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Adjuvant immunogenicity of nanosecond pulsed electric field anti-cancer treatments

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Depending on the initiating stimulus, cancer cell death can be immunogenic or non-immunogenic. Inducers of immunogenic cell death (ICD) rely on endoplasmic reticulum (ER) stress for the trafficking of danger signals such as calreticulin (CRT) and ATP. We found that nanosecond pulsed electric fields (nsPEF), an emerging new modality for tumor ablation, cause the activation of the ER-resident stress sensor PERK in both CT-26 colon carcinoma and EL-4 lymphoma cells. PERK activation correlates with apoptotic cell death induction and is accompanied by the externalization of the "eat me" signal CRT and release of both ATP, a chemotactic factor for dendritic cells (DCs), and chromatin-binding protein high-mobility group B1 (HMGB1), a DC maturation signal. We also find evidence for the immunogenicity of nsPEF-induced cell death in vaccination experiments where nsPEF-treated CT-26 and EL-4 tumor cells protected 78% and 50% of the animals from tumor challenge, respectively. Similar results were also obtained when CT-26 tumors were treated in vivo with nsPEF. Notably, 78% of the tumor bearing mice cured by nsPEF were protected from a secondary tumor cell challenge administered at five months post treatment, suggesting the induction of a long-lasting anti-tumor immunity. Finally, we provide evidence that nsPEF-induced tumor cell death primes naïve antigen-specific cytotoxic T cells as measured by IFNγ release from OVA-specific OT-I CD8+ T cells. All together these results reveal the inherent capacity of nsPEF to induce cell death-associated exposure of danger signals and trigger a potent and persistent anti-cancer immune response.