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Commentary

A novel therapeutic avenue: pharmacological induction of tumor cell pyroptosis

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Abstract: Emerging preclinical evidence indicates that pharmacological induction of tumor pyroptosis promotes immune responses, representing a new therapeutic avenue for relapsed/refractory cancer patients. For example, a recent study in Communications Medicine has demonstrated that histone deacetylase inhibitors de-repress transcription of a tumor suppressor *GSDME* in B-cell lymphoma cells, and synergize with cisplatin and etoposide to promote GSDME cleavage by caspase-3 and subsequent pyroptosis of lymphoma cells. Furthermore, the anti-lymphoma efficacy of this combination therapy *in vivo* depends on CD8 T cells. This article provides a brief introduction of the pyroptosis pathway in cancer, comments on this promising 'One action, two benefits' therapeutic strategy for cancer treatment, and discusses the significance and unaddressed questions in recent therapeutic studies targeting pyroptosis-suppressing mechanisms in cancer.

Keywords: HDACi, pyroptosis, GSDME, chidamide, cisplatin, DLBCL, epigenetic, gasdermin, apoptosis, Caspase cleavage

Cancer treatments include chemotherapies and targeted therapies as direct approaches to kill tumor cells, as well as immunotherapies as indirect approaches via host immune responses to reject tumors. However, tumor cells often develop various anti-apoptotic mechanisms to survive conventional cancer treatment. Hence, non-apoptotic types of tumor cell death are critical for overcoming treatment resistance, and have become of interest for novel therapeutic development. Among these non-apoptotic mechanisms, pyroptosis is an inflammatory form of programmed cell death, which differs from apoptosis and ferroptosis in terms of immunogenicity, and differs from necroptosis in terms of whether the cell death is regulated. Pyroptosis was originally described in myeloid and epithelial cells, canonically induced by inflammasome assembly upon recognition of bacterial components by pattern recognition receptors, followed by Caspase-1 cleavage and activation, and mediated by cleaved gasdermin D (GSDMD) pore forming activities on the plasma membrane [1-3], resulting in releasing cytosolic contents and pro-inflammatory cytokines, such as IL-1β and IL-18, after cleavage of their precursors [4]. It was not until 2017 that pyroptosis was linked to cancer, discovering gasdermin E (GSDME) as a tumor suppressor in normal tissues but silenced in most cancer cells, whose N-terminal domain has pore-forming activities to initiate pyroptosis, as shown in various solid tumor cells and T lymphoma cells [5]. Chemotherapeutic agents activate Caspase-3 (which is previously known for its key role in apoptosis) [5, 6], whereas tumor-infiltrating natural killer (NK) lymphocytes [7] and genetically modified chimeric antigen receptor (CAR) T cells [8] release granzyme B into tumor cells, which directly [7] or indirectly [8] cleave GSDME, thereby triggering immunogenic tumor cell pyroptosis and amplifying the antitumor immune responses.

The practical therapeutic potential of pyroptosis induction by pharmacologic modulation have been demonstrated in a recent publication in *Communications Medicine*, "Chidamide synergizes with cisplatin-etoposide to trigger

