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Immunogenic oncolysis by tigilanol tiglate

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ABSTRACT

Tigilanol tiglate is an oncolytic small molecule that is undergoing clinical trials. A recent study revealed the capacity of this pyroptosis inducer to elicit hallmarks of immunogenic cell death. In addition, intratumoral injection of tigilanol tiglate can sensitize subcutaneous cancers to subsequent immune checkpoint inhibitors targeting CTLA-4 alone or in combination with PD-1.

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Main text

In the ever-evolving landscape of cancer therapy, the pursuit of interventions that amplify cancer immunosurveillance stands as a cornerstone in the quest for enhanced efficacy. Among these strategies, the induction of immunogenic cell death (ICD) emerges as a promising avenue. ICD, characterized by the release of danger signals from dying cancer cells, serves as a potent stimulant for the immune system, triggering a cascade of events that culminate in the recognition and elimination of tumor cells by effector/cytotoxic lymphocytes.[1]

The concept of ICD encompasses a spectrum of cellular demise pathways endowed with immunostimulatory properties. Apoptosis, the most well-characterized form of programmed cell death, has long been recognized for its immunologically silent nature. However, accumulated evidence unveiled the immunogenic potential of apoptotic cell death when accompanied by the exposure or release of danger-associated molecular patterns (DAMPs) such as calreticulin, annexin A1, ATP, and high mobility group box 1 (HMGB1). Similarly, necroptosis, ferroptosis, or pyroptosis, have emerged as alternative immunogenic cell demises, offering novel targets for therapeutic intervention.[2,3]

Intratumoral injection of immunostimulatory factors has gained considerable attention in recent years to reach improved tumor debulking together with limited systemic adverse events. Such local therapies are attempted with a wide range of agents, including adopted immune cells, antibodies, cytokines, pattern recognition receptor (PRR) agonists, vaccines, as well as ICD-inducing oncolytic viruses, peptides, and small molecules.[4–7]

Along this line, tigilanol tiglate (TT) is a natural activator of the protein kinase C (PKC) family members that is approved for intratumoral treatment of cutaneous cancers in dogs and currently under investigation in humans. Mechanistically, preclinical studies have shown that intralesional administration of TT triggers tumor ablation by disrupting local vasculature and promoting hemorrhagic necrosis. Yet, its local administration has been associated with antitumor effects of distant untreated ("abscopal") lesions in a Phase I clinical trial, thus indicating that TT has immunosurveillance-enhancing potential.[8]

In a recent study published in the *Journal for the Immunotherapy of Cancer*, Cullen and colleagues investigated the immunogenic properties of tigilanol tiglate (TT).[9] In squamous cell carcinoma and melanoma cell lines, TT successively promoted dissipation of the mitochondrial membrane potential, mitochondrial swelling, outer mitochondrial membrane permeabilization, mitochondrial degradation, cytoplasmic vacuolization, and cellular swelling prior to cell death. At the molecular level, the in vitro TT treatment triggered proteolytic activation of caspases, Bid, poly [ADP-ribose] polymerase (PARP) as well as of gasdermin E (GSDME). Thus, TT apparently induces caspase-dependent GSDME-mediated pyroptosis. Of note, this effect seemed largely PKC-independent. Cellular assimilation of TT was accompanied by the phosphorylation of Ire1α and eiF2α, indicating the activation of the endoplasmic reticulum (ER)/mitochondrial unfolded and integrated stress responses. Importantly, treatment with TT stimulated ROS production, release of ATP and HMGB1 into the extracellular milieu, and externalization of the ER chaperone calreticulin. Moreover, whereas type I interferon (IFN-I) secretion was not detected, production of pro-inflammatory cytokines like interleukin (IL)6, IL8, C-X-C motif chemokine ligand (CXCL)9, and CXCL10 was detected. In vivo, mouse vaccination with cancer cells treated with a high (but not low) dose of TT protected against rechallenge with live malignant cells.

