Electric fields have potential as a cancer treatment

Low-intensity alternating fields can hinder or destroy dividing cells and slow the growth of brain tumors in cancer patients.

Healthy cells have regulating mechanisms that generally limit how rapidly they can divide. Skin cells, for example, normally divide about once every 30 days, but they can divide faster in response to a wound that needs healing. Cancer, however, is characterized by cell division that has gone out of control. In cancer cells, the mechanisms that regulate division break down, and the cells spend less time in the quiescent state and more time dividing.

Many chemotherapy drugs work by interfering with the cell-division cycle. The drugs reach healthy cells and cancer cells alike, but they do most of their damage to the cancer cells. Unfortunately, some types of healthy cells divide as rapidly as cancer cells and are badly damaged as well. Such cells are found in bone marrow, the lining of the digestive tract, and hair follicles, so chemotherapy patients often lose their hair and are susceptible to infection. The damage to healthy cells limits the drug dose that a patient can tolerate and therefore limits the treatment's effectiveness.

Yoram Palti, of the Technion–Israel Institute of Technology in Haifa, and his colleagues have demonstrated another way to disrupt cell division: alternating electric fields with intensities of just 1–2 V/cm. The fields they use, with frequencies in the hundreds of kilohertz, were previously thought to do nothing significant to living cells other than heating them. But Palti and colleagues have conducted a small clinical trial showing that the fields have an effect in slowing the growth of tumors.[1]

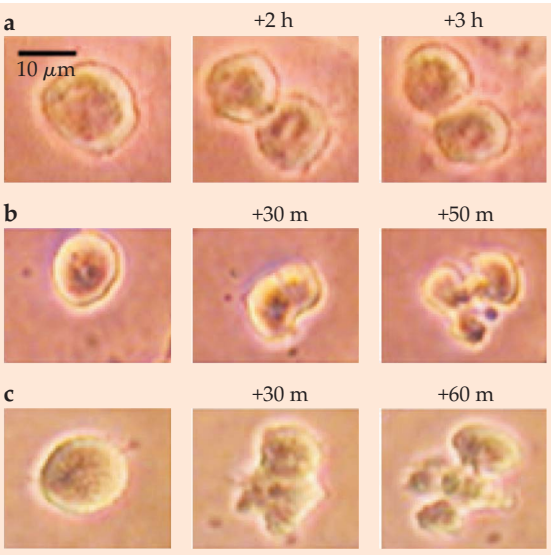

Figure 1. Dividing cells are hindered in two ways by alternating electric fields, as illustrated by time-lapse microphotography. **(a)** Cells whose division normally takes less than one hour have not completely split after three hours. **(b, c)** Other cells disintegrate in the late stages of dividing. (Adapted from ref. 2.)

Proposed mechanisms

In studies of tumor cells in vitro, Palti and colleagues observed two distinct effects, both of which depend on the direction of cell division with respect to the applied field.[2] First, they found that cells in the electric field take longer than usual to divide, as shown in figure 1a. Second, they found that dividing cells sometimes disintegrate just before the division process is complete, as shown in figure 1, panels b and c. They offer an explanation for each effect.

The researchers suggest that cell division is slowed because the electric field hinders the formation and function of the mitotic spindle, the structure that guides the newly replicated chromosomes as they separate into the two daughter cells. The mitotic spindle is made up of microtubules, formed by the polymerization of dimers of the protein tubulin. (Microtubules and other cellular structures are illustrated in PHYSICS TODAY, September 2006, page 80.) The tubulin dimers and polymers have large dipole moments, so they are affected by the electric field. But most other biochemical processes

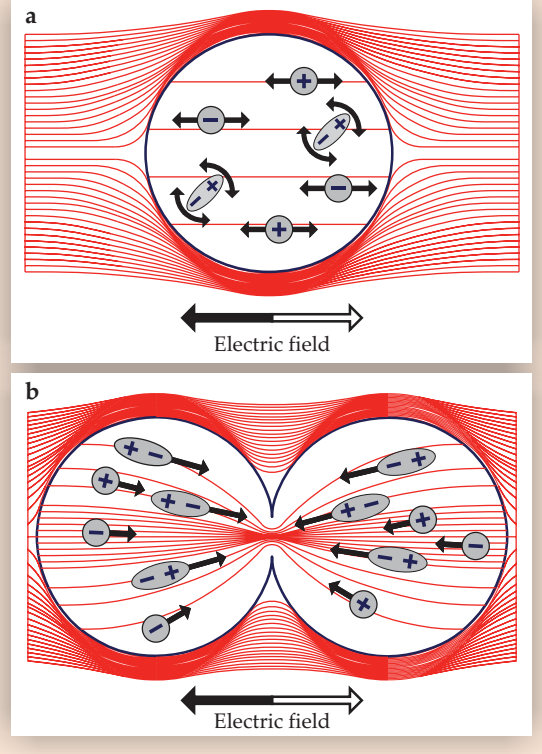

Figure 2. Simulations of the electric-field distribution (red lines) in a cell in response to an applied alternating field of frequency 100 kHz. The cell membrane, a lipid bilayer, has a high impedance at that frequency, so the field does not readily penetrate the membrane. **(a)** In a cell that is not dividing, the electric field is weak and uniform and results in oscillatory forces (black arrows) on charged and polar molecules and organelles. **(b)** When a cell divides along an axis parallel to the electric field, a region of higher field forms at the bottleneck between the two newly forming cells. Over the course of many field cycles, polarizable molecules and organelles experience a force in the direction of the higher-field region, regardless of their permanent charge or dipole moment; their movement may contribute to the destruction of the cell. (Adapted from ref. 1.)

also involve polar molecules and structures, and small oscillating electric forces don't appear to have much of an effect on them. The difference, says Palti, is that when the tubulin dimers assemble into the mitotic spindle, they all line up in the same direction. If that direction happens to be orthogonal to the direction of the electric field, the microtubules are less likely to function normally.

