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Cover Story

Vascular modification by electropermeabilization

In electropermeabilization (EP), also called electroporation, electric pulses are applied to cells or tissues to induce reversible permeabilization of the cell membranes under suitable conditions, and thus to facilitate entry of non-permeant or poorly permeant molecules into the cells. The combination of EP and cytotoxic drugs, such as bleomycin and cisplatin, is termed electrochemotherapy (ECT) and is routinely used in the clinics in the treatment of melanoma skin metastases or deep seated tumors, where the complete responses are in the range of 70–80%. Another field, where the merits of EP are increasingly exploited, is the delivery of different nucleic acids (plasmid DNA, small interfering RNA, microRNA, small hairpin RNA) into cells in vitro and also into different tissues in vivo, including muscle, skin and tumors. This application is termed electrogene therapy (EGT), where clinical trials with electrotransfer of IL-12 in melanoma patients showed positive results. Moreover, the use of EP in DNA vaccination protocols greatly increases efficiency of DNA vaccines [1–3].

In addition to the improved delivery of exogenous molecules to tissues, EP also has blood flow modifying effects in tumors and normal tissues. Different indirect techniques have been used for measuring blood flow changes after EP. The changes were measured after EP and ECT of tumors and after EP in muscles. It is interesting to note that a transient reduction of blood flow in tumors was observed with all the techniques used. In vitro studies on cultured primary endothelial cells have shown that EP results in a loss of contractility and in the disruption of the barrier function of the endothelium by affecting the cytoskeletal organization and integrity of cell junctions. Based on the evidence obtained with the indirect methods, a model of blood flow modifying effects of EP was proposed. The model proposes a two-phase phenomenon, where the first phase is a rapid, sympathetically mediated vasoconstriction, followed by a second much longer lived phase (up to 30 min in muscle), which is supposed to follow the kinetics of cell membrane resealing after EP. When ECT is used, the second phase is prolonged and results in the disruption of tumor vasculature [4,5]. Thus, EP and ECT appear to modify local blood flow without systemic vascular effects.

In this issue, Dr. Muriel Golzio and Professor Maja Cemazar with their colleagues describe the direct in vivo observations of the early events in blood vessels after EP using a dorsal window chamber (DWC) model in mice [6]. The use of DWC in combination with fluorescein isothiocyanate-labeled dextrans of different sizes enabled them to observe directly, at the single blood vessel level, the effects of electric pulses on the dynamics (vasomotricity, permeability and recovery) of subcutaneous blood vessels and the subsequent delivery of molecules with increasing sizes in the surrounding tissue. Their data analysis of acquired images confirmed the previously proposed model of blood flow modifying effects of EP, revealing that immediately after EP there is a constriction of blood vessels which is more pronounced in arterioles than in venules. This vasoconstriction results in an obstruction of blood flow, i.e., vascular lock, which lasts for ~10 min. The technique used permitted the authors to follow the dynamics of the increased permeability of the blood vessels following EP. They have shown that EP transiently increases the permeability of blood vessels for different sizes of molecules (20, 70, and 2000 kDa), which can last up to 1 h. This approach enables to gain an insight into the actual physiological processes of the tissues altered by EP that has been only speculated before.

The fluorescent intravital microscopy in DWC used by the Golzio–Cemazar team is also directly applicable to the studies on tumor vasculature, where the high temporal resolution combined with the large field of view of the macroscope enables a simultaneous observation of the tumor vasculature as well as the surrounding blood vessels. In combination with their specific image analysis, phenomena like enhanced permeation and retention (EPR) effect in the surrounding tumor vessels as well as increased interstitial fluid pressure (IFP) in the tumors could be observed and quantified. The EPR effect has been routinely used to explain targeted drug delivery to tumors, but the phenomenon is still not fully understood. The approach used by Dr. Golzio, Professor Cemazar and their coworkers can shed light on the mechanisms of extravasation across the blood vessels of a plethora of drug delivery systems.

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