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Nanosecond pulsed electric fieldsabolish orthotopic rat hepatocellular carcinoma and bypass cancer mutations that evade apoptosis induction

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Abstract

Pulse power using nanosecond pulsed electric fields (nsPEFs) induced cell death inN1-S1 hepatocellular carcinoma (HCC) and Jurkat cells. To induce cell death, nsPEFs disruptedthe mitochondria membrane potential (ΔΨm), which is independent of nanoporation and Ca2+-dependent, and induced an influx of calcium through nanopores in the plasma membrane.This follows the “two hit” hypothesis where Ca2+ overload and another pathological stimulus, dissipation of ΔΨm, must be present to cause loss of cell viability.Effects of nsPEFs on Jurkat cells with deficiencies in FADD or caspase-8 had no effects on cytochrome *c* release or cell death, indicating oncogenic mechanisms for apoptosis evasion through death receptor pathwaysare readily surmountable by nsPEFs.Using Jurkat cells with deficiencies in APAF-1, nsPEF-induced cell death was caspase-dependent at lower electric fields and caspase-independent at higher electric fields. Thus, nsPEFs induce multiple forms of intrinsic cell death.Unlike apoptosis induced by heat or genotoxic stress, overexpression of Bcl-xl (8-fold) in Jurkat cells had no effect on nsPEF-induced dissipation of ΔΨm or viability. Thus, nsPEFs can bypass cancer mechanisms that protect mitochondrial function.*In vivo*nsPEFs ablated 90% of orthotopic HCC.Caspase-9 and caspase-3, but not caspase-8, were activated. For rats with N1-S1 HCC tumors that were eliminated, a challenge injection of the same HCC cells in the same or adjacent liver lobes failed to establish tumors, while age-matched naïve control rats readily grew tumors. These results suggest a host-mediated immune response after clearance of rat N1-S1 HCC with nsPEFs.

Abstract

Stephen J Beebe received his PhD at the Medical College of Ohio, now The University of Toledo College of Medicine. He was as post-doctoral fellow in the Howard Hughes Medical Institute in the Department of Molecular Physiology and Biophysics at Vanderbilt University. He then was a Fulbright Scholar in Oslo Norway before serving as an Assistant and Associate Professor at the Eastern Virginia Medical School in Departments of Physiological Sciences. He is now a Professor in the Frank Reidy Research Center for Bioelectrics at Old Dominion University, Norfolk Virginia. He is the author of over 100 peer reviewed published manuscripts.