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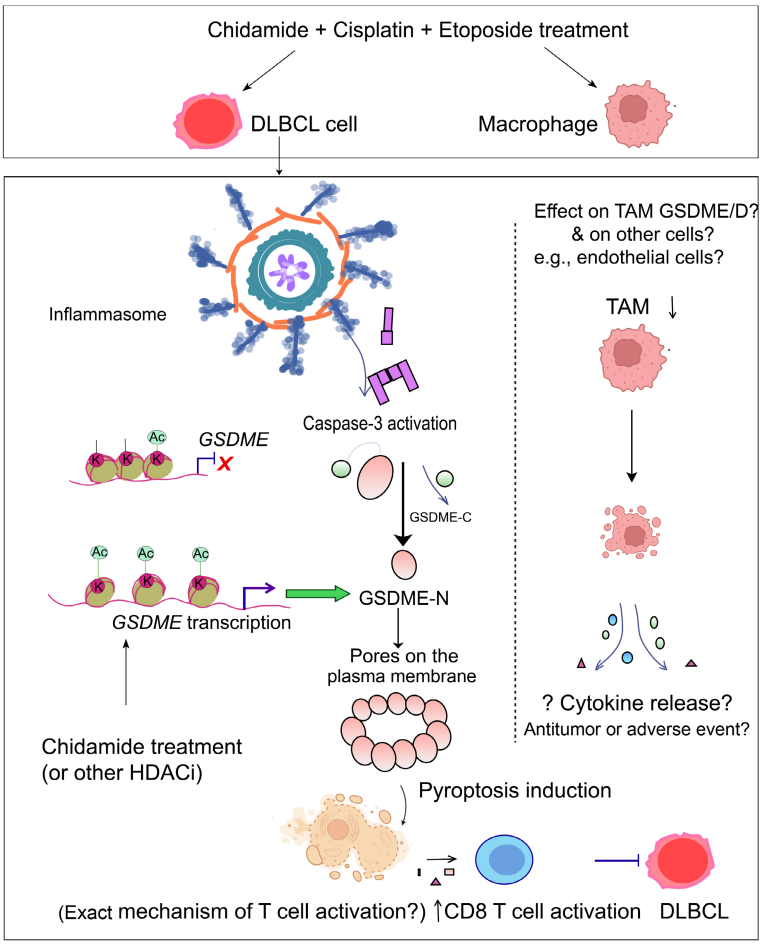

Figure 1. Schematic illustration of findings in the therapeutic study by Wu et al and unaddressed questions as discussed in the article. Abbreviations: TAM: tumor-associated macrophage; HDACi, histone deacetylase inhibitor.

pyroptosis and anti-tumor immunity in diffuse large B-cell lymphoma" (DLBCL) [9]. DLBCL is the most common type of aggressive B-cell lymphoma. Majority of DLBCL patients are cured with the standard therapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]), whereas patients with refractory or relapsed disease have low survival rates after salvage treatment. Wu et al found *in vitro* and *in vivo* that pyroptosis is a mechanism of action of an epigenetic drug chidamide in combination with cisplatin and etoposide, two agents in a standard second-line regimen for DLBCL (dexamethasone, ifosfamide, cisplatin, etoposide, DICE, traditionally used as DLBCL's salvage therapy). Chidamide (other names: tucidinostat and Epidaza) is a selective class I histone deacetylase inhibitor (HDACi) which specifically inhibits HDAC1/2/3/10 activities [10]. Chidamide in combination with R-CHOP has been approved in China as the first-line treatment for previously untreated MYC/BCL2 double expressor DLBCL [11, 12].

The pro-pyroptosis mechanisms of the combination therapy are twofolds. Through promoting transcriptional activation and Caspase-3-dependent cleavage of GSDME, the combination regimen not only induces pyroptosis of DLBCL cells, but also activates antitumor immune responses (**Figure 1**) *in vitro* and *in vivo*. Previously, a key GSDME study [5] showed that cisplatin and etoposide triggered Caspase-3-mediated pyroptosis in various GSDME$^+$ cancer cells. However, the clinical use of cisplatin is hindered by its serious side effect on body weight loss, so that the dose is generally reduced, which limits its antitumor efficacy [9]. Wu et al demonstrated that chidamide and other HDACi drugs enhanced chromatin accessibility at the promoter region of *GSDME* gene (**Figure 1**), and increased the levels of both GSDME expression and cleavage of GSDME and Caspase-3. The role of GSDME in pyroptosis was confirmed by GSDME knockout which significantly reduced pyroptosis. Similarly, the Bak/Bax-Caspase-3-GSDME pathway mediates pyroptosis induced by several chemotherapy agents in solid tumors [6], as well as the efficacy of STING agonist monotherapy and combination therapy with PD-1 inhibitor in DLBCL cells *in vitro* [13]. In contrast, other studies showed that tumor GSDMD activation mediates tumor cell pyroptosis in solid tumors, triggered by treatment of omega-3 docosahexaenoic acid or a novel molecule α-NETA [14, 15].

