Review

Cells Tissues Organs

Effects of Electromagnetic Fields on Cells: Physiological and Therapeutical Approaches and Molecular Mechanisms of Interaction

A Review

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Abstract
This review concentrates on findings described in the recent literature on the response of cells and tissues to electromagnetic fields (EMF). Models of the causal interaction between different forms of EMF and ions or biomolecules of the cell will be presented together with our own results in cell surface recognition. Naturally occurring electric fields are not only important for cell-surface interactions but are also pivotal for the normal development of the organism and its physiological functions. A further goal of this review is to bridge the gap between recent cell biological studies (which, indeed, show new data of EMF actions) and aspects of EMF-based therapy, e.g., in wounds and bone fractures.

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Introduction

In the last decades, biology and medicine have made enormous progress in deciphering chemical and mechanical (molecular machines) aspects of cell and molecular biology. The complex picture of the processes in the cell as well as in the tissue was supplemented by recent studies which show a correlation between the presence of electromagnetic field (EMF) gradients and cellular reactions. Such studies arose in embryology, physiology, as well as in molecular biology. Thus, EMF studies in experimental biology and (already applied) EMF therapies in medicine may now have the chance to show the link between the clear-cut causal explanations of physics and the observed cellular and organic changes.

From our own experiments dealing with cell/implant surface interactions, we realized that EMF play an important role in the cascade of processes determining cell mi-

Abbreviations used in this paper	
dc	direct current
ECM	extracellular matrix
EF	electric field
EGF	epidermal growth factor
ELF	extremely low frequency
EMF	electromagnetic field
MF	magnetic field
PEMF	pulsed electromagnetic field
TEP	transepithelial potential difference
Ti	titanium

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gration, adhesion and differentiation. The experiments show that these forces can now be studied in detail in the micrometer and nanometer scale. Therefore, we tried to get an overview over the complex subject by compiling this review.

We will use the term 'electromagnetic fields' as a general term that includes the termini electric fields (EF), magnetic fields (MF) and EMF. The respective abbreviation 'EMF' will be used when dealing with this specific field form.

Cell Guidance

Directed cell migration is essential in embryo development, tissue formation, inflammation and wound healing. However, cell migration and cell-surface interaction studies (especially dealing with implant materials) mainly discuss mechanical or chemical cues as cause for the recognition of migration directions and for generation of attachment sites. After seeding on an implant surface with micrometer-sized groove and ridge pattern, adherent growing cells often migrate and align in the direction of the surface structure. This process is known as contact guidance [Brunette, 1986]. Depending on the surface topography, the cells can finally form a well-organized structure. However, on smooth implants, random cell orientations are often found that may lead to increased scar-tissue formation during wound healing [Wang et al., 2000a; Soboyejo et al., 2002]. Recently, it was shown that even nanosized structures, i.e. nanopits [Curtis et al., 2004; Dalby et al., 2004; Martines et al., 2004] or ridges [Monsees et al., 2005], were able to influence cell migration, orientation and function.

In the latter study [Monsees et al., 2005], we used patterns of parallel titanium (Ti) oxide lines with different widths (0.2–10 µm) and distances (2–20, 1,000 µm) but a common height of only 12 nm. We observed that a significant portion of osteosarcoma cells stretched their cytoskeleton to align along the lines. The cells also formed small filopodia to make contact with the oxide lines (fig. 1), with the majority of the focal contacts placed onto them. Thus, the nanosize difference in height between Ti surface and Ti oxide lines seemed to be sufficient to induce contact guiding in osteosarcoma cells. Due to the different physicochemical properties of the Ti/Ti oxide surface, other mechanisms may additionally influence focal contact formation and cell guidance.

Besides chemotaxis, i.e. concentration gradients of for example growth hormones or extracellular matrix (ECM)
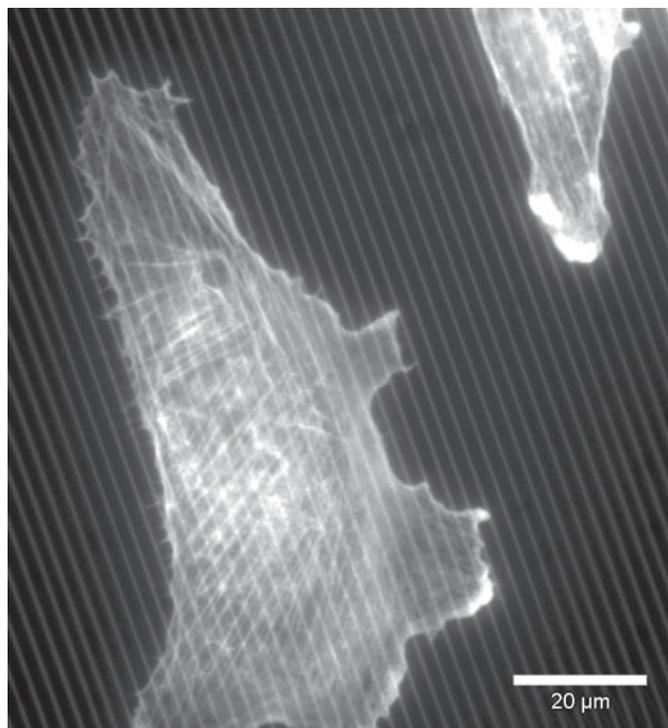
Fig. 1. Guidance of SaOS-2 osteoblast-like cells on a structured Ti/Ti oxide surface 2 days after plating. Dimensions of the parallel Ti oxide lines are: height 12 nm, width 0.7 µm, distance 5 µm. Cells were fluorescence stained for actin cytoskeleton (white fibers). Ti oxide lines appear in white.

components, guiding cues such as gradients in electrostatic potential or surface charge density at the Ti/Ti oxide interface are likely. From recent studies, we conclude that at least osteoblasts could 'sense' the transition of two materials, such as Ti/Ti oxide [Monsees et al., 2005] and Ti/glass [Funk, unpubl.], because the cells were significantly more attracted by those transitions than by one material alone. In the first pilot experiments using a raster Kelvin probe, we showed that differences in the electrical potential (approximately 150 mV) at the Ti/Au interface occur. This observation is not only interesting for possible coating or structuring of implants but might lead to more general insights into cell biology. Thus, the following question arises: What is known from the literature about cells and tissues in relation to EF, MF or EMF?

Physiological Relevance of EMF

Directed Cell Migration

In the embryo, cells move and grow in appropriate directions to form tissues and organs. In this respect, EF normally arise during the various stages of embryo development. During the early development of amphibian or chicken embryos, endogenous ionic currents can be measured. The currents and the related fields are generated by passive Na^+ uptake from the environment leading to an internally positive transepithelial potential difference (TEP). Differences in the TEP between various regions form an intraembryonic voltage gradient. The magnitude of these endogenous static EF is in the order of 1–5 V/cm and therefore above the minimum level needed to affect shape and migration of embryonic cells in vitro [Hotary and Robinson, 1990; Metcalf et al., 1994]. Levin et al. [2002] found that even the development of left-right asymmetry utilizes an EF between the blastomeres, which is generated by an asymmetrical distribution of the K^+/H^+-ATPase. Similar fields are also present during neurulation.

Thus, EF gradients develop in the embryo leading the way to the migrating cells. The spatial, localized dc (direct current) EF are switched on and off at different developmental stages [for a review, see McCaig et al., 2005]. The same may be true for the differentiation of single organs: in the vertebrate eye lens, basolateral membranes of the anterior epithelial cells produce a dc EF by Na^+/K^+ pumps [Wang et al., 2003b]. However, it still has to be shown if the epithelial cells use the field lines as a guidance cue to migrate from the equator to the anterior and posterior pole.

Wound Healing

Endogenous EF also exist in the immediate vicinity of wounds, where they are created due to a disruption of the TEP in the epithelial layer. The electric potential collapses at the wounded site but rises to the potential of healthy cells with increasing distance (0.5–1 mm) [Song et al., 2002; Zhao et al., 2002]. For example, epithelial wounds can generate a 1.5-V/cm field just below the stratum corneum, and corneal epidermal wounds exhibit a field of 0.4 V/cm lateral to wounds [Nuccitelli, 2003]. A disruption in the area of the neural plate and tube during amphibian embryonic development disturbed the endogenous EF and caused subsequent abnormalities in the central nerve system [Hotary and Robinson, 1990; Sta Iglesia and Vanable, 1998]. In surgically amputated arms of salamanders, Becker [1962] initially found a positive electric potential and a reversal to negative potential which gradually drifted back to zero over a period of days as an entirely new limb grew. In frogs which cannot restore a new limb, the initial positive signal only shifted to zero as the stump healed. Regarding the electric currents in wound healing, large currents (10–100 $\mu A/cm^2$ with a voltage drop of approximately 0.6 V/cm within the first 125 μm of extracellular space) were found at the cut ends of stumps of regenerating newt limbs [for a review, see McCaig et al., 2005].

