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A look back: a shock to the system

Since the days of Benjamin Franklin, scientists have been keenly aware of the dangerous (and painful) potential of a strong electric current; likewise, at a smaller scale, scientists have been aware for some time that a strong electric pulse can kill cells by inducing membrane lysis. However, some researchers in the 1970s were surprised to find that for pulses of milder strength, cells seem to follow the principle of 'whatever doesn't kill you only makes you stronger'—or at least bigger. Indeed, a landmark study by Kinosita and Tsong demonstrated that the application of electrical pulses could be used to induce the formation of transient, reversible openings in the plasma membranes of human erythrocytes, triggering cell expansion as a result of the uptake of a variety of ions and organic compounds from the surrounding medium[1].

Another pioneer in the field, Eberhard Neumann of the Max-Planck-Institut in Munich, had also spent several years characterizing this phenomenon in a variety of mammalian cell types. Building on his own work, as well as that of fellow German cell biologist Ulrich Zimmermann, Neumann ultimately arrived at the idea of using this process as a method for delivering DNA into mammalian cells. Using moderate voltages, Neumann was readily capable of coaxing mouse fibroblasts into taking up and stably expressing plasmid-based foreign genes, with an efficiency that rivaled existing techniques for transfection, such as calcium phosphate and liposomes[2]. In a subsequent paper, Neumann's group investigated the mechanics of this process, which they now dubbed 'electroporation', theorizing that interactions of the lipid membrane with the external electric field led to shifts of certain lipid head groups into more favorable dipole configurations—shifts that result in the thinning and eventual perforation of certain portions of the plasma membrane[3]. Surprisingly, the picture has not grown especially clearer in the subsequent quarter of a century, and the actual mechanics behind this electrically induced membrane pore formation remain vague and controversial, particularly with regard to the highly temporary nature of the resulting openings[4].

What was immediately clear, however, was that electroporation offered a simple and effective strategy for performing eukaryotic transfection when other approaches fall short. Neumann's initial work had centered on fibroblasts, but researchers from Philip Leder's group at Harvard Medical School soon adapted his approach for use with a wide variety of mammalian cell types, culminating in a highly cited 1984 paper that demonstrated the successful stable transfection of mouse pre-B lymphocytes with human immunoglobulin genes using electroporation[5]. The method also proved a boon in the early days of embryonic stem cell manipulation[6], offering a less stressful alternative to microinjection for biologists hoping to achieve targeted homologous recombination. Today, it remains one of the most popular methods for the stable transfection of mammalian cell lines, and the preferred nonviral option when working with embryonic stem cells for the production of genetically modified animals.

As the field of gene therapy grew in the 1990s, some scientists began to wonder whether this simple and effective system for *in vitro* gene transfer might also have potential as a system for DNA uptake *in vivo* as well. Theoretically, as long as the cells to be targeted are in the proximity of the applied electric field, the process of reversible pore formation—and thus the easy entry of DNA molecules—should still take place. A pair of early studies confirmed the principle, showing that it was possible to use electrical current to stimulate the enhanced delivery to tumor cells of the drug bleomycin[7,8], inhibiting tumor growth by a process that one group termed 'electrochemotherapy'[8]. The first successful demonstration of this approach for *in vivo* DNA transfer was announced shortly afterward, by a group that had used electroporation to stably transfect the skin cells of neonatal mice[9]; within a few years, numerous other reports would be published, describing the successful stable introduction of foreign DNA into a variety of targets, including muscle, liver and tumor tissue, laying the groundwork for the potential application of this technique in human therapeutics. The field is still young (for a recent review, see ref. 10), but the early findings nonetheless offer the possibility that electrically induced gene uptake could still provide a powerful jolt for clinical research.

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