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Clinically relevant GABARAP deficiency abrogates bortezomib-induced immunogenic cell death in multiple myeloma

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ABSTRACT

Recently, it was revealed that the high-risk, poor-prognosis downregulation of GABA type A receptor-associated protein (GABARAP) causes a defect in both autophagy and surface exposure of calreticulin (CALR) in multiple myeloma (MM) cells responding to bortezomib. Hence, GABARAP-defective MM cells fail to undergo immunogenic cell death.

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Main text

Immunogenic cell death (ICD) elicited by antineoplastic drugs relies on an increase in the adjuvanticity and antigenicity of cancer cells which together ignite adaptive anticancer immune responses.[1,2] ICD inducers can impact the immunopeptidome while triggering premortem stress circuitries that promote the release and surface exposure of a specific set of danger-associated molecular patterns (DAMPs). Eukaryotic translation initiation factor 2 subunit 1 (eIF2α) serves as the main integrator of ICD-related cellular stress pathways, orchestrating the onset of autophagy as well as endoplasmic reticulum (ER) stress, which in turn facilitate the liberation of ATP and the translocation of calreticulin (CALR) from the ER to the plasma membrane, respectively.[3] Extracellular ATP can ligate purinergic receptor P2Y2 (P2RY2) expressed on dendritic cells (DCs), thus attracting DCs to the tumor bed, while surface exposed CALR acts as an 'eat-me' signal that interacts with CD91 on the membrane of DCs, thus causing DC-mediated phagocytosis of portions of the cancer cell. Other DAMPs that participate to the dialogue between DCs and cancer cells succumbing to ICD include ligands released from malignant cells acting on pathogen recognition receptors expressed on DCs, as this has been described for annexin A1 acting on formyl peptide receptor 1 (FPR1) and high-mobility group box 1 (HMGB1) acting on toll-like receptor 4 (TLR4) to trigger DC chemotaxis and maturation, respectively. Moreover, in the course of ICD, malignant cells produce type I interferon (IFN) which further promotes inflammatory cytokine release to attract T cells into the tumor microenvironment. Altogether, ICD promotes the DC-mediated processing and presentation of tumor antigen, eventually leading to the activation of cytotoxic T lymphocytes (CTLs) that can induce the IFN-γ-mediated lysis of residual cancer cells, while establishing immune memory, thus preventing tumor recurrence and facilitating durable therapeutic efficacy.[1,4]

Over the past decade, it has become evident that several distinct pharmacological classes of anticancer agents can induce ICD. Thus, chemotherapeutics such as anthracyclines and oxaliplatin, as well as the proteasome inhibitor bortezomib, have been described to induce ICD. Moreover, certain targeted agents, cardiac glycosides, as well as the antibiotic bleomycin, showed ICD-inducing properties, contrasting with other standard-of-care cytotoxicants such as cisplatin that fail to elicit anticancer immunity.[2–9]

In the past the mechanisms of especially anthracycline-induced ICD have been deciphered in their molecular details, as this applies to the ER stress-dependent vesicular transport of CALR to the plasma membrane and the autophagy-mediated lysosomal liberation of ATP. Moreover, several strategies to ameliorate the immunostimulatory effects of ICD have been proposed. Those include, but are not limited to, the induction of autophagy by IGF-1 receptor inhibitors, chalