninjured tissues. The duration, intensity and orientation of these fields can affect the proliferation and differentiation of cells as well as drive cell migration. Tissue repair and regeneration might generate endogenous electric fields (up to 2 V/cm) [20] and may be influenced by applied electric fields [22].

Nevertheless, in addition to non-thermal effects, which are the cornerstone of the electroporation-based therapies, the electric filed may also induce heating. The latter can be attributed to the Peltier–Seebeck effect and the Thomson effect, as well as the resistive (Joule or Ohmic) heating [23]. Electrophoretic heating can also occur when an electric field is applied [24]. These phenomena are often referred to as "adverse effects of the electric field", but could potentially also be exploited as thermal therapy for cancer treatment [25].

This review describes the main therapeutic trends and overviews the main physical, chemical and biological mechanisms underlying the actions of the electric field (Fig. 2). In the first part of this review, we focus on electro-responsive drug delivery systems based on conductive polymers and electro-responsive hydrogels. Subsequently, we address the main therapeutic effects of electric fields following the increasing field strength.

2. Therapeutic electroresponsive systems

Electric field responsive systems, particularly the conductive polymer-based ones, represent a class of materials, which could enable a controlled release of active ingredients (including not only small molecules, but also polypeptides and proteins) [26,27].

Electroresponsive systems could be used as biomedical implants or as drug delivery systems, and could be administered in the form of (thin) films or nanoparticles. These systems could be either implanted or injected, and would (ideally) locally and evenly release their cargo or electrically stimulate adjacent cells and tissues over an extended period, upon electrical stimulation. Promising matrices for controlled drug release or bioactive scaffolds include conductive polymers [1,28] and hydrogel-based materials [2].

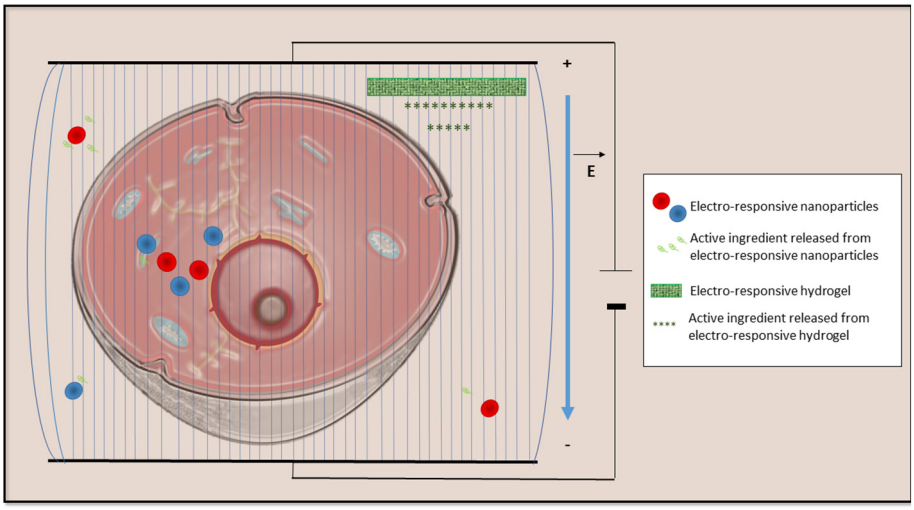

Fig. 1. Schematic representation of a cell and electro-responsive drug carriers (nanoparticles and hydrogel) placed between electrodes. When the electric field is applied, it affects electro-responsive systems *and* the cell (E denotes the electric field).

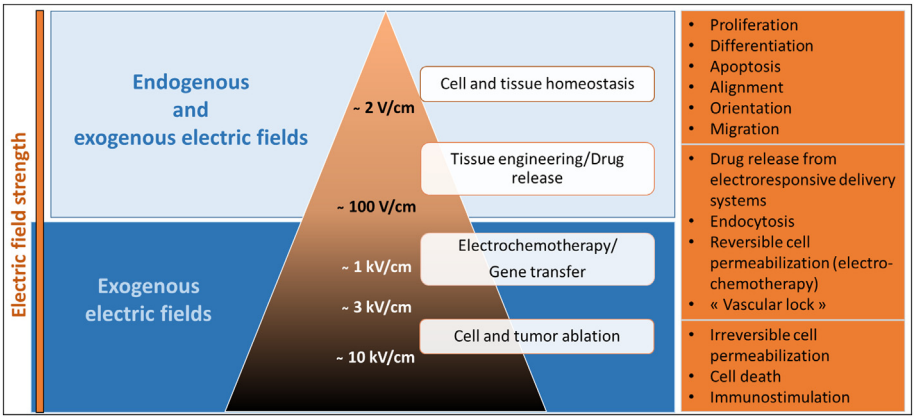

Fig. 2. Schematic summary of the effects induced by electric fields as function of field strength.

2.1. Conducting polymers

Intrinsically conducting polymers are organic polymers that conduct electricity. Among conductive polymers that could be used for biomedical applications, doped polypyrrole (Fig. 3) is the most extensively studied one. Other promising candidates include *N*-methyl pyrrole, polyaniline, polytyophene and its derivatives, such as poly(3,4-ethylenedioxythiopene) as well as poly(*p*-phenylene vinylene) and its derivatives [1,28,29]. Moreover, other polymer composites, spiked with conductive polymers (polypyrrole and polyaniline) or conductive fillers, such as graphene, carbon nanotubes or metallic nanoparticles, can also be used [29].

The drug release responsiveness of the systems, which is induced by electrical stimulations, depends on the surface area of the polymer matrix. Therefore, micro- [30] and nanostructures [1] are of particular interest for controlled drug release, and will be reviewed in detail in this review.

2.1.1. Mechanisms of electrical conductivity and active ingredient release

The electrical conductivity of conductive polymers is due to the delocalization of π-electrons along the π-conjugated backbone. Delocalized electrons are stabilized by the addition of (anionic) dopant ions to the oxidized polymer, which creates a continuous conduction band. This endows the polymer with conductive properties. When conductive polymers, which contain active ingredients, undergo redox reactions, the changes in polymers charge affect polymers conductivity and volume, which results in the release of the active ingredient [28].

The drugs that are incorporated in the polymer are mainly released by electrostatic repulsion. When a potential is applied (generally in the range of – 1 V) [1], the conducting polymer is reduced and the drug (which had either been used as the anionic dopant, or was incorporated within the polymer matrix) is discharged in the surrounding environment. The rate of drug release depends, on one hand, on the polymer's morphology (including its density) and its electromechanical properties, and on another hand on the media surrounding the drug delivery system. The processes used during the polymerization protocol (especially to the amount and rate of charge passed during polymer synthesis) directly affect polymers electric properties and the drug release rate, and can therefore be employed to customize the release pattern of the active ingredient. In addition, drug release is affected by the pH and the temperature of the solution in which the polymerization occurred and/or by the addition of different dopants [28].

The polymerization protocol thus affects the rate of drug release as it affects polymers responsiveness to the field applied during the drug release protocol. Nevertheless, active ingredients may also spontaneously release from the polymer. Spontaneous release depends on polymers density/porosity/surface area and on the affinity of the loaded molecule for the polymer matrix.

The molecules used as active ingredients, retained within the conducting polymers, should not be electroactive at applied potentials (applied either during conductive polymer manufacturing process or

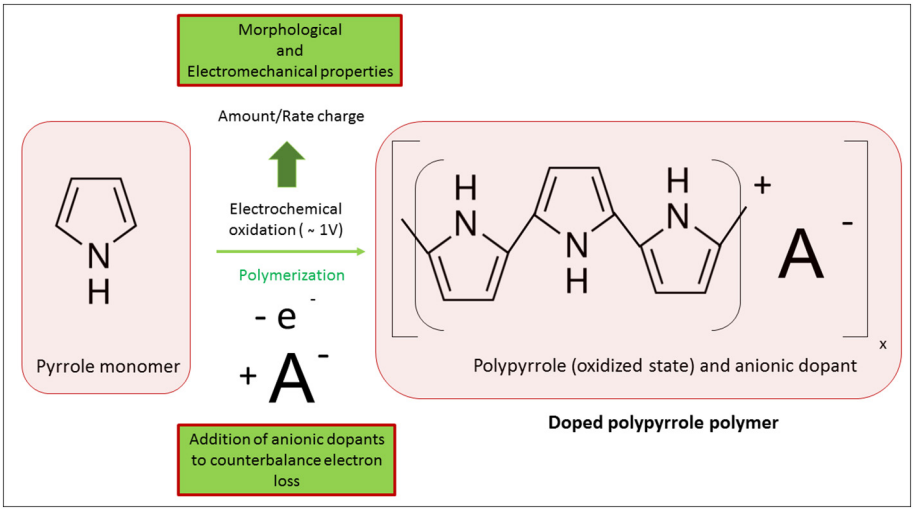

Fig. 3. Synthesis and loading of the intrinsically conductive polymer polypyrrole. (A^- denotes the anionic dopant).

during the onsets of drug release from the delivery system). The pK_a of the molecule is a factor influencing the loading and release from the conductive polymer [28]. Apart from the acid dissociation constant, the charge of the drug is not necessarily a limiting factor; negatively and positively charged, as well as neutral active ingredients, can be loaded into the conducting polymer [28].

2.1.2. Nanoparticles made of intrinsically conducting polymers

Owing to their increased specific surface, which results in larger and faster active ingredients release, nanoparticles made of [31] or coated with [32] conductive polymers, could become the drug delivery systems and/or biosensors of choice. Electroresponsive nanoparticles for potential therapeutic applications mainly include polypyrrole or poly(3,4-ethylenedioxythiopene) (PEDOT). These conductive polymers either form the nanoparticles matrices, or can be used as coating for metal nanoparticles. Noble metal nanoparticles, such as the ones made of gold (Au) or silver (Ag), can chemically bind to sulfur atoms within conductive polymers. Among different conductive polymers (polypyrrole, poly(3-methylthiophene), and PEDOT), PEDOT is not only the most conductive at connection sites with Au and Ag nanoparticles, but it also has the highest affinity for Au/Ag nanoparticles [33]. Some of the studies employing nanoparticles made of intrinsically conducting polymers, that have a potential therapeutic use are summarized in Table 1.

2.1.3. Biocompatible polymers spiked with conductive fillers

As due to their rigidity and brittleness, conducting polymers are difficult to process, efforts have been directed in the studies involving biocompatible polymers composites or polymers spiked with conductive polymers (polypyrrole, polyaniline or PEDOT) or conductive fillers, such as graphene, carbon nanotubes or metallic nanoparticles. Some of the studies employing spiked conducting polymers with potential therapeutic use are summarized in Table 2.

While enormous progress is being made in the synthesis of conducting polymers, these systems were not translated yet into clinics. The unstimulated release of drug is among the main obstacles for their practical use.

2.2. Electro-responsive hydrogels

Electro-responsive hydrogels are water-swollen macromolecules (networks of polyelectrolyte chains that are hydrophilic and contain a high number of ionisable groups along the polymer backbone), which can additionally swell or shrink after electrical stimuli. The use of electro-responsive hydrogels in therapeutic approaches is at a developmental stage [43], but it indeed holds a great promise in electro-stimulated drug delivery [44].

2.2.1. Mechanisms of current-related response and active ingredient release

When an electric field is applied to polysaccharide hydrogels, the changes in polarity, ionic strength and pH alter the net osmotic pressure within polymers (cause electro-osmosis), which results in bending, swelling, shrinking or erosion of the polymer and a consequent release of the active ingredient [44]. While, to some extent, the cross-linking of the hydrogel reduces the diffusion of the loaded active ingredient, due to the smaller mesh size of the matrix, other mechanisms of cargo release depend on the charge of the hydrogel and the ionic charge of the drug (Fig. 4) [2]. When chitosan hydrogels are exposed to the electric field, they generally collapse, and the drugs either leave the hydrogel matrix because of diffusional forces (in case of neutral drugs) or exhibit electrophoretic migration towards the electrodes (in case of charged drugs). Conversely, in alginate-based hydrogels, the negative charge of carboxylate groups in the matrix exert repulsive forces that promptly expel the anionic drug from the scaffold [45]. In contrast, the negatively charged matrix retains positively charged drugs. In addition, the reduced diffusion of cationic drugs is additionally diminished after the application of an electric field [45].

2.2.2. Hydrogel films and implantable systems with potential therapeutic use

Electroresponsive hydrogels principally include chitosan, alginate, chondroitin sulfate and hyaluronic acid and acrylate derivatives [2,40,44,47–51]. In order to enhance the responsiveness to electrical stimuli, additives, may be added to hydrogels. Among additives, inorganic nanoparticles, such as carbon nanotubes [52], appear particularly attractive. Electro-responsive hydrogel nanoparticles and hydrogels spiked with inorganic nanoparticles are summarized in Table 3.

Electro-responsive hydrogels are substantially under-investigated, but there is an increasing interest in hydrogel use, which is due to hydrogels features, such as soft consistency, biocompatibility, and external-stimuli triggered release. To date, their use is limited to preclinical studies [43,53].

3. Therapeutic effects of electric fields

Endogenous electric fields, which occur in the cytoplasm and in the extracellular space, are pivotal in biological processes, such as long-range protein interactions [54], electron transfers in chemical reactions [55], embryogenesis [56], cell differentiation [57] and growth [58], wound healing, tissue repair and tissue remodeling [59] *etc.*

The advantageous effects induced by electric fields thus prompted a series of therapeutic approaches, including neuromuscular stimulation, and the stimulation of tissue remodeling and wound healing [60]. In addition, the use of exogenous electric field pulses to deliver therapeutic molecules to tissues and organs has been developed over the last decades, has been established as efficient and safe, and is now increasingly implemented in clinical practice [61,62].

Electric field pulses may induce an increase in the permeability of cell membranes (Fig. 5) [63]. Electropermeabilization or electroporation allows hydrophilic molecules that are otherwise non-permeant, such as the highly toxic drug bleomycin, to gain direct access to the cytosol of cells. This treatment modality, also known as electrochemotherapy [6], is successfully used in clinics for cancer treatment. In addition to the commonly used electroporation procedure, other modalities are of particular interest. The latter include i) non-permeabilizing electric field pulses that can enhance the uptake of molecules by endocytosis

Table 1
Nanoparticles made of intrinsically conducting polymers releasing their cargo when low voltage electric fields are applied.

Reference	Polymer	Filler/Drug	Potential therapeutic use
Cantu et al. [34]	poly(diethyl-4,4′-{[2,5-bis(2,3-dihydrothieno[3,4-b][1,4] dioxin-5-yl)-1,4-phenylene] bis(oxy)}dibutanoate) and poly(3,4-ethylenedioxythiophene) (PEDOT)	4-dodecylbenzenesulfonic acid and poly(4-styrenesulfonic acid-*co*-maleic acid)	Laser-mediated photothermal ablation of cancer cells
Koh et al. [35]	2,2′: 5,5″-terthiophene-3′-benzoic acid	Gold nanoparticles, Anti-iNOS antibodies	Detection of inducible nitric oxide synthase in neuronal cell
Samanta et al. [36]	Polypyrrole	Fluorescein, piroxicam, insulin	Controlled drug delivery
Ge et al. [37]	Polypyrrole	Fluorescein, daunorubicin	Controlled drug delivery

Table 2
Conducting polymers spiked with conductive fillers.

Reference	Conductive polymer	Filler/Drug	Potential therapeutic use
Mazloum-Ardakani et al. [38]	Poly (catechol)	Graphene, Gold nanoparticles	Detection of acute lymphoblastic leukemia
Chen et al. [39]	Polyaniline	Polylactide	bioac- tive scaffolds for bone tissue engineering
Shi et al. [40]	Polypyrrole	Nanoporous cellulose gels	Bioactive scaffolds for bone tissue engineering N Nerve regeneration
Shahini et al. [41]	Poly(3,4-ethylenedioxythiophene) (PEDOT)	Poly(4-styrene sulfonate)	Scaffolds for bone tissue engineering
Luo et al. [42]	PEDOT	Carbon nanotubes	c Chronic neural stimulation

[64] and ii) high intensity electric field pulses that can induce the irreversible permeabilization of the cells [18], leading to cell death (Fig. 5).

Prior detailing the biological responses of the cells to the electric field, let us first review the physical response of the cell, submitted to electric field.

3.1. Basic principles of the physical effect of the electric field

Beside the well-known physical and chemical effects of the electric field in a conductive medium (Joule effect, dielectrophoresis, bioelectrochemical phenomena at the vicinity of the electrodes), it has been widely accepted and known for more than 30 years, that the key effect of the electric field on cell membranes is a position-dependent change in the resting transmembrane potential difference ($\Delta\Psi_0$) of the plasma membrane [65]. The electrically induced potential difference $\Delta\Psi_E$, which corresponds to the difference between the potential inside the cell Ψ_{in} and the potential outside the cell Ψ_{out}, at the point M on the cell surface, is given by the equation:

$$\Delta\Psi_E(t) = \Psi_{in} - \Psi_{out} = -fg(\lambda)\, rE\, \cos\theta(M)\left[1 - e^{-t/\tau}\right] \quad (1)$$

where **t** is the time after which the electric field pulses are switched off, **f** is the factor indicating the cell geometry (f = 1.5 for a sphere), **g(λ)** is a factor related to different conductivities, **r** is the radius of the pulsed cell, **E** is the electric field strength, and **θ(M)** is the angle between the direction of the field and the normal of the cell's surface at the point **M**, which denotes the point on the cell's surface that is being considered, and **τ** is the characteristic time constant of the membrane charging [63].

The field-induced potential difference is thus added to the resting potential:

$$\Delta\Psi = \Delta\Psi_o + \Delta\Psi_E \quad (2)$$

The electric field effect depends on the position on the cell's surface. The side of the cell facing the anode is hyperpolarized, while the side of the cell facing the cathode is depolarized. The transmembrane potential of a cell submitted to an electric field is critical for efficient cell permeabilization, and depends on the cell's size, shape, and orientation [63].

3.2. Chemical phenomena occurring at cell membrane

The potential chemical modifications of the cell membrane, induced by (pulsed) electric fields, have not been a matter of extensive research. The studies performed thus far indicate that pulsed electric fields increase the level of reactive oxygen species (ROS) at the periphery of cells [66], as well as induce membrane peroxidation [67]. In parallel, molecular dynamics simulations and *in vitro* experiments indicate that the oxidation of membrane components enhances the susceptibility of cell membranes to electropermeabilization [68].

In order to shed light on factors involved in the effects of pulsed electric fields on membrane oxidation, a recent study evaluated chemical processes occurring at the level of membranes of giant unilamellar vesicles (GUVs), made from phospholipids with various degrees of fatty acid unsaturation [69]. The oxidation of phospholipids was studied in presence of metal ions, light, oxygen and antioxidants [69]. The application of pulsed electric fields induced the oxidation of the GUV phospholipids and the oxidation level depended on the duration of the pulse [69]. Light and oxygen increased electric field pulse-induced lipid peroxidation, but antioxidants completely suppressed peroxidation. In order to ascertain the implication of membrane constituents, pulses were applied to a GUV-free solution, where pulsed electric fields did not generate any additional ROS when GUVs were not present in the medium. The occurrence of lipid peroxidation was related to the ROS already present in the solution before exposure to pulsed electric fields, and was not attributed to a direct pulse-induced peroxidation [69]. The electric field pulses are thus suggested to facilitate the entrance of

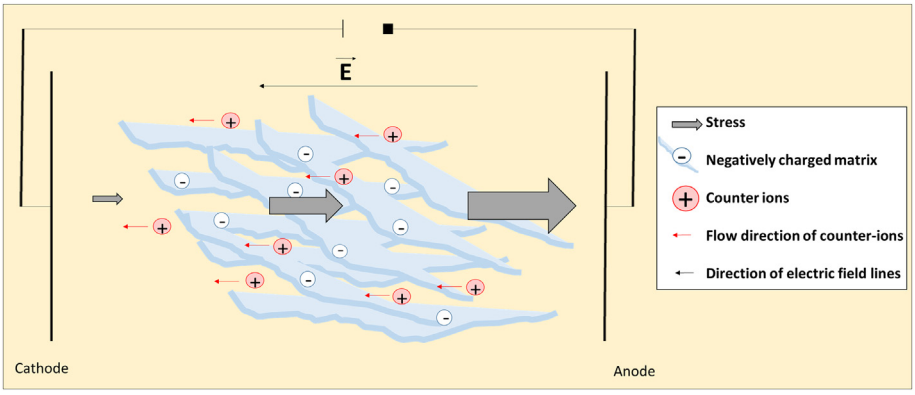

Fig. 4. Effect of the electric field on a polyelectrolite gel. Positively charged ions migrate towards the cathode, while the immobile anionic groups of the polymer are attracted towards the anode. The attraction of the matrix towards the anode is higher than the attraction of the mobile counter ions to the cathode and a stress gradient is established. *Adapted from Ref* [46].

Table 3
Hydrogel materials with potential therapeutic applications.

Reference	Hydrogel	Additive/Drug	Potential therapeutic use
Ying et al. [47]	Acrylate and acrylamide derivatives	Angiopep-2 and phenytoin sodium	Anticonvulsant
di Luca et al. [48]	Acrylamide and Polyethylene glycoldimethacrylate	Graphene oxide, gelatin or trypsin	Smart skin bandages
Servant et al. [49]	Polymethacrylate and *N,N′*-methylene bisacrylamide	Graphene, sucrose, doxorubicin	Controlled drug delivery agent
Servant et al. [50]	Polymethylacrylate and N, N′ -methylene bisacrylamide	Carbon nanotubes, sucrose	Controlled drug delivery agent
Zhao et al. [40]	Chitosan	Mesoporous silica nanoparticles, ibuprofen	Controlled drug delivery agent
Atoufi et al. [51]	Agarose/alginate-aniline tetramer	Dexamethasone	Controlled drug delivery agent
Verbrugghle et al. [44]	Pluronic methacrylic acid	–	Arterial occlusion agent
Guillet et al. [52]	Agarose	Carbon nanotubes	Transdermal drug delivery agent

ROS within the membrane, allowing the contact between ROS and lipid chains and causing oxidation [69]. These findings suggest that the application of electric pulses on cells might result in the oxidation of the membrane phospholipids [69].

3.3. Biological mechanisms underlying the effects of the electric field

Cells are sensitive to electric fields, which constitute a directive factor for cell proliferation [70] and migration [71], play an essential role in embryonic development, affect cell orientation, and impact the growth and cell differentiation [72]. Electric fields can, for example, induce neurite sprouting from neurons, promote neurite growth along the field axes, induce the elongation of spherical myoblasts in the direction perpendicular to the field, or stimulate the differentiation of fibroblasts and pigment cells [73], as well as affect cell division [58]. Interestingly, the effects of electric fields might be stimulating or inhibiting, and depend on the exposure conditions and the cell type [74]. Consequently, electric fields may be used in both regenerative therapies (such as the ones affecting stem cell differentiation) to stimulate (stem) cell proliferation [57] or in cancer treatment techniques to inhibit cancer cell growth [75].

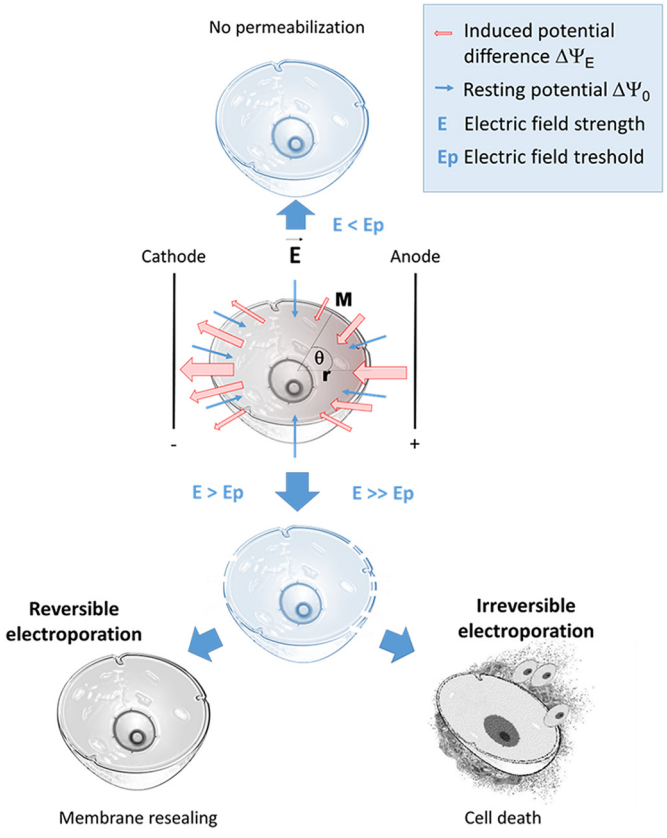

Fig. 5. Schematic representation of the effect of the external electric field applied on a living cell. The external electric field induces a change in the resting transmembrane voltage. The value of the induced change depends on the shape of the cell and the conductivity of the media. Since the resting transmembrane potential is negative, the first part of the membrane that will be permeabilized is the pole facing the positive electrode. If the applied electric field is lower than the threshold that induces the permeabilization, no overt effects are observed on the membrane level (top of the figure). Conversely, when the applied electric field is high enough, the cell undergoes either transient permeabilization or an irreversible electropermeabilization, that finally leads to cell death. The **r** is the radius of the pulsed cell, **E** is the electric field strength, and **θ(M)** is the angle between the direction of the field and the normal of the cell's surface at the point **M.**

3.3.1. Electric field induced cell proliferation

Among the causes related to higher proliferation rates of cells submitted to electric fields, it was suggested that electric fields might increase the convection of nutrients and increase nutrient transport due to the electrokinetically driven flow [76]. In a similar fashion, as electrophoretic mobility may cause accumulation of molecules at the surface of cell membranes, especially in the vicinity of (charged) proteins embedded in the phospholipid bilayer, this might result in conformational changes in protein molecules and asymmetrical protein redistribution within the membrane, leading to alterations in cell symmetry and orientation [77,78].

Proliferative abilities of cells may also be correlated with transmembrane potentials, which arise from combined activities of ion channels, pumps and gap junction complexes [78]. Cells with a very high resting potential (*i.e.* muscle cells and neurons) show poor mitotic activity [79], whereas highly proliferative cancer cells exhibit lower transmembrane potential [80]. The transmembrane potential also varies through the cell cycle [81]. Remarkably, when the membrane of neurons is depolarized, even mature neurons can undergo mitosis [82]. The signaling pathway involving calcium/calmodulin, nitric oxide synthase, nitric oxide and cGMP is also suggested to induce proliferation *via* electrical stimulation [83].

3.3.2. Electric field induced cell migration

The electric field induced cell migration is called electrotaxis or galvanotaxis [71]. Electrotaxis plays an important role in embryogenesis, inflammation, wound healing, and tumor metastasis. In this part we will focus on tissue repair, especially at the epithelium level.

In an intact epithelium cells actively pump sodium ions out of the cell through the Na^+/K^+ATPase (sodium–potassium pump) action and eNaC channels, leading to a sodium gradient, which is maintained between the basal layer of the epidermis and the upper layer by tight junctions [84]. This active process creates a transepithelial potential (TEP) within the epithelium. At skin scale, depending on the body part, this TEP was measured between 0.15 and 0.45 V/cm with the basal side positive in relation to the skin surface [84].

When the skin is damaged, the passive relocation of ions leads to the creation of a local endogenous electric field at wound margins. This

endogenous electric field, with a strength estimated between 0.42 and 1 V/cm [85,86], was experimentally measured in humans and animals and was shown to display some major effects on cells *in vitro* and *in vivo* [87,88]. On the genetic level, it was observed that signaling pathways guiding cell migration and electric-field-induced wound healing lay on phosphatidylinositol-3-OH kinase-ϒ, PTEN activation and integrin β4 [88,89]. Indeed, a genetic deletion of phosphatidylinositol-3-OH kinase-ϒ abolishes the electrically induced movement of epithelial cells during wound healing. On the contrary, a deletion of PTEN enhances the electrotactic responses. Interestingly, studies performed on a corneal epithelial monolayer cell culture, showed that the greatest electro-induced epithelial cell migration was obtained with a field strength, comparable to endogenous electric field measured in wounds (i.e 1-2 V/cm) [88]. Although it remains unclear how external electric field cues transform into cellular responses, the most commonly suggested mechanism is based on asymmetrical distribution of membranes receptors, such as epidermal growth factor receptor, concanavalin A receptor, acetylcholine receptor or extracellular binding receptors integrins [90].

Thus, applying external electric fields in the range of 1 V/cm strength is an emerging technology in wound care [91,92]. Interestingly, in the wound-healing context, the application of therapeutic electro-responsive nanoparticles could benefit from this endogenous electric fields generated at wound margins.

3.3.3. Electric field induced cell differentiation

Electric fields have morphogenetic potential and can therefore play a significant role in the induction and modulation of stem cell differentiation [57]. Specific electric field parameters together with inherent and induced electrical conductivities of tissues, as well as exposure time intervals and cells microenvironment are critical parameters affecting stem cell differentiation into a particular lineage [93].

The use of external electric fields was reported to induce chondrogenic, osteogenic, neurogenic and cardiomyogenic differentiation of stem cells [94–97]. While the field strengths for osteogenic differentiation can be as low as 0.02 V/cm [98], neurogenic and cardiomyogenic differentiation occurs at higher electric field strength values (about 1 V/cm and 2 V/cm, respectively) [99,100].

The induction of responses to electric fields are believed to occur after the electro-coupling at the plasma membrane. In order to transfer the electrical energy from “one circuit segment” to another, the electrically charged membrane receptors (which are otherwise disseminated throughout the membrane, which itself has insulating, rather than conductive properties) asymmetrically redistribute throughout the cell membrane [101]. This induces a series of signaling cascades.

In addition, the depolarization of the cell membrane induced by the application of exogenous electric fields, activates the voltage gated Ca^{2+} channels, which results in the elevation of intracellular calcium ions concentration [102]. Electrical stimuli may also affect the tensions in the cytoskeleton due to the reorganization of actin [103]. In such way, the cytoskeleton and the processes, in which the cytoskeleton is involved, may be altered [104]. One of such processes is namely the electric field-induced redistribution of membrane receptors [105].

The electric field induced stem cell differentiation is briefly mentioned in this review, but if readers are interested in this field, we warmly suggest a very recent review extensively dealing with this subject [57].

3.3.4. Electric field induced endocytosis and endocytosis-like processes

Non-permeabilizing and permeabilizing pulsed electric fields can both induce endocytosis [64,106–111]. In this section, we focus on the effects of non-permeabilizing electric fields, because they are of particular interest for the induction of endocytic pathways.

The exposure of cells to trains of non-permeabilizing, low voltage electric field pulses (typically less than 100 V/cm), may lead to a stimulated uptake of low and high molecular weight molecules, adjacent or adsorbed to the cell membrane [108,112,113]. The exposure of cells to bipolar asymmetric electric pulses (exposures of 2 to 20 min, electric field strength of 5.7 to 18 V/cm, pulse durations 100-500 μs and frequency 100–500 Hz) increased the endocytosis up to 1.5 fold [113]. The bipolar signal allowed a minimization of electrophoresis and minimized the electrochemical reactions at the electrodes [64,107], but unipolar pulses were also reported as very efficient inductors of endocytosis-like pathways. The exposure of cells to unipolar low electric fields pulses (of 20 and 43 V/cm) showed an induction of bovine serum albumin, dextran and DNA adsorption on cells surfaces and an increased uptake of these macromolecules *via* endocytosis-like processes [106]. While the adsorption of molecules did not depend on temperature, the internalization only occurred when low electric field pulses were applied at 24 °C. Adsorption and internalization are both initiated by electrophoretically induced segregation of charged membrane components, located in the outer monolayer of the plasma membrane. The resulting asymmetric charge density between the outer and inner monolayer of the cell membrane affects the Gaussian curvature and causes membrane bending towards the inside of the cell. This phenomenon is followed by membrane fissions, which result in the formation of endocytic vesicles [106]. The absorption of molecules in the presence of a train of low electric field pulses was thus increased up to10 fold and internalization of molecules increased up to 5 fold [106].

Interestingly, high concentration of hydrogen ions can also induce the formation of endocytic vesicles [114], and, coincidentally, protons are among the electrochemical byproducts created at the electrode-solution interface [115].

In addition to increased molecules adsorption and uptake, low electric field pulses induce cell aggregation. The latter was favored even 20 min after exposure to electric fields [106].

3.3.5. Electric field induced cell fusion

Electric fields can move cells by dielectrophoresis, and when the electric field strength is high enough, the membranes of adjacent cells can undergo fusion [116]. This phenomenon relies on the polarization of the cell's membrane. When the membrane is rapidly polarized (*e.g.* 10 to 100 μs) to a high voltage (in the kV/cm range), cell membranes undergo a reversible electrical breakdown [117]. The breakdown induces the appearance of membrane pores, allowing a channeled kind of contact between cells, which allows the exchange of materials between the cells and the medium and contributes to the amalgamation of the membranes [118]. Cell electrofusion has a particular interest in the production of hybridomas and production of antibodies.

3.3.6. Electropermeabilization

Electropermeabilization (or electroporation) occurs when applied electric fields are beyond a specific threshold (please refer to chapter 3.1 and the eq. (2)). The permeabilization of the membrane only occurs within the places on the membrane where the transmembrane potential difference has been brought above a critical threshold. This value is generally situated between 200 and 300 mV [119]. Thresholds at which permeabilization occurs can be obtained at field strength as low as 100 V/cm in muscle cells [120]. In contrast, high electric field strengths (several kV/cm) are required for the electroporation of bacteria [121]. If values beyond the ones required for a reversible electropermeabilization are applied, the cells can undergo irreversible damage. Electric field parameters should therefore be adapted to each cell type in order to preserve the viability of pulsed cells.

During the process of reversible electropermeabilization transient permeant structures (often referred to as “pores”) are formed in the cell membrane [122,123]. This temporarily increases the permeability of the cell membrane and allows the penetration of chemicals, hydrophilic drugs, or large and charged molecules, such as DNA into the cytoplasm [3]. Theoretical considerations and insights from molecular dynamics simulations suggest that aqueous pores are formed in the lipid bilayer during the electric pulse application [124], and this is

currently considered as the most probable mechanism of initial membrane perturbation. However, the leakiness of cell membranes can persist from seconds to minutes, and even hours following electric pulse applications, when the cells are kept at 4 °C [123]. Therefore, membrane leakiness can not be attributed exclusively to highly dynamic lipid pores. The term "pore" thus defines any local defect, which is responsible for a higher permeability of the membrane, and the term electroporation should be understood in a broader sense [63].

The electropermeabilization of the membrane is controlled by applied electric field parameters, which include the electric field strength, pulse duration, number of applied pulses, and pulse frequency [63,122]. The techniques of electroporation mainly rely on square-wave-shaped electric pulses. Their duration generally ranges from nanoseconds to milliseconds and the field strengths comprise several kV/cm when nanosecond pulses are applied, and hundreds or thousands V/cm when micro- and millisecond pulses are applied. In addition to cellular outcomes defined by applied electrical parameters, other components play a role, and include the composition of the electroporation buffer (as cells are generally not exposed in cell culture medium), the temperature, and the intrinsic properties of the cells (such as size, shape, adherence, cell density) [63,122].

Beyond the (more or less) established processes occurring at the cell membrane, other effects at the intracellular level should also be of note [125]. The latter include transient or permanent modifications of cell organelles (namely the mitochondria) (Fig. 6) [126], the cytoskeleton and intercellular connections [127]. Moreover, (pulsed) electric fields induce structural changes related to osmotic imbalance (Fig. 6) [128], contribute to the generation of reactive oxygen species [66], or trigger the release of cell derived microvesicles [129], to mention but a few additional events that are associated with electropermeabilization.

3.3.7. Irreversible electroporation

The term "irreversible permeability" is used when cells cannot repair the bio-electrochemical defects in the plasma membrane (can not reseal the "pores") or cannot compensate for the chemical imbalances that occur due to the influx and efflux of molecules through transient or permanent defects leading to cell death [130,131]. Irreversible electroporation (IRE) can be performed using hundreds of pulses lasting 100 μs and having a field strength of 2-3 kV/cm, or can be obtained by applying trains of nanosecond pulses with the field strength of 60–90 kV/cm. Both approaches lead to cell death, but the target of the electric fields is not necessary the same (Fig. 7). While microsecond pulses preferentially act on the membrane, nanosecond pulses affect cell organelles [132].

Mechanisms inducing cell death with IRE have been widely investigated, and included the examination of histological morphology and staining characteristics [133,134], as well as transmission and scanning electron microscopy [135,136]. While the exact pathways by which cells die are still a matter of discussion, it seems that several mechanisms are involved and tightly related to the energy and field exposure parameters [133,137,138]. *In vivo*, several other possible effects of IRE have been observed at tissue-level, such as edema induced by capillary-disruption, hypoxia induced by temporary vascular occlusion [139–141] or immune system activation [142,143].

In this context, several studies performed on the liver demonstrated complete apoptotic cell death occurrence, with a sharp distinction

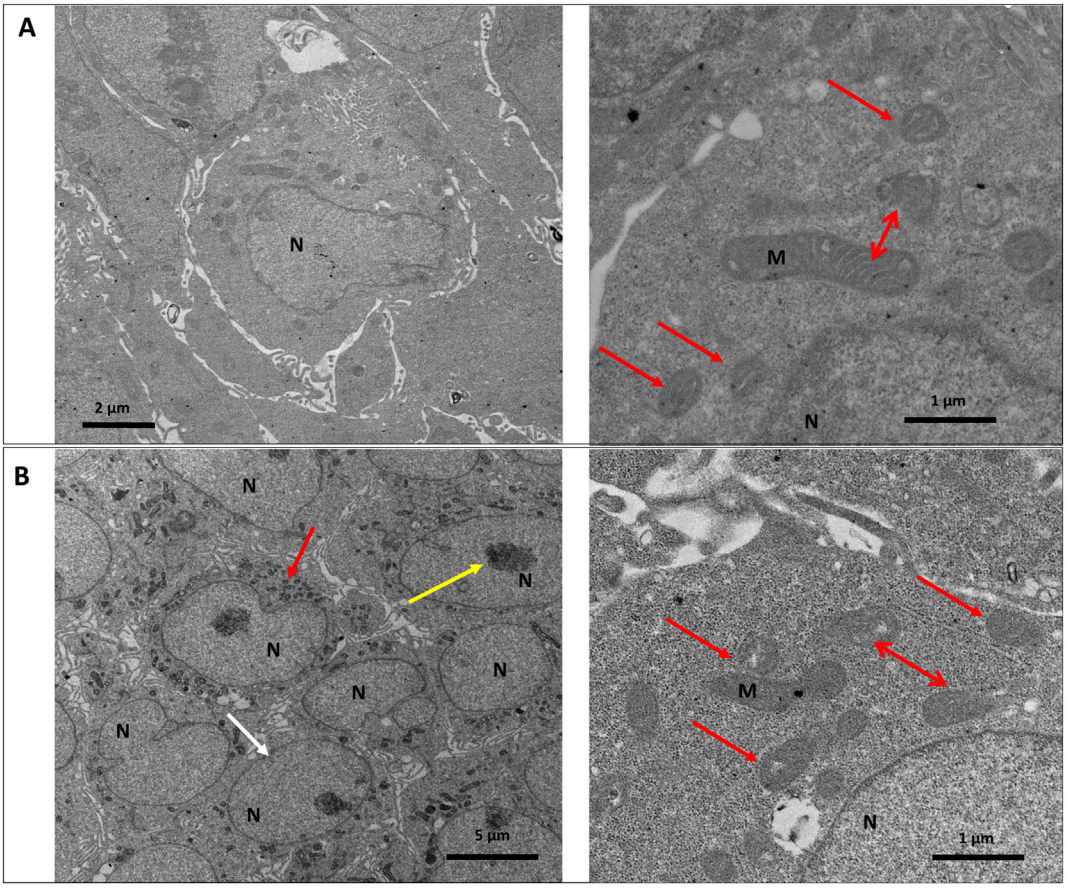

Fig. 6. Transmission electron micrographs of HCT-116 spheroid sections: non-submitted (A) or submitted (B) to the electric field (2000 V/cm, 80 pulses of 100 μs, 1 Hz). The cells in the spheroid that underwent electric field pulses (similar to the ones that are generally applied in clinics for irreversible electroporation) exhibit several morphological anomalies. Red arrow indicate mitochondria, white arrow points to the swollen nucleus and yellow arrow indicates a condensed nucleolus. Please note that the mitochondria that underwent electric fields (B) are denser when compared to the control (A) and that mitochondrial cristae structure changes in comparison to the control (Kolosnjaj-Tabi et al., previously unpublished results). (N denotes most nuclei and M denotes some of the mitochondria).

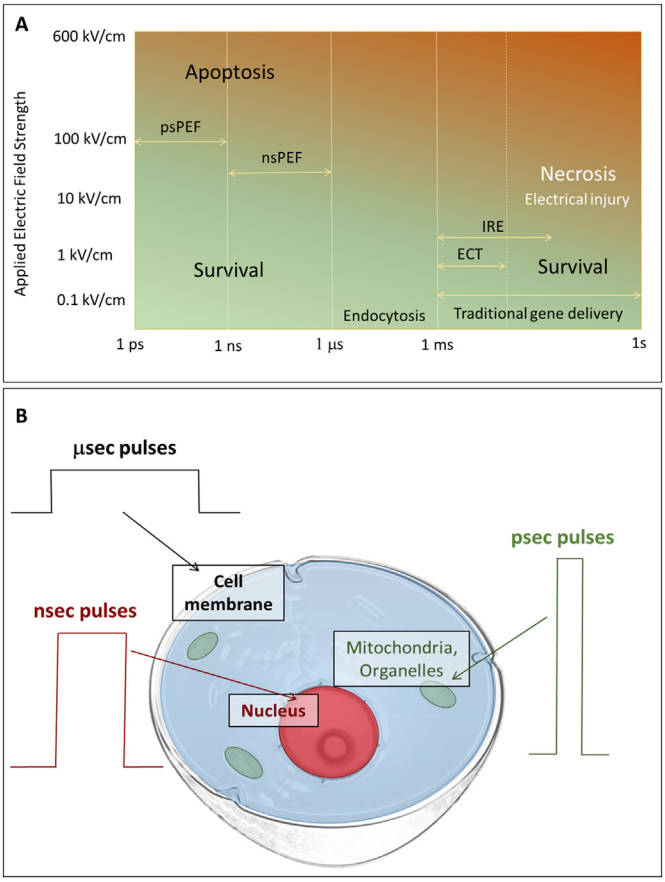

Fig. 7. The effects of electric fields pulses in relation with the pulse length. (A) Map of the approximate effects and applications in relation with field strength and pulse duration. *Adapted from Weaver* et al. [155]. (B) Preferential effects of electric field pulses on different cellular structures. *Adapted from Zhang* et al. [153].

between the ablated zone and the non-ablated zone [134], preserving bile ducts and blood vessels [144]. Similarly, a histological study on tumor tissues after IRE showed a peak apoptotic rate occurring 24 h after treatment, located within the treated tissues, whereas tissues around the IRE zone were not affected [145]. Irreversible electropermeabilization on pancreatic carcinoma showed potent anti-tumor effects (tumor necrosis, proliferation decrease, micro vessels disruption) with only transient effects on liver and pancreas enzymes [141]. This ability of IRE to achieve cell death in the proximity of large vessels without harming vessels themselves, made IRE a promising and safe treatment targeting cancer without the use of drugs. However, care must be taken in IRE protocols, to choose pulsed electric field parameters carefully, in order to achieve the electroporation-induced cell death. If the number of pulses is too large and/or the tissue conductivity is too high, thermal damages occur in the immediate vicinity of the electrodes [146]. Thermal effects induced by clinical IRE protocols using high-energy regimes, are reported to moderate the effects of IRE, which is otherwise referred to as a non-thermal ablation technique [147]. Furthermore, the important role of the local electrical environment surrounding the tissues was demonstrated, and the choice of electrical parameters (orientation, location of electrodes) was shown to influence the outcome of IRE [137].

Studies evaluating IRE's effects on the immune system are rather contradictory. Some findings suggest an efficient role, with a demonstrated immune response, which is stronger after IRE in comparison with the immune response induced by surgery in an osteosarcoma rat model [142]. In addition, a better anti-tumor response was observed after IRE in immunocompetent mice, in comparison with immunodeficient mice, both bearing renal carcinoma tumors [136]. Furthermore, a systemic protective effect was suggested in immunocompetent mice, because when re-challenged with the same cell line, the second tumor in these mice had a significantly reduced growth, or its growth did not occur, and CD3+ cells infiltrated the tumor [136], whereas such findings effects were not observed in immunodeficient mice. In contrast, another study performed on sarcoma tumors in mice failed to show any infiltration of immune cells in IRE-treated tissues [133]. A recent study hypothesized that the extent of the effect of IRE on the immune response could be conditioned by pulse parameters. This hypothesis was confirmed by demonstrating that above a critical threshold, electric field strength could down regulate a pro-cancerous signaling factor, having an effect on immune-cell trafficking [148]. These results assertively encourage the investigations on the role of IRE on the immune response. Be that as it may, the irreversible electroporation technique is currently principally used for non-thermal ablation of tumors and was introduced in clinics for cancer treatment [18,149].

Indeed, this chapter provides basic information in the field of irreversible electroporation, but if the readers are interested in detailed mechanisms and applications of irreversible electroporation, they should refer to specialized reviews dedicated to this field of research.

3.3.8. Intracellular manipulation

Pulsed electric fields may have different effects on cellular structures, which are related to pulse durations and strengths (Fig. 7). When nanosecond electric pulses are applied, the cell membrane effects decrease, and intracellular effects are more pronounced [132]. The intracellular effects alter nuclear processes and increase gene expression [150], induce DNA and chromosome damage [151], cause intracellular calcium release [152] and induce apoptosis [125]. Recent advances in generators designs allowed the application of picosecond pulsed electric fields, which allow field strength of several hundreds of kV/cm. Picosecond pulsed electric fields inhibit the growth of HeLa cells *in vitro* and induce apoptosis in a dose-dependent manner [153]. The apoptosis of HeLa cells is believed to follow the mitochondria mediated pathway [154].

4. Conclusion and perspectives

This review summarizes the basic knowledge obtained in different research areas, involving the use of electric fields, which are appealing physical triggers for different and numerous therapeutic applications. Electric fields can be used to set on the release of drugs from electro-responsive matrices, made of conductive polymers or electro-responsive hydrogels. While electro-responsive carriers are not yet used in clinical practice, they certainly do appear particularly appealing for future applications. The fields applied to induce drug release from electro-responsive containers are in the range of 1 V, which, interestingly, also corresponds to endogenous electric fields, which can be generated in our bodies under certain conditions (*e.g.* wounds). Such field strengths can be also applied exogenously to stimulate tissue regeneration or stimulate endocytosis. When the applied field strength is much higher, cells undergo a series of additional biological effects. The most "popular" concerns the appearance of "pores" on cells membranes. Electroporation can be used to deliver otherwise non-permeant molecules into cells (in electrochemotherapy) or to induce cell death (tumor ablation with irreversible electropermeabilization). In summary, electric fields can be used for different therapeutic approaches, acting on drug carriers, cells and tissues. Understanding the multiple effects of this powerful tool will help harnessing electric fields full therapeutic potential in an efficient and safe way.

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Disclosures

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