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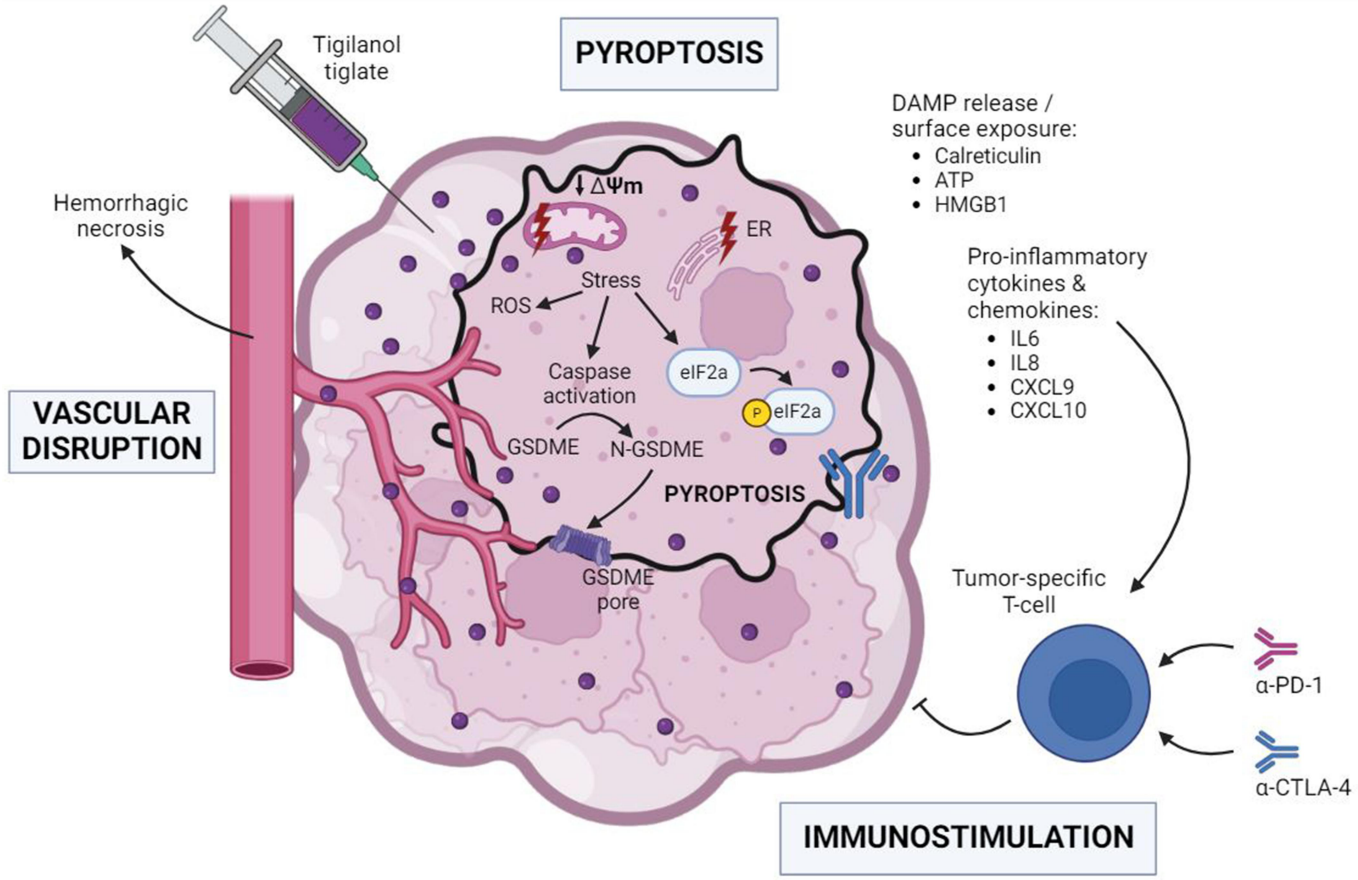

Figure 1. Tigilanol tiglate promotes pyroptotic cell death and sensitizes to immune checkpoint inhibitors. IT administration of TT initiates mitochondrial and ER stress responses, leading to generation of ROS, induction of the ISR as illustrated by the phosphorylation of elf2alpha, caspase activation, and subsequent GSDME-mediated pyroptotic cell death. This cell demise shows immunogenicity due to the release/surface exposure of DAMPs (e.g., calreticulin, ATP, HMGB1) together with pro-inflammatory cytokines (e.g., IL6, IL8, CXCL9, CXCL10). This cascade of events triggers a tumor-specific T cell response which can be enhanced by systemic immunotherapy with inhibitors of the CTLA-4 and PD-1 immune checkpoints. CTLA-4, cytotoxic T lymphocyte associated protein 4; CXCL, chemokine (C-X-C motif) ligand; DAMP, damage-associated molecular pattern; ER, endoplasmic reticulum; GSDME, gasdermin E; HMGB1, high mobility group box 1; IL, interleukin; ISR, integrated stress response; IT, intratumoral; PD-1, programmed cell death protein 1; ROS, reactive oxygen species; TT, tigilanol tiglate. Created with BioRender.com.

Collectively, these data supported the immunogenicity of TT-induced pyroptotic cell death. Accordingly, in the therapeutic B16-F10 melanoma model, intratumoral delivery of TT stimulated infiltration by T lymphocytes of this otherwise immune cold tumor. Furthermore, such intervention reverted resistance to dual immunotherapy blocking the immune checkpoint cytotoxic T lymphocyte-associated protein 4 (CTLA-4), alone or in combination with programmed cell death protein 1 (PDCD1, best known as PD-1) (Figure 1).[9]

In conclusion, the induction of ICD through intratumoral delivery of TT or other oncolytic agents presents a promising avenue for cancer treatments. This approach holds the potential to invigorate cancer immunosurveillance, particularly in immune cold tumors, which typically exhibit resistance to conventional immunotherapies. By triggering ICD, TT may effectively convert immune cold into hot tumors, thereby restoring their responsiveness to systemic immune checkpoint blockers that are widely used in clinical practice.[5,10] Thus, TT enters a competitive space in which a number of oncolytic agents are being compared for their capacity to elicit clinically relevant anticancer immune responses that can be amplified by blockade of immune checkpoints.

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