Bone, Muscles and Nerves

Endogenous EMF arise by the movement of muscles and tendons, as well as by the actions of the musculoskeletary system itself. Mechanical deformation of dry bone caused piezoelectricity of several 100 mV, i.e. the bending strain couples to the spatial gradients of permanent dipoles in collagen molecules [Hastings and Mahmud, 1988]. However, in the moist surrounding of living bone, the small piezoelectric potentials are rapidly shielded [Otter et al., 1992]. At physiological conditions, mechanical stress-generated potentials are in the order of several microvolt and are formed by different mechanisms: (1) by the streaming potential (the electric potential difference between a liquid and a capillary, diaphragm or porous solid through which it is forced to flow) currents, or (2) by electrokinetic processes, i.e. by entrainment of ions because of fluid motion through the bone [Otter et al., 1998]. These electrokinetic processes are different from electroosmosis (see below). Charged molecules (e.g., negatively charged membrane proteins) are driven (e.g., to the anode) by an EF, and counterions (Na^+, K^+) accumulate in a nanometer-thin water layer. Electrophoresis of these counterions induces a fluid movement and a hydrodynamic force that draws the negatively charged molecules (within 1–10 min) to the cathode [McCaig et al., 2005].

In any case, the EMF caused by these reactions are able to penetrate the tissue, and the MF component can induce electric currents in the bone or muscle tissue by Faraday coupling.

Vibrations of human muscles induce mechanical strains and currents of certain frequencies: 5–20 Hz were found during postural muscle activity (quiet standing) and <10 Hz during walking [Antonsson and Mann, 1985]. These currents grow with increasing power and frequency of mechanical strain and reach field strengths of 0.1–100 mV/m. At maximum physiological strain, a field strength of 1 V/m around the bone cortex with a corresponding current density of 1–10 $\mu A/cm^2$ was observed [MacGinitie, 1995]. Muscle contractions also induce EF

in the underlying bone tissue and are important in maintaining bone mass: a vertical whole body vibration of 30 Hz with an acceleration of 0.2 g causes tibial strains, which in turn significantly stimulate gain in trabecular bone density [Inbar and Noujaim, 1984; McLeod et al., 1997]. Interestingly, bone cells have a strong frequency selectivity, with EMF effectiveness peaking in the range of 15–30 Hz. Fields as low as 0.01 mV/cm affect the remodeling activity [McLeod and Rubin, 1993]. Interestingly, the muscle vibrations correlate very well with the 8–12 Hz of the Schumann resonance. This resonance arises by the reflection of charges between the earth surface and the ionosphere causing EMF [Sentmann, 1985]. It seems that also living organisms have incorporated these natural frequencies: in the human brain stem, an intrinsic basic frequency of about 10 Hz exists in the sympathetic part of the autonomic nerve system [Gebber et al., 1999]. Furthermore, these are also the frequencies of the alpha rhythm of the electroencephalogram. On the other hand, a direct influence of the static geomagnetic field on human subjects is not known, although some reactions of patients on magnetic disturbances point to at least a partial susceptibility [Kay, 2004].

The piezoelectric property of bone very closely links EMF and mechanical vibration. Thus, it is often difficult to separate both components; however, this characteristic can be used for therapy.

Therapeutic Relevance of EMF

The use of EMF has a long history. In the first century AD, use of an electric fish was described to cure headache and gout. Later, Paracelsus (1493–1542) studied the medical use of lodestone, and Sir Kenelm Digby (1603–1665) described the magnetic cure of wounds [Macklis, 1993]. Modern – and more serious – medical applications of EMF are used to heal nonunions of bone fractures and treat some bone-related diseases (e.g., osteoporosis, osteoarthritis), although the specific molecular mechanisms are not fully understood. The application of EMF to stimulate osteogenesis is based on the idea of stimulating the natural endogenous streaming potentials in bone. At first, currents were directly applied via electrodes or induced by external EMF. Later, MF were produced by forcing electric currents through a wire coil placed over the fracture. Periodic changes of the MF then produced the required EF in bone via Faraday induction. The most effective medical devices today use time-varying (pulsed) EMF (1–100 Hz) inducing EF (on the microvolt/centime-

ter level) at the fracture site [Otter et al., 1998; Pilla, 2002]. The physiological frequencies (8–30 Hz) caused by natural muscle contractions and the subsequently induced EF in bony tissue are also used in therapy. These frequencies are applied as mechanical vibrations to the connective tissue and to the muscle [Randoll and Funk, 2004]. It is important to realize that MF or EMF only induce physiological effects at certain parametric 'windows', i.e. at extremely low frequency (ELF; 8–60 Hz) and low amplitudes (≤ 1 Gs) [Gartzke and Lange, 2002]. It must be pointed out that not all reports pay attention to this topic. Thus, a healthy skepticism is indicated.

Nevertheless, based upon multicenter, randomized and prospective clinical studies, the Federal Drug Administration, USA, approved pulsed EMF (PEMF) as safe and effective for treating nonunions and for osteoporosis therapy [Otter et al., 1998; Pilla, 2002; Chao and Inoue, 2003; Chao et al., 2004]. Bone remodeling is a highly integrated process of resorption (by osteoclasts) and formation (by osteoblasts) of bone tissue that results in precisely balanced skeletal mass with renewal of the mineralized matrix. In bone diseases such as osteoporosis, the balance between bone resorption and bone formation is disturbed. Resorption outstrips formation, eventually leading to reduction in bone mineral density which enhances the risk of various fractures. PEMF could enhance osteoblast activity but caused significant reduction in osteoclast formation [Otter et al., 1998; Hartwig et al., 2000; Chang et al., 2004]. Thus, treatment with PEMF may shift the balance towards osteogenesis.

Besides bone, EMF could also stimulate regenerative processes in other tissues [for electrical control of wound healing and tissue regeneration, see the review of McCaig et al. 2005]. Interestingly, ELF EMF were also able to stimulate progenitor cells, e.g., neurogenesis in the subventricular zone of adult rats [Arias-Carrión et al., 2004].

In vitro Response of Single Cells and Cell Organelles to Externally Applied EMF

Directed Cell Migration
In vitro, the application of static dc EF of physiological power caused directed movement and guiding of bone cells and various other cell types. This phenomenon is called electrotaxis (or galvanotaxis) [Zhao et al., 2002]. In vitro, at field strengths of 0.1–10 V/cm, cells often migrate to the cathode (neural crest cells, fibroblasts, keratinocytes, chondrocytes, rat prostate cancer cells and many

Table 1. Influence of dc EF on directed cell migration and orientation

| Cell type	Direction	PO	dc EF, V/cm	References
Lens epithelial, bovine	cathode	yes	0.5	Wang et al., 2003b
Lens epithelial, human	cathode	yes	1	Wang et al., 2000a
Corneal epithelial, human	cathode	ND	1	Farboud et al., 2000
Corneal epithelial, rabbit	cathode	yes	4	Soong et al., 1990
Corneal epithelial, bovine	cathode	yes	1–2.5	Zhao et al., 1996
3T3 fibroblasts, rat	cathode	yes	1–4	Brown and Loew, 1994
3T3 fibroblasts, rat	cathode	yes	2–6	Finkelstein et al., 2004
Keratinocytes, human	cathode	ND	1	Fang et al., 1999; Farboud et al., 2000
Chondrocytes, bovine	cathode	yes	0.8–10	Chao et al., 2000
Osteoblast-like, rat	cathode	ND	1–10	Ferrier et al., 1986
Neural crest cells, amphibian	cathode	yes	0.1	Stump and Robinson, 1983
Spinal neurite, amphibian	cathode	ND	1–1.4	Rajnicek et al., 1998
Prostate cancer cells, rat	cathode	ND	0.1–4	Djamgoz et al., 2001
Aortic endothelial, bovine	cathode	yes	2–10	Li and Kolega, 2002
Embryo fibroblasts, mouse	cathode	yes	1–10	Onuma and Hui, 1988
Stromal fibroblasts, rabbit	anode	yes	6	Soong et al., 1990
Cornea endothelial, rabbit	anode	yes	2–6	Chang et al., 1996
Cornea endothelial, human	anode	yes	2–6	Funk and Monsees, this paper
Vascular endothelial, human	anode	yes	0.75–2	Zhao et al., 2004
Granulocytes, human	anode	ND	1–10	Rapp et al., 1988
Lens epithelial, bovine	anode	yes	1–1.5	Wang et al. 2000a
Lens epithelial, bovine	anode	yes	1.5–2.5	Wang et al. 2003b
Osteoclasts, rabbit	anode	yes	1–10	Ferrier et al., 1986, 1994

PO = Perpendicular orientation towards EF vector; ND = not determined.

epithelial cell types). Only few cell types move to the anode (corneal endothelial cells, bovine lens epithelium, human granulocytes and human vascular endothelial cells). Speed and direction of the movement are voltage dependent. Details and references are listed in table 1. The data suggest that species and cell subtype differences affect electrotaxis: human vascular endothelial cells migrate towards the anode, whereas bovine aortic endothelial cells move to the cathode. During movement, ruffled membranes, lamellipodia and filopodia are formed preferentially in the direction of the anticipated electrotaxis migration [Sulik et al., 1992; Zhao et al., 2002] (fig. 2). Several cell types changed their initial direction of movement by 180° when the current polarity was reversed [Harris et al., 1990; Soong et al., 1990; Brown and Loew, 1994; Chao et al., 2000; Wang et al., 2000b]. EF-induced cell migration can be modified by proteins of the ECM. For example, highest cathodal migration was noticed with keratinocytes plated on collagen and plastic, whereas lowest locomotion occurred on laminin. Cell response on fibronectin was in between the two [Sheridan et al., 1996]. Similar results were observed for epithelial cell electro-

taxis on laminin or fibronectin coatings [Zhao et al., 1999]. Sun et al. [2004] noticed directed movement of fibroblast migration at a field strength as low as 0.1 V/cm in 3-dimensional collagen gels, but not in conventional 2-dimensional cultures. Thus, 3-dimensional conditions seem to reflect the in vivo situation, where dc EF of 0.1–0.2 V/cm occur that are important for embryonic development [Nuccitelli, 2003].

Several steps are involved in cell migration: (1) due to their connection to several adaptor proteins, the growing of actin filaments will push the cell membrane in the direction of movement; (2) formation of focal contacts at the leading edge, i.e. specific bindings via membrane-bound integrin receptors and ECM proteins, which will also influence several signaling pathways and structural elements of adhesion; (3) focalized proteolysis by recruitment of surface proteases to ECM contacts; (4) cell contraction driven by myosin II binding to actin filaments, and (5) disassembly of focal contacts and detachment of the trailing edge [Lauffenburger and Horwitz, 1996; Friedl and Wolf, 2003]. Many of these events have also been observed in EF-induced cell movement.

Fig. 2. Electrotaxis of human corneal endothelial cell line (4 h dc EF, 4 V/cm). Cells move towards the anode (arrow) and form lamellipodia (small arrows). For application of dc EF, cells were plated in the channel of a μ-slide (ibidi, Munich, Germany). Electrical contact was made by agar bridges. One end rested in culture medium the other in phosphate buffer solution. Platinum electrodes in the buffer solution were attached to a dc power supply.
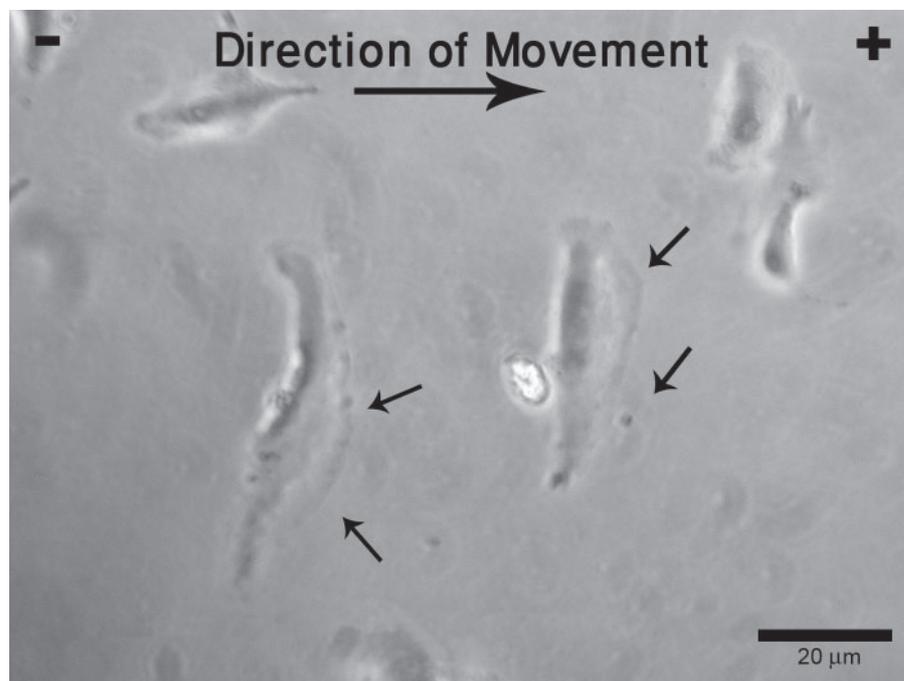
Fig. 3. Perpendicular alignment of primary human corneal endothelial cells after exposure to dc EF (4 h dc EF, 4 V/cm). Direction of the EF vector is indicated in figure 2.
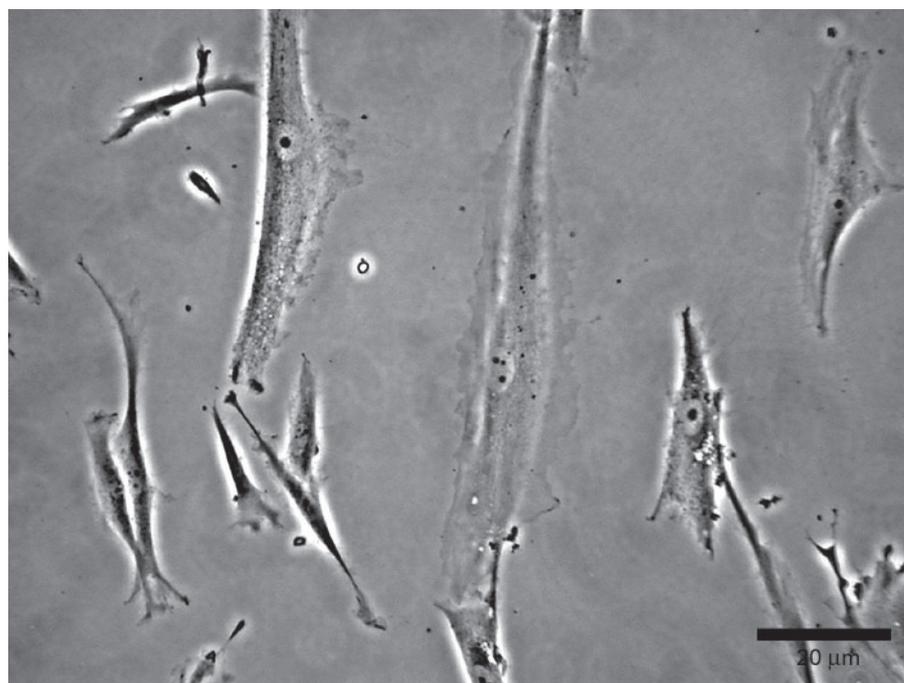
Cell Shape and Cytoskeleton

If one looks at the level of a single cell in an EF, then elongation of the cell body and alignment of its long axis perpendicular to the field lines are striking phenomena (fig. 3). This behavior was first described for Xenopus myoblasts [Hinkle et al., 1981] and thereafter observed in many other cell types including fibroblasts, osteoblasts, chondrocytes, keratinocytes, endothelial and epithelial cells (table 1). As dc EF trigger migration and orientation, cells must orchestrate cytoskeletal elements and shape in response to this trigger. In fibroblasts, a perpendicular orientation of actin stress fibers and microtubules to the

Fig. 4. Specific distribution of vinculin in a human corneal endothelial cell line before (**A**) and after (**B**) exposure to dc EF. Vinculin is one of the adaptor proteins in focal contacts linking membranous integrin receptors to the actin cytoskeleton. Integrins are thus visualized by fluorescent staining for vinculin (light dots). The cell oriented perpendicular to the field vector. The direction of the EF vector is indicated in figure 2.
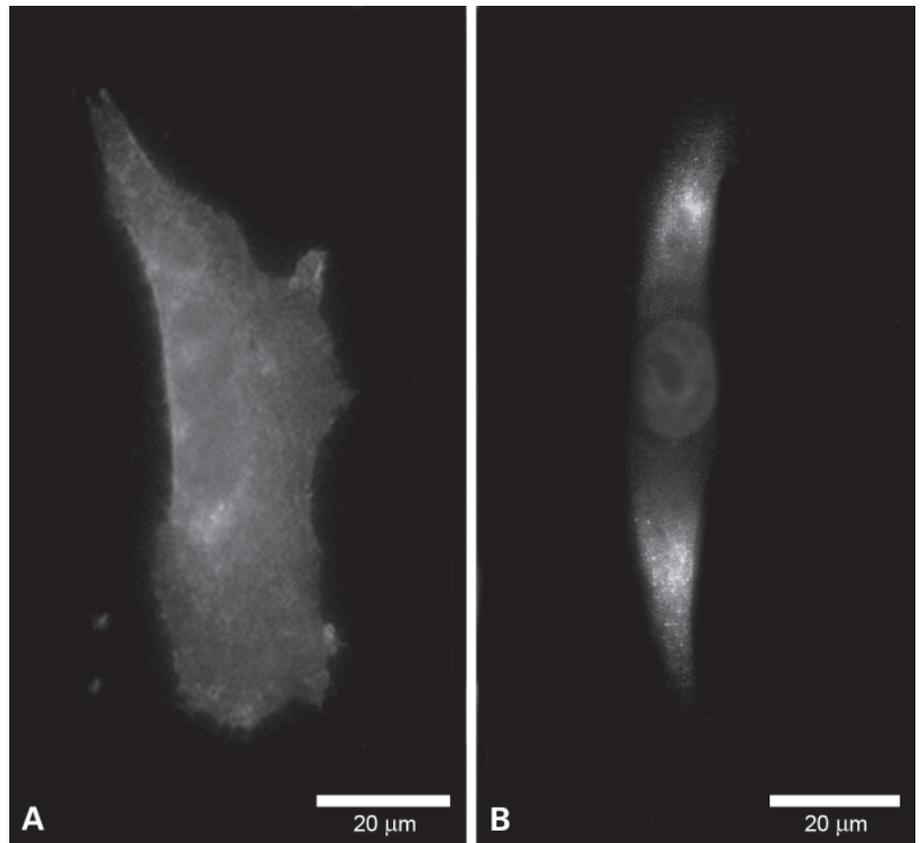
EF was found after EF exposure [Harris et al., 1990]. An accumulation of actin stress fibers was observed on the cathodal (leading) edge of several cell types [Sulik et al., 1992; Zhao et al., 2002]. Often, the total amount of filamentous actin transiently increased and became selectively enriched in the leading lamellipodia [Li and Kolega, 2002]. Here, focal contacts were also accumulated [Chang et al., 1996]. Recent experiments showed that EF-mediated motility in fibroblasts can be halted by inhibition of microfilament dynamics, whereas inhibition of microtubules only reduced migration speed [Finkelstein et al., 2004]. Membrane extensions from the trailing edge of chondrocytes were concomitantly retracted [Chao et al., 2000]. Also osteoblasts and osteoblast-like cells undergo processes of retraction and elongation ultimately resulting in the realignment of the long cellular axis perpendicular to the EF [Curtze et al., 2004]. These authors presented a theory to explain the EF-induced perpendicular orientation of cells: cell attachment is made by the adhesive interaction of ECM proteins with a group of transmembrane adhesion receptors, the integrins. They consist of two subunits, α- and β-integrin, building sev-

eral heterodimers that display different binding properties towards ECM proteins. Integrin-$\alpha_5\beta_1$ particularly binds to fibronectin, whereas integrin-$\alpha_2\beta_1$ binds to collagen type I, and integrin-$\alpha_V\beta_3$ binds to vitronectin [Dzamba et al., 2001; Geiger et al., 2001]. After binding to their specific ligands, integrins cluster within the membrane and recruit several adaptor and signaling proteins to form focal contacts (also called focal adhesions) that anchor the ends of intracellular actin filaments (stress fibers). Vinculin is one of these adaptor proteins and is frequently used as a marker for integrin-based focal contacts.

As stated here and elsewhere [Jaffe, 1977; Poo and Robinson, 1977; Poo, 1981], dc EF trigger the separation of charged membrane components. In order to achieve perpendicular elongation, a certain self-induced cytoskeletal tension is required along the axis. Assuming that all free integrin receptors drift towards an electrode and accumulate there, the cell is only able to connect to two focal adhesions and increase tension between them if they are on an axis perpendicular to the drift. Cell adhesion is a dynamic process, thus after some time, disassembly of

focal contacts on the opposite side of the drift destination leads to another drift. Consequently, the cell is no longer able to maintain protrusions with the same orientation as the EF [Curtze et al., 2004]. Our experiments using corneal endothelial cells support this hypothesis: vinculin proteins, used as a marker for integrin receptors, are normally randomly distributed within the cell with a preference for the cell border (fig. 4A). However, after dc EF application, they concentrate on two major spots of focal contacts oriented perpendicular to the EF vector (fig. 4B).

Mechanical load is also discussed as a possible transducer of EF. EF-induced effects such as dynamic changes in intracellular calcium concentration, cell traction and orientation are similar to the cellular response after mechanical stimulation [Oliver et al., 1999; Munevar et al., 2001; Curtze et al., 2004]. Converse flexoelectricity may thereby be a way for cells to sense small dc EF. Charged proteins in the lipid bilayer of the cell membrane repel each other, influencing membrane tension [Petrov et al., 1993]. If the charge on one side of the membrane is changed by dc EF, the membrane tension also changes, resulting in a modified curvature of the membrane. Such flexoelectric effects have already been demonstrated on voltage-clamped cells [Zhang et al., 2001]. Using traction force microscopy, Curtze et al. [2004] noticed a 5–30% increase in average traction force magnitude 10–30 s after dc EF exposure as the first detectable reaction of osteoblasts. The visible retraction phase started after 5–10 min, and then, cells subsequently elongated and oriented perpendicular to the EF lines. Traction forces at the margins tangential to the EF decreased 2–15 min after the start of EF exposure below their initial values. A mean delay of 85 s between EF application and first observable changes in Ca^{2+} levels occurred, suggesting that stretch-activated Ca^{2+} channels [Glogauer et al., 1997] may be responsible for the Ca^{2+} influx. Appropriate strain sensors that produce biochemical signals to modulate cell reactions were proposed by Sheetz et al. [1998].

Static MF (10 T) also oriented glioblastoma cells in the presence of collagen fibers possibly due to the rearrangement of microtubules [Hirose et al., 2003].

Cell Surface Recognition

Studies of Erskine and McCaig [1997] and Ohgaki et al. [2001] as well as our own results (fig. 5) showed that negatively charged surfaces are a sometimes better inter-face for cell adhesion and further cell function than positively charged ones. Using controlled surface charge induction on implants, it was shown that the above mentioned charge densities are sufficient to alter cell growth, adhesion and phenotypic expression [Vander Molen and McLeod, 1995; McLeod and Hadjiargyrou, 1996]. Moreover, specific effects can be observed when cells are plated onto substrates which have been exposed to ELF EMF before plating [McLeod and Rubin, 1994]. Together, these results strongly suggest that the observed effects are associated with an alteration in absorption of charged proteins, and change in the cellular response results from the altered 'charge environment'.

Seen 'with the eyes of a cell', the surface of an implant is covered with water and ions (in vivo serum, in vitro cell culture medium). Then, amino acids and proteins (especially albumin, fibronectin and vitronectin) are absorbed to the surface due to unspecific charge interactions (fig. 6A) [Vroman, 1988]. At negatively polarized (e.g., glass) and negatively charged surfaces, inorganic cations like calcium (fig. 6B) and cationic amino acids and proteins (fig. 6C) may bind to the surface, making it a suitable interface for the negatively charged surface of the cell (fig. 6C) [Ohgaki et al., 2001]. Additionally, Ca^{2+} ions are required for the formation of focal adhesions. Thus, a higher local concentration of Ca^{2+} will accelerate specific integrin receptor-mediated binding. In the next step of the attachment sequence, the cell recognizes RGD motifs (a sequence of amino acids which is important for binding processes) of surface-bound proteins (fig. 6D), and finally, specific binding occurs at focal adhesions via integrin receptors (early and late) (fig. 6E). As the 'missing link' between the patterns of surface charges and special adhesion proteins described above, Botti et al. [1998] described a class of adhesion proteins that, because of their common electrostatic and structural motif, were called 'electrotactins'. These proteins had a functional region common to cholinesterases and exhibited a special pattern of electrostatical surface potentials.

Bone Cell Function

There is a vast amount of literature dealing with effects of various kinds of EMF on defined functions of different cell types. Some of them are cited in this review. In this paragraph, we report on bone cells as an example. Chang et al. [2004] examined the effect of PEMF stimulation (7.5 Hz) on osteoclast (bone-resorbing cells) formation in bone marrow cells from ovariectomized rats (a procedure inducing osteoporosis). Secretion of the cytokines tumor necrosis factor-α, interleukin-1β and interleukin-6 was
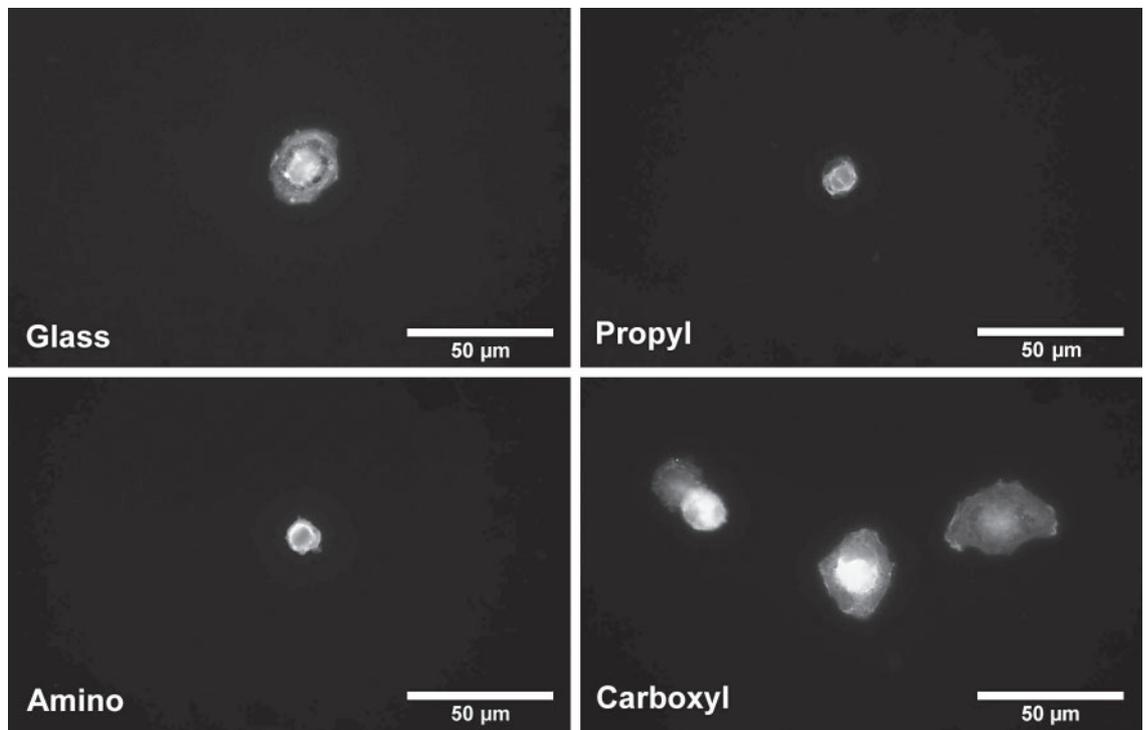
Fig. 5. Effect of surface charge on adhesion of SaOS-2 osteoblast-like cells. Cells were fixed 30 min after plating and triple fluorescence stained for actin filaments, vinculin and nuclei. Glass = Negatively polarized; Propyl = neutral propyl spacer on glass surface; Amino = positively charged endgroup at spacer; Carboxyl = negatively charged endgroup at spacer. Cells placed on negatively charged or polarized surface are much larger, more spread and display starting reorganization of actin cytoskeleton compared with cells on positively charged or neutral surface.

significantly lowered, and formation of osteoclasts was significantly reduced compared with cells isolated from sham-operated rats.

On the other hand, EF can boost several functions of bone-forming cells. In calf osteoblasts, capacitively coupled EF enhanced proliferation, differentiation and secretion of ECM formation [Hartig et al., 2000]. Exposure of osteoblast-like cells to static MF enhanced bone sialoprotein transcription through a tyrosine kinase-dependent pathway [Shimizu et al., 2004]. PEMF stimulation (15 Hz, 0.6 mT) of osteoblasts led to an enhanced proliferation which was mediated by an increase in nitric oxide synthesis [Diniz et al., 2002]. Nitric oxide is known to stimulate proliferation and wound healing [Luo and Chen, 2005].

Cell Proliferation and Differentiation

EMF can affect cell proliferation and differentiation by influencing the expression of relevant genes and proteins. Depending on the kind of EMF, both stimulation

and inhibition of proliferation were observed. ELF EMF stimulated embryonic stem cell differentiation into cardiomyocytes by triggering the expression-specific cardiac lineage-promoting genes [Ventura et al., 2005]. Similar MF also stimulated proliferation and differentiation of neurons [Arias-Carrión et al., 2004]. In contrast, static dc EF (2 V/cm) inhibited proliferation of vascular endothelial cells or lens epithelial cells by inducing a cell cycle arrest at the G1/S phase [Wang et al., 2003c, 2005]. In both cell types, dc EF significantly decreased the expression of cyclin E, whereas levels of the inhibitor of the cyclin E/Cdk2 complex, $p27^{kip1}$, increased. Further, the healing of lens epithelial monolayer wounds was inhibited at the cathodal side after exposure to dc EF. Extracellular signal-regulated kinase 1 and 2 activity was increased, but became asymmetrically distributed, with much weaker activity on the cathodal side than on the anodal side [Song et al., 2002; Wang et al., 2003a].
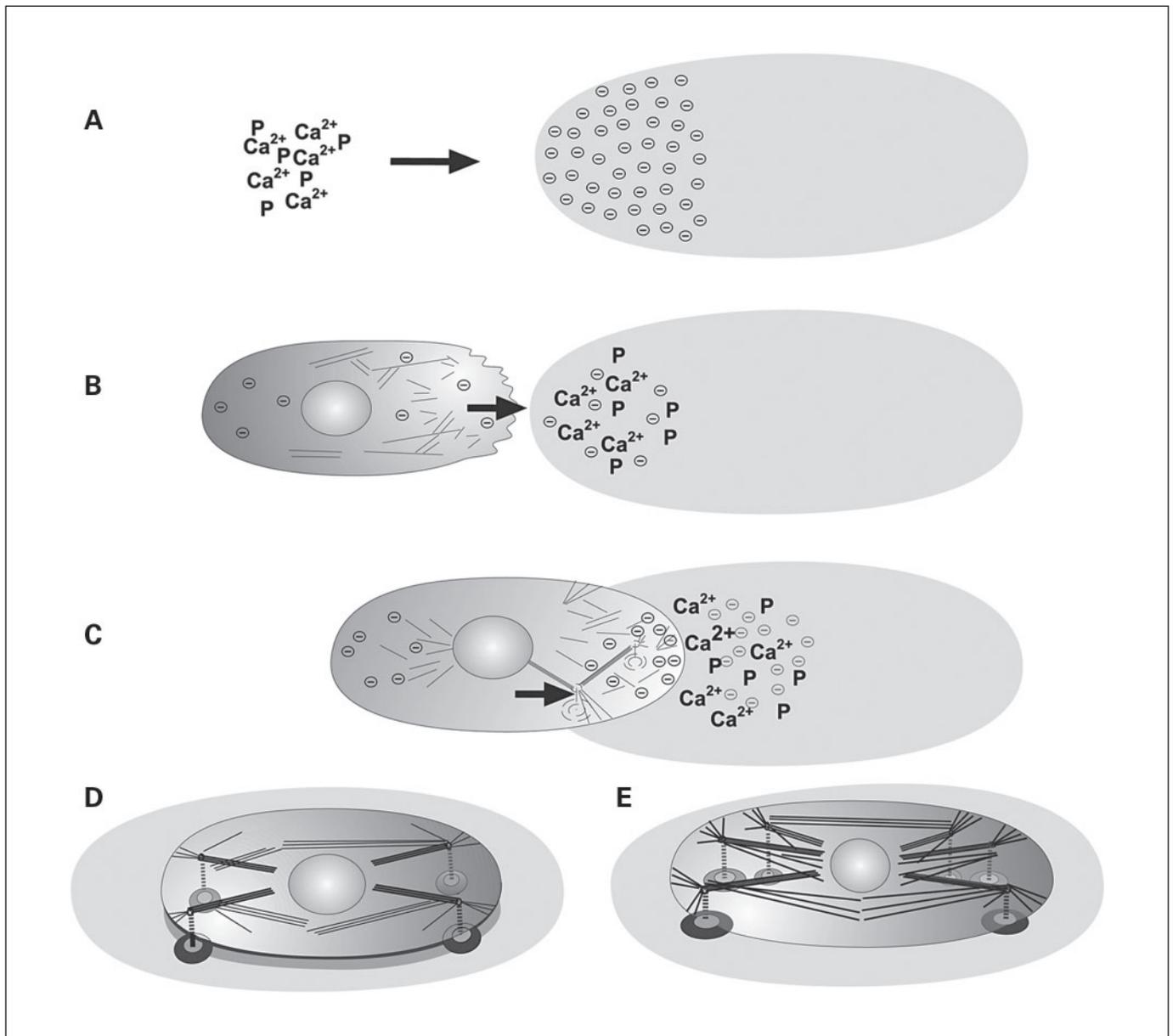
Fig. 6. From migration to adhesion. Proteins (P) and inorganic cations (especially calcium) adsorb to the negatively charged implant surface (**A**). Due to charge shift (long reaching effects), the mainly negatively charged cell is attracted and moves to the now positively charged area (**B**). **C** Beginning adhesion (electrostatic effect). **D** Early adhesion (recognition of RGD motifs). Specific binding occurs at focal adhesion sites during complete adhesion (**E**). For reasons of clarity, only parts of the surface charges and adsorbed proteins and ions are shown.

Wound-generated endogenous dc EF can control the axis of cell division by orientation of mitotic spindles perpendicular towards the field vector [Song et al., 2002]. Higher MF densities were also able to orient the cleavage plane during mitosis [Valles et al., 2002] or to distort the mitotic spindle [Denegre et al., 1998].

Mechanisms of Interaction of Cells and Cell Organelles with EMF

dc EF-Induced Migration

Responding to extracellular cues like EMF involves a cascade of events, transducing signals from the cell sur-

Table 2. Influence of dc EF on $[Ca^{2+}]_i$ and the effect of calcium channel antagonists on EF-induced cell migration (electrotaxis)

| Cell type	$[Ca^{2+}]_i$	Electrotaxis	EF, V/cm	References
Embryo fibroblasts, mouse	up	inhibited	1–10	Onuma and Hui, 1988
Keratocytes, fish	ND	inhibited	0.5–15	Cooper and Schliwa, 1985
Keratocytes, fish	up	inhibited	55–120, pulsed	Brust-Mascher and Webb, 1998
Osteoblast-like, rat	up	ND	$100 \, \mu A/cm^2$	Wang et al., 1998
Osteoblast-like, bovine	up	ND	10	Curtze et al., 2004
Prostate cancer, rat	up	ND	10–15, pulsed	Perret et al., 1999
Keratinocytes, human	ND	inhibited	1	Trollinger et al., 2002
Fibroblasts, mouse	unchanged	ND	4	Brown and Loew, 1994
Spinal neurites, frog	unchanged	ND	1	Palmer et al., 2000

ND = Not determined.

face to the cytoskeleton. Due to the high dielectric property of the lipid bilayer membrane, externally applied dc EF will be considerably attenuated. For example, a dc EF of 5 V/cm will produce an intracellular field of only 0.5 mV/cm, which is unlikely to produce significant effects [Poo, 1981].

What is the sensor for EF gradients? A suggested mechanism is the electrophoretic mobility of charged molecules in the cell membrane in a dc EF [Jaffe, 1977; Poo, 1981]. In this respect, electroosmosis (see also above) plays a role: the imposition of a dc EF on the negatively charged cell membrane produces a flow of positive counter ions, which will result in a flow of fluid towards the cathodal site of the membrane. By this flow, a negatively charged receptor will be swept to the cathodal side of the membrane if its ξ potential is less negative than the ξ potential of the cell surface; otherwise it will accumulate on the anodal site [Poo, 1981; McCaig et al., 2005]. The ξ potential is the electric potential at the interface between a solid surface or membrane and a liquid. Such lateral movements and enrichments of membrane components towards the cathode have been observed in several cell types. Examples are concanavalin A and acetylcholine receptors or positively charged membrane lipids in Xenopus myotomal membrane [Poo, 1981], fibronectin receptor in fibroblasts [Brown and Loew, 1994], lipids and epidermal growth factor (EGF) receptor in keratinocytes [Song et al., 2002], membrane lipids or EGF and hepatocyte growth factor receptors in corneal epithelial cells [Zhao et al., 2002; McBain et al., 2003]. Thus, one can imagine that redistributed membrane molecules can be sensed inside the cell by components of the cytoskeleton and be used as an orientation cue.

Some of these mechanisms have been explored in more detail. Finkelstein et al. [2004] recently demonstrated that microtubules are involved in EF-induced cell migration. Signaling molecules such as Rho GTPases and protein kinases interact with microtubules and can effectively hitchhike microtubule-based transport. In this way, they pass signals from the leading edge of the cell via the nucleus to the trailing edge [Gundersen and Cook, 1999]. An EF induces redistribution of hepatocyte growth factor receptors and triggers the mitogen-activated protein kinase pathway downstream that is involved in epithelial cell migration [McBain et al., 2003]. Similarly, EGF receptor kinase activity and redistribution in the cell membrane are necessary for electrotaxis in keratinocytes [Fang et al., 1999]. In chondrocytes, antagonists of the inositol phospholipid pathway were able to inhibit cathodal migration [Chao et al., 2000].

In contrast to the arising weak internal field, the externally applied dc EF can induce substantial alterations of the membrane potential. The resting potential of a non-excitable cell is approximately –45 to –75 mV. A usual dc EF of 1–10 V/cm applied to a cell of 10 μm in radius will hyperpolarize the membrane facing the anode by 1.5–15 mV and depolarize the cathodal site by the same amount. This is sufficient to induce several physiological effects such as changes in the levels of calcium ions [Poo, 1981; Mycielska and Djamgoz, 2004; Robinson, 1985]. In many cells, dc EF-induced migration depends on changes in intracellular Ca^{2+} concentration – $[Ca^{2+}]_i$. Details and references are listed in table 2.

A model of Ca^{2+} – induced contraction and a push forward – mechanism was presented by Mycielska and Djamgoz [2004]. Since the cytoplasm on the anode-facing site became more negative, the inward driving force of
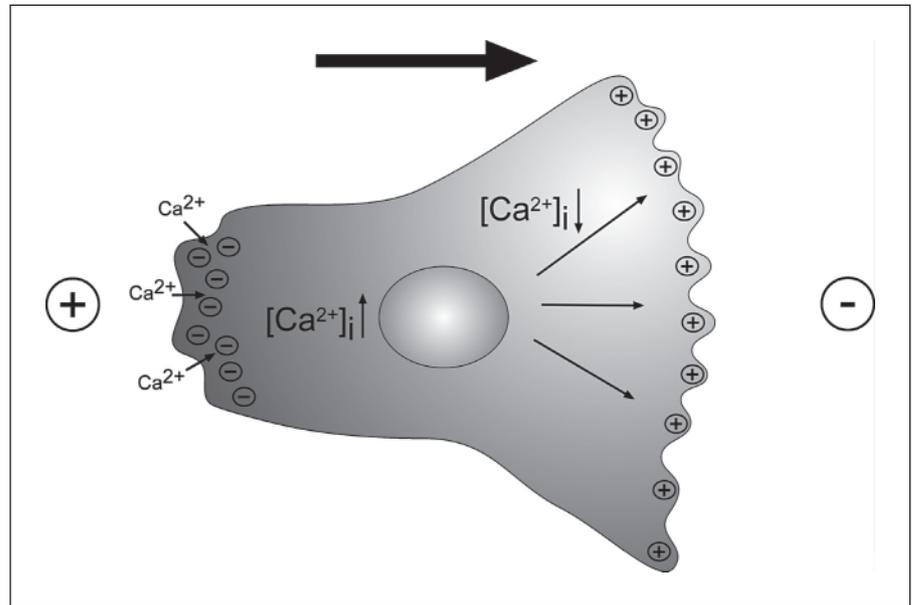
Fig. 7. Influence of dc EF on membrane potential and $[Ca^{2+}]_i$ level. The anode-facing site became hyperpolarized after EF exposure, which led to increased passive Ca^{2+} influx and cellular contraction, moving the cell towards the cathode. Modified after Robinson [1985] and Mycielska and Djamgoz [2004].

Ca^{2+} was increased at the anode, whereas that on the cathodal site decreased (passive influx) (fig. 7). Increasing $[Ca^{2+}]_i$ often activates myosin light chain kinase that phosphorylates the regulatory light chain of myosin II. This in turn triggers the actin-activated myosin ATPase, a major regulator in cell contraction [Stull et al., 1998]. In consequence, the anodal site contracts and the cell will be propelled towards the cathode. If voltage-gated Ca^{2+} channels are present, a cathode-faced membrane depolarization should open them, and the Ca^{2+} influx following this opening will cause cell migration towards the anode (fig. 7). The calcium waves measured were fast (22.5–50 µm/s, i.e. faster than electroosmosis) which could possibly explain the very fast cell reactions reported in other EMF studies [for a review, see Mycielska and Djamgoz, 2004]. However, the net movement (and direction of cell migration) depends on the balance of passive influx and voltage-gated influx of Ca^{2+}. Calcium ions are also essential for the coupling of other forms of EMF to a biological system. This topic will be discussed below.

EMF and MF

Unlike EF which are shielded by the high dielectric property of the cell membrane, magnetic gradients can intrude into cells and even deeper layers of living tissue. Therefore, MF may act directly on cell organelles. Although many studies show effects of EMF on the tissues mentioned, it is still debated how the weak MF component of EMF can exert signals in a single cell, e.g., to cause migration or proliferation. This is called the problem of coupling the EMF to biological systems. Bone cells, for instance, respond to extremely small (≤ 0.01 mV/cm) induced sinusoidal EMF [McLeod et al., 1995]. These effective EF or MF have very low energies. Thus, two questions arise: (1) which cellular mechanism is able to convert this very low field energy to the physiological responses which require much higher energies, and (2) why does thermal noise not interfere with the conversion and transduction of the much smaller energy of the EMF? Several mechanisms have been proposed to solve these problems.

The paramagnetic property of metal atoms might be a mediator for sensing EMF, as significant increase in norepinephrine and glutamine levels were found after ELF EMF exposure to chicken embryos [Rajendra et al., 2004]. The authors suggest that the enzyme dopamine beta hydroxylase is the coupling mediator because of its two copper atoms. Copper is paramagnetic and its role in the activity of dopamine beta hydroxylase may be altered by external MF. The same may be true for glutamine synthetase, which requires paramagnetic manganese for activity. The finding that ion-protein complexes can rotate under static MF supports this theory [Binhi et al., 2001].

EMF have the property to induce surface charges on the cell membrane [McLeod et al., 1995]. Coupling of an EF component was described between Coulombic forces at the surface of the cell membrane that are able to distort
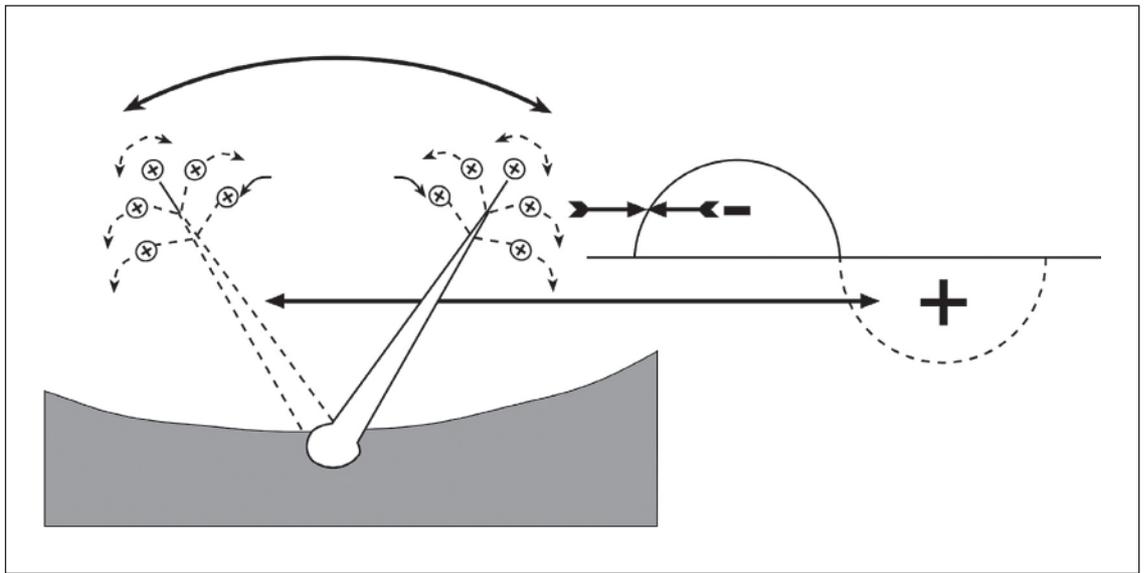
Fig. 8. Resonance of molecules with charges on a movable lever (left). Such levers can be part of a receptor and are addressed 'unspecifically' by, for example, a sinusoidal EMF wave (right).