The proposed mechanism for the destruction of dividing cells stems from the distribution of the electric field in each cell. The cell membrane, a lipid bilayer, acts as a capacitor with high impedance at the frequencies used, so the electric field doesn't readily penetrate the cell membrane. In a quiescent cell, the electric field inside the cell (shown in figure 2a) is much smaller than the field outside the cell and is largely uniform. But in the late stages of cell division, a higher-field region forms at the bottleneck point, or furrow, between the two newly forming cells, as shown in figure 2b. The nonuniform electric field generates a so-called dielectrophoretic force that draws polarizable molecules and structures in the direction of the higher-field region. The researchers calculate that the force, which can be as large as 60 pN, is enough to cause the organelles to pile up at the furrow within a few minutes.

Just how that pileup destroys the cell is still largely a matter of speculation, but Palti and his colleagues have a few ideas. "The organelles are attached to a cytoskeleton," Palti says. "They're not just floating around in the cytoplasm," so maybe the dielectrophoretic force rips them from that connective structure and kills the cell. Also, the pinching-off mechanism, by which the furrow closes and one cell becomes two, is a sensitive process that could be disrupted by the presence of molecules and organelles that are supposed to be elsewhere in the cell.

Palti's 100-kHz fields are not the only form of electrical stimulation that can hinder cell division. Luca Cucullo, Damir Janigro, and their colleagues at the Cleveland Clinic have found that low-intensity alternating current with a much lower frequency—about 50 Hz—can keep some types of cells from dividing.[3] They don't yet know exactly how the process works, but their experiments suggest that the mechanism involves a particular protein that forms pores in the cell membrane to transport potassium ions into the cell. Cells whose division was halted by electric current contained more than the usual amount of the protein. And when the stimulated cells were exposed to cesium or barium, which block the potassium-transport pores, they divided at the same rate as unstimulated cells.

Clinical trial

Palti and colleagues had extensively studied the effects of the electric fields on tumor cells in vitro and in laboratory mice and rats when in 2003 they began their first clinical trial on human patients. They used their electric fields to treat glioblastoma multiforme (GBM), a type of brain tumor with a very low survival rate. When the tumor is treated by surgery, radiation, or chemotherapy, it nearly always progresses, or starts to grow again. The tumor usually kills the patient, often by the buildup of intracranial pressure that results from the tumor's sheer size.

The researchers recruited 10 patients for their trial. All had recurrent GBM, meaning that their tumors had been treated by other methods and had begun to grow again. The patients were fitted with electrodes, as shown in figure 3, that applied a 200-kHz electric field to their brains. At one-second intervals, the field orientation switched between front to back and side to side, so that the field would have the greatest effect on tumor cells dividing in all directions. Patients wore the electrodes 18 hours per day for up to 18 months.

Healthy cells in an adult brain don't divide, so there was little danger that the electric field would damage the normal tissue surrounding the tumor. In fact, because of the way applied fields are distributed in the body, the researchers are confident that when they apply their treatment to tumors in other parts of the body, the fields will do little damage to the bone marrow or the digestive tract. The field strength that could be used was limited not by toxicity to healthy tissues but by thermal effects in the skin: The field intensity was automatically lowered if the skin was heated enough to be in danger of thermal damage. The patients didn't lose their hair, but they had to keep their heads shaved in order for the electrodes to make good contact.

Because their small trial had no control group, the researchers compared their device's performance with historical data from other studies of GBM patients. Palti's trial found a median time to progression of 26 weeks and a median survival time of 62 weeks, whereas studies of recurrent GBM treated by other means found a time to progression of about 10 weeks and a survival time of about 30 weeks. Two years after their treatment began, 3 of the 10 patients in Palti's trial were still alive, and two were progression free.

To better evaluate their treatment's effectiveness, Palti and colleagues are currently working on a controlled study in which patients are randomly assigned to receive either the electric-field treatment or a chemotherapy regimen. They are also looking into combining the electric-field treatment with low-dose chemotherapy.

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Figure 3. A brain-tumor patient receiving electric-field treatment. Electrodes affixed to the scalp, fed by the 3-kg battery-powered device in the gray and black bag, apply alternating electric fields to the tumor site. Since the device is portable, patients can go about their normal activities while being treated for 18 hours a day.

References

1. E. D. Kirson et al., *Proc. Natl. Acad. Sci. USA* **104**, 10152 (2007).
2. E. D. Kirson et al., *Cancer Res.* **64**, 3288 (2004).
3. L. Cucullo et al., *Glia* **51**, 65 (2005).