Wu et al further showed the essential role of T cell responses in the antitumor efficacy of chidamide combination therapy *in vivo*. The addition of chidamide to the combination treatment

for immunocompetent BALB/c mice bearing A20 lymphoma tumors significantly increased tumor-infiltrating CD8 T cells, NK cells, and dendritic cells ($CD11b^+CD11c^+$), as well as antitumor efficacy. In contrast, tumor-associated immunosuppressive macrophages ($CD11b^+F4/80^+$) were decreased. The superior therapeutic benefit *in vivo* depends on the CD8 T cell response, as depletion of CD8 T cells using anti-CD8 antibody significantly attenuated the therapeutic antitumor effects. Together, this novel combination therapy using drugs clinically used in China provides dual therapeutic benefit by directly inducing tumor cell death and enhancing antitumor immune responses, as demonstrated *in vivo*. However, a potential caveat of this study is that the identification of pyroptotic cells was based on morphology (cell swelling and membrane bubbling) and SYTOX staining, which could not well distinguish cells at the late stage of apoptosis. In addition, as the chemotherapy and chidamide treatment for mouse models can act on all cells, and macrophages are especially susceptible to pyroptosis, the Caspase-3-GSDME and/or Caspase-1-GSDMD pathway in macrophages in mice undergoing treatment need to be examined, as well as whether cytokine release plays a role in the therapeutic efficacy (**Figure 1**). A previous study showed that the extensive pyroptosis of tumor cells induced by CAR-T cells activates Caspase-1 and GSDMD in macrophages, triggering release of proinflammatory cytokines, and causing cytokine release syndrome [8]. Moreover, in contrast to the notion that GSDMD pores lead to pyroptosis, a different concept is that GSDMD pore formation is not sufficient for macrophage cell death; furthermore, it leads to a hyperactivation state of living macrophages secreting IL-1 for an extended time [16], which can potentiate T cell activation and adaptive immune responses [17].

In addition to results *in vitro* and *in vivo*, Wu et al also showed that GSDME expression levels assessed by immunohistochemistry were significantly decreased in 97 DLBCL samples from patients than in 92 normal control lymph nodes (approximately mean levels, 3.7 *vs*. 1.2; how the 1-4 expression levels were defined was not specified in the article). This result is consistent with our recent immunohistochemical findings in patients with DLBCL [18], that lymphoma cell GSDME expression was rare but had favorable prognostic effects. However, we observed more frequent GSDME expression in endothelial cells in majority of cases in our training and validation cohorts, and endothelial GSDME expression in the vascular endothelium correlated with significantly poorer survival of our cohorts of patients with DLBCL [18]. As chidamide treatment which induces GSDME expression potentially can induce GSDME also in endothelial cells, the side effects should be taken into account in future clinical investigations, as well as whether the endothelial GSDME induction adversely affects the antitumor efficacy of chidamide. Moreover, our study showed that in both our training and validation DLBCL cohorts, cytoplasmic GSDMD expression was frequently expressed in macrophages and lymphoma cells and associated with significantly better survival in DLBCL. $GSDMD^+$ cells in diagnostic biopsies often showed viable cell phenotypes; however, it is possible that they could undergo pyroptosis upon first-line treatment with R-CHOP, resembling the chemotherapy-induced GSDME-dependent pyroptosis demonstrated by the GSDME discovery study [5].

Together, the preclinical study by Wu et al demonstrates that clinically available drugs induce pyroptosis of tumor cells and shape the tumor microenvironment, implying clinical relevance of emerging pyroptosis studies. This 'one action, two benefits' strategy represents a promising therapeutic avenue for relapsed/refractory DLBCL, warranting clinical investigation. Different from this strategy of enhancing tumor suppressor (GSDME) expression, future studies can also identify oncogenic factors which inhibit pyroptosis and target overexpressed oncoproteins, like the therapeutic strategies to target anti-apoptosis (such as BCL2 inhibitors) and ferroptosis-suppressing mechanisms.

Disclosure of conflict of interest

None.

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