the shape of the membrane and the underlying cytoskeleton [Peskin et al., 1993]. If a Coulombic force is large enough, insertion of an actin monomer between the cytoskeleton and cell membrane can occur – after the polymerization of actin, the long-term cell shape is altered. Such manipulations distort transmembrane proteins (ion channels) and thus lead to intracellular signaling to the cytoskeleton. Cell membrane surface charges can also change with the pathophysiological state. Malignant cancer cells showed increased negative surface charges, and this could affect field-induced effects such as electrotaxis [Mycielska and Djamgoz, 2004].

It was proposed that charged receptors or other kinds of 'antennae' at the outer side of the cell membrane should recognize EMF by their ability to resonate with varying EMF frequencies because of the appropriate lengths of the moving parts which hold a charge on the free end, the resonance frequency thereby depending on the length of the lever (fig. 8). Induced surface charge movements on the membrane would thus trigger a signaling pathway [Fitzsimmons et al., 1992; Fitzsimmons and Baylink, 1994]. This phenomenon would be similar to the electrophoretic mobility of charged molecules in the cell membrane in a static EF. However, this reaction could be faster than the 2- to 10-min reaction during electroosmosis. The induced charge movement would represent at least a modification of Coulombic forces at the outside of the cell [Otter et al., 1996, 1997] or a modification of the charge distribution on the surface where the cell is attached. An EF of 0.01 mV/cm is capable of inducing a sufficient charge density (1–10 $\mu C/m^2$) to elicit a cell reaction [Otter, 1998].

Audioreceptor cells of the ear or photoreceptor cells of the retina are examples of such antennae. In the ear, bundles of microvilli of hair cells can be laterally moved by applied acoustic fields. This swinging movement generates a synchronously oscillating membrane potential changing about 10 mV around its normal value. Additionally to this mechanoelectrical transduction, hair cells display high sensitivity and frequency selectivity by adding self-generated mechanical energy to low-level signals. Thus, detection of signals that are much smaller than thermal molecular motion is possible [Gartzke and Lange, 2002].

On the other hand, this mechanism via surface charges will not affect the 'classical' membrane potential, which is established by ionic concentration gradients across the cell membrane through the action of different ATPases or other transport proteins and ion channels. With a 0.01 mV/cm extracellular field, one would only get a 10 nV perturbation of the membrane potential and would need at least 100 μV to ensure a cellular response [Otter, 1998]. In addition, a channel 'noise' of 100 μV will mask the 10 nV signal. Even the coupling of more cells by gap junctions to reduce the noise would not suffice to solve the problem [Spach and Heidlage, 1992].
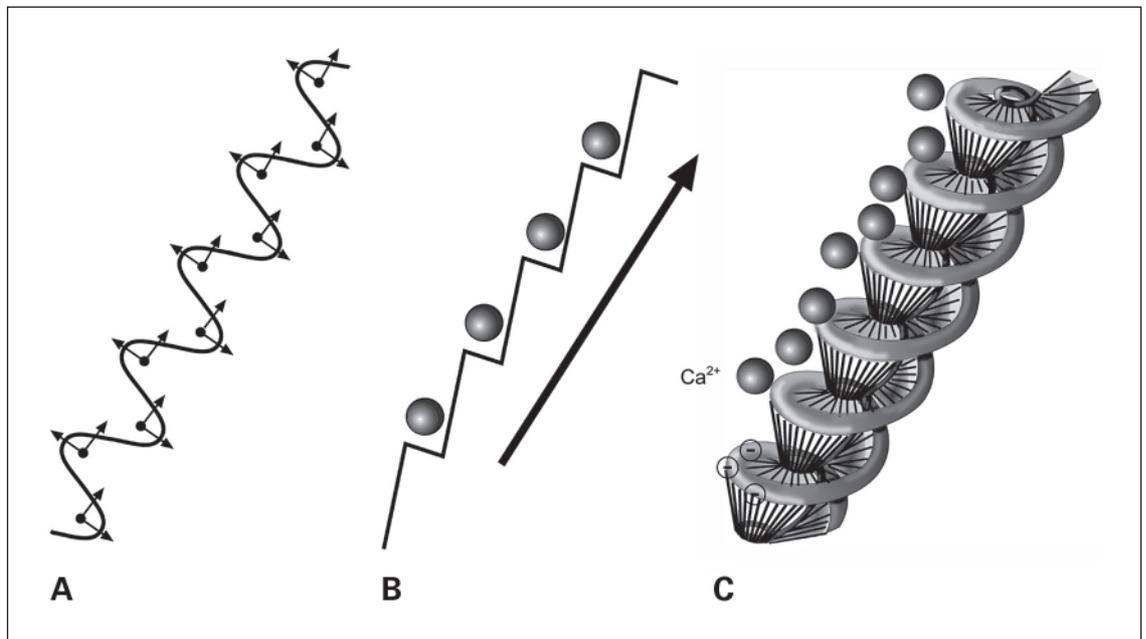
Fig. 9. A Sinusoidal EMF wave (with vector components). **B** Principle of a molecular ratchet which is able to direct the random 'Brownian' molecular movement if a triggering vector is present. **C** model of ion clouds (Ca^{2+} ions) moving along a ratchet-like molecule (e.g., actin) leading to a polarization of charges. Modified after Gartzke and Lange [2002].

The problem of thermal molecular motion (thermal noise) might generally be overcome by stochastic resonance [Kruglikov and Dertinger, 1994] or by molecular 'Brownian' ratchets [Astumian, 1994, 1997]. The phenomenon of stochastic resonance can amplify weak signals more than 1,000 fold by using the system-inherent noise. Stochastic resonance can actually enhance the information and thus improve the sensing and processing of otherwise undetectable signals – also for example in oscillations between different quantum energy levels [Badzey and Mohany, 2005]. Brownian or thermal ratchets can bias the thermal noise into one direction. This can be achieved by very small periodic forces which bias cytoskeletal Brownian ratchets or receptors or other parts of the cell membrane (fig. 9).

Coupling of EMF to Molecular Reactions

However, there is still the problem of coupling of EMF energies to conformational changes of biomolecules which might be able to transfer the information to 'classical' signaling pathways. In the case of MF or EMF action on biological systems, the following findings are important: (1) specific effects were observed at very low MF energies, and (2) physiological responses are only observed at certain 'windows' of MF parameters, i.e. at very low amplitudes (≤ 1 Gs) and frequencies (8–60 Hz) [Gartzke and Lange, 2002]. This frequency dependency suggests a nonlinear, i.e. discrete or quantized, physical mechanism of energy transfer. Many experiments on isolated cell systems point to the Ca^{2+} signaling pathway as the target of EMF in the first step of coupling [Carson et al., 1990; Walleczek and Liburdy, 1990; Lyle et al., 1991; Liburdy, 1992; Walleczek and Budinger, 1992; Liburdy et al., 1993; Fitzsimmons et al., 1994; Barbier et al., 1996; Gölfert et al., 2001; Pessina et al., 2001]. Alternating MF mostly cause an increase in Ca^{2+} in many cell types [Carson et al., 1990; Lyle et al., 1991; Lindstrom et al., 1993; Fitzsimmons et al., 1994; Lindstrom et al., 1995; Barbier et al., 1996; Pessina et al., 2001]. However, a decrease in Ca^{2+} for signaling was also reported with retardation of metabolic activity and block of action potentials [Cavopol, 1995; Rosen, 1996; Sabo et al., 2002].

In this respect, two physical models for a direct energy coupling between Ca^{2+} and MF are discussed: (1) the ion parametric resonance model [Lednev, 1991] and (2) the ion interference model [Binhi, 1997]. Lednev's theory

uses the phenomenon of Zeeman splitting of excited states of bound ions by a static MF (nonlinear effect). ELF EMF might modulate these states, and thus, be a mechanism for the interaction of MF with Ca^{2+} and other cations bound to biomolecules. Binhi suggested the ion interference model, which is based on the interference of nonlinear energy states of bound Ca^{2+}. As an example, exposure of ELF EMF (10–100 Hz) to human dermal fibroblasts in a collagen matrix demonstrated a 'window' behavior. Nonlinear quantum interference effects on protein-bound substrate ions are therefore proposed: due to EF in the media or biological tissues, ions experience electric gradients as small as 0.01 mV/cm produced by polarized binding of the ligand atomic shells. By this effect, the electric gradients cause an interference of ion quantum states [Binhi and Goldman, 2000].

Both theories reflected the observed optimal amplitude and frequency windows of EMF action. Both models work with the cyclotron frequency – a frequency which is able to accelerate a Ca^{2+} ion moving on a curved pathway. The force (based on the Lorentz force) tends to bend the path of a charged ion moving through a constant MF [Liboff, 1985]. Since such charges tend to circulate, they may gain energy from an alternating field, at a frequency determined by the charge/mass ratio and the strength of the MF. For ions (like Ca^{2+}) the resonance occurs at frequencies of 10–100 Hz.

On the other hand, a direct energy transfer via cyclotron resonance on larger biomolecules [Karnaukhov, 1996] is considered unlikely because an appropriate biological target system is unknown. The coupling of EMF to a biological system is a multistep procedure. The coupling of the EMF energy to a bound cation would represent the first step, the second step being the interaction with larger biomolecules. The third step is the triggering of a classical signaling cascade.

It is very important to keep in mind that the dissociation energy of single bound Ca^{2+} in organic molecules exceeds, by orders of magnitude, the energy level of ELF EMF. Thus, coupling with larger biomolecules cannot occur by changing only single bonds. To close the gap between the EMF coupling steps, Gartzke and Lange [2002] proposed ionic conduction along actin fibers in charged clusters or vortices formed by Ca^{2+} ion clouds (fig. 9). Preferentially, this should happen in the microvilli. Each of the negatively charged actin bundles has 5–6 binding sites for cations, preferentially for divalent cations such as Ca^{2+} or Mg^{2+}. The proposed concept is appealing because actin has a central role in Ca^{2+} signaling and its polyelectrolyte nature has specific ion conduction properties. Therefore, the actin core of the microvilli may allow Ca^{2+} entry into the cytoplasm via a nonlinear cable, like cation conduction through arrays of condensed ion clouds. Consequently, free ionic movement along an EF is restricted. The transport of cations along the linear matrix of fixed negative charges requires a simultaneous jump of counterions between all centers at the same time and in the same direction (fig. 9). Thus, in contrast to stochastic activation of ion transfer by thermic effects, energy transfer from the applied EMF may result in time-, space- and vector-coherent excitation of ions within the whole conducting path. Thus, an array of coupled low-potential barriers between the charge centers efficiently discriminates thermal activation of ion conduction along the polyelectrolyte. The activation energy for an ion transfer between charge centers of the ion cloud is lower than or similar to the thermal energy level. Therefore, MF of similar low energy can move ions between the centers [Gartzke and Lange, 2002]. The resulting influx of cations (Ca^{2+}) into the cell induces the third step, the triggering of classical signaling cascades.

Microvilli with actin bundles shielded by a lipid membrane can function like electronic integration devices for signal noise enhancement – the influence of EMF on cation transduction is amplified, whereas that of random noise is reduced. Thus, microvilli are some kind of antennae for EMF. In this respect, it is interesting to note that for instance in macrophages, the formation of microvilli-like structures (podosomes) is induced at 1 Hz and a 2-V/cm field [Cho, 2000]. Thus, one should apply this concept of coupling not only to microvilli but also to microvillus-like structures like podosomes and filopodia. On the other hand, microvillus-like structures can be damaged by 'wrong' (frequency, steepness of the signal) EMF. PEMF at frequencies between 50 and 70 Hz and a 0.6-V/cm field caused loss of microvillus-like structures and a collapse of apical parts of endoderm cells in the embryonic yolk sack [Zhang et al., 1997].

However, the model proposed by Gartzke and Lange [2002] (ionic conduction along actin fibers in charged clusters or vortices formed by Ca^{2+} ion clouds), together with the model of the cyclotron frequency of Ca^{2+} ions, remains to be proved in living cells.

EMF can accelerate certain dynamic chemical systems (like oxidation of malonic acid in the oscillating Belousov-Zhabotinski reaction) [Blank and Soo, 2001] or activities of enzymes such as cytochrome oxidase [Blank and Soo 1998a, 1998b, 2001, 2003] and Na^+/K^+-ATPase [Yoda et al., 1984; Blank, 2005]. For both enzymes, the frequency optimum in the response to EMF is very close to the en-

zyme turnover number indicating that the EMF interact with components critical for determining reaction rates. Recent work has pointed to coupling mechanisms via transient electrons, where measurements of flickering in H-bonded molecule networks [Fecko et al., 2003] indicate that protons regularly move between oxygens, suggesting that electrons (where the de Broglie wavelength is much greater and can thus tunnel over greater distances) would do the same. Like in water, flickering protons and electrons would also be expected in hydrated and internally H-bonded proteins at a similar flicker rate (nanometers/picosecond). Furthermore, covalent bonds have been shown to be preferred paths for quantum tunneling [Wenger et al., 2005]. In the model of Blank [2005], the speed of the moving charges (1,000 m/s) is comparable with electron speeds in DNA [Wan et al., 1999], proposing that electrons are the moving charges affecting the rate of the enzymatic reaction.

This model also offers a rationale for why large static MF do not have an effect on enzymes like the Na^+/K^+-ATPase, even though weak ELF EMF do. In weak ELF EMF, electrons moving at 1,000 m/s could be displaced approximately 1 nm/ps. This distance is smaller than the membrane thickness (approximately 10 nm) and well within a protein. In contrast, MF penetrate the protein and interact with transient electrons throughout the membrane. EF do not penetrate the protein but can change the charge distribution at the interface. Therefore, effects can only be propagated indirectly, and thus, differences between responses of membrane enzymes to MF and EF can be explained.

In summary, EMF can accelerate such chemical (e.g., Belousov-Zhabotinski) or enzymatic reactions, also via a ratchet mechanism, where the effect of an induced EF is reversed in the second half of the sine wave. An MF generates a force orthogonal to the direction of movement of the electron, and in the second half of the sine wave, the force is orthogonal in the opposite direction. However, in both halves of the sine wave, the electron has a component in the original direction. Therefore, interaction with an MF provides a ratchet mechanism that allows a process to proceed essentially in one direction only [Blank and Soo, 2001].

Future Developments

By comparing different models, we have seen how EMF coupling could occur and that molecules not only represent mechanical molecular machines but also nanodevices comparable with transistors in a microchip, 'molecular electronics' [Piva et al., 2005]. However, those molecules are not the only elements representing the current 'technical standard', but wisdom of nature has endowed them with additional properties, which are just beginning to be explored by today's scientists. Possibly, they are elements for quantum computing and quantum holography – phenomena already found long ago in solid state physics and soon to be found in the 'wet lab' of the cell. Indeed, some papers discuss that EMF coupling also occurs via interference with quantum coherence, as an actin filament sliding on myosin molecules in the presence of ATP always exhibits magnetization as a marker of quantum processes [Matsuno, 2001]. These kind of processes can get a coherent 'swing' from EMF applied from the outside. Another example for additional physical properties of biomolecules is the interior of the microtubules which is working as an electromagnetic wave guide, full of water in an organized collective state which is able to transmit information [Rosa and Faber, 2004]. A gelatinous state of water (found as water bound to biomolecules) favors a collective effect of coherent nonlinear (quantized) states which favor a readout by other biomolecules [Watterson, 1996]. Concerning subtle forces (like London forces) which can act for example on microtubules, Hameroff and Penrose [1996a, 1996b] formulated a hypothesis on the ability of biomolecules such as microtubules as quantum computing devices [Hameroff, 2004].

Conclusion

In conclusion, compared with the effects of static MF or ELF EMF, the cell-guiding effects of static EF have a good explanation with the observations of the electrophoretic mobility of charged cell membrane molecules. However, a cascade of events must be initiated for this effect to be linked to classical biochemical pathways. The cascades involved in linking subtle fields like quantum coherence or cyclotron resonance to larger biomolecules, as for example actin or signaling molecules, requires even more complicated coupling mechanisms, so that a functional reaction occurs in the cell. Several parameters including information, doses, frequencies and phases of the EMF are decisive as to whether or not the cells respond, and if so, in which manner they respond.

In order to classify the intensity of the forces found in cells and organs, it should be remembered that EMF are far more subtle than the signaling pathways which trigger

chemotaxis or intracellular biochemical pathways. Furthermore, cells and organs are normally shielded against false 'technical' EMF from outside, and the organism is very robust against disturbances by such fields. However, in rare cases, enigmatic processes can be triggered, as is seen in the 'electrosensitivity' of patients.

In principle, the subtlety of the EMF mechanisms makes it difficult to easily get clear-cut results in patients and in lab experiments for example with applied fields. Furthermore, the whole scientific field is riddled with very poor science and sometimes fabrication data [for a review, see McCaig et al., 2005]. Thus, to regain credibility in this area, high standards are necessary in conducting future studies (including good scientific practice with well-chosen controls and triple blinded studies). In this sense, it is encouraging that recently more and more realistic and provable models have occurred, which may some day thoroughly explain the various EMF effects.

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