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International Society for Electroporation-Based Technologies and Treatments

ISSN: 2463-9850

July 2021

read online at goo.gl/k2q9A0

Newsletter No. 62

Electric fields induced cell death and the immune system

Newsletter by: Boris Rubinsky, University of California Berkeley, CA, USA
rubinsky@berkeley.edu

Minimally invasive surgery has enriched the surgeon's armamentarium with valuable means to treat tissues in the body, without the need to resort to crude surgical knife-based resection techniques, which were the main tools of surgery for millennia. Minimally invasive surgery emerged from advances in physics. For example, the minimally invasive surgical techniques of electrolytic ablation [1] and cryosurgery [2] emerged in the 18th century from the fundamental research of Faraday on the physics of mixtures and electrochemistry. These procedures belong to the class of minimally ablation surgery techniques whose hallmark is that some or all molecules survive intact the process of cell death. As a consequence, the immune system can recognize or be trained to recognize this mode of cell death. An early paper in this field is the work of Soares, Ablin, and Gonder, who found remission of metastatic tumors after cryosurgery of a primary prostate cancer tumor and attributed this effect to the immune system [3]. Electromagnetic fields based minimally invasive surgical techniques are notable for inducing cell death in a mode that preserves many of the molecules of the cells in their native form. Therefore, electromagnetic fields (EMF) based minimally invasive surgical techniques hold the greatest potential for developing medical treatments in conjunction with the immune system. EMF based minimally invasive surgery techniques were first brought to clinical practice by the group of Lluis Mir, who developed electrochemotherapy. Electrochemotherapy employs electric fields that induce reversible permeabilization of the cell membrane (reversible electroporation) to introduce compounds that are toxic to cells and to whom the cell membrane is impermeable, into the interior of the cells, and thereby cause cell death. Among these compounds are bleomycin and cis-platinum which affect cells by binding to DNA, to inhibit cell division by breaking the DNA strands. Two other techniques that employ reversible electroporation to affect cell death have recently emerged. One technique that combines increased extracellular calcium concentration with reversible electroporation (CaEP), leads to cell death from changes in the intercellular Ca2+ homeostasis. The other technique, electrolytic electroporation (E2), combines electrolysis induced changes in extracellular pH with reversible electroporation, to also cause cell death from changes in the intercellular homeostasis. It was found that cell death from E2 is associated with pyroptosis and necroptosis. Cell death from CaEP was found to be associated with evidence of necrosis although some studies suggest apoptosis. Another technique in which EMF's affect the interior of the cell involves the use of nanosecond pulses (nsEP).

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In nsEP, cell death appears to be associated with a modified apoptosis path. A different class of EMF induced cell death relates to the effect of the electromagnetic fields on the cell membrane and the permanent permeabilization of the cell membrane. This minimally invasive surgery technique is usually referred to as irreversible electroporation (IRE). A recent variant which employs bipolar pulses is known as HFIRE. There is some controversy on the mechanisms of cell death from irreversible electroporation with some groups reporting necroptosis and pyroptosis and others apoptosis. This brief write-up lists the various EMF based minimally invasive techniques whose hallmark is that, unlike thermal ablation techniques, immune system relevant organic molecules of the cell remain intact in the process cell death. Why is this important? Because, in my opinion, the great potential of these EMF based minimally invasive surgery techniques is in their combination with the systemic immunology response. Evidence for that begins to emerge. For example, combinations of irreversible electroporation with stimulator of interferon genes agonists or checkpoint blockade are showing promise. A recent finding by the group of Miklavčič [4], shows that irreversible electroporation yields the release of "damage associated molecular pattern molecules", which can trigger an immune response. An important step in developing a systematic approach that combines minimally invasive surgery with an immunological response is to understand precisely the processes of cell death from electric fields induced minimally invasive surgery. There is confusion over the mechanisms of cell death from these minimally invasive surgery techniques. An important paper towards establishing an understanding of the mechanisms of cell death from electric fields based minimally invasive surgery is the recent comprehensive review of the various mechanisms reported in the literature compiled by the group of Miklavčič [5] . This valuable publication illustrates the lack of a generally accepted understanding and consensus on the mechanism of cell death. I hope that additional work will follow this hallmark paper towards generating a fundamental understanding of the mechanisms of cell death towards a systematic combination of systemic induced immunology and EMF based minimally invasive surgery.

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[3] Soanes WA, Ablin RJ, Gonder MJ. Remission of metastatic lesions following cryosurgery in prostatic cancer: immunologic considerations. J. Urol. 104 (1970) 154–159. doi:10.1016/S0022-5347(17)61690-2.
[4] Polajžer T, Jarm T, Miklavčič D. Analysis of damage-associated molecular pattern molecules due to electroporation of cells in vitro. Radiol. Oncol. 54: 317-328, 2020. https://doi.org/10.2478/raon-2020-0047
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Forthcoming events

15th interdisciplinary postgraduate course and international workshop Electroporation Based Technologies and Treatments (EBTT)
Ljubljana, November 14 – 20, 2021
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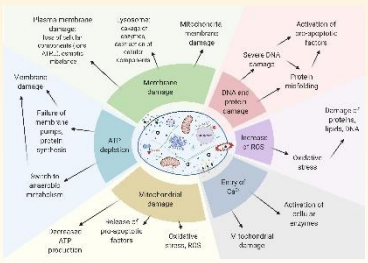

Mechanisms of cell injury. Reproduced from Batista Napotnik et al., Bioelectrochemistry 141 (2021).

Newsletter is issued in electronic form only by The International Society for Electroporation-Based Technologies and Treatments (ISEBTT).

ISSN: 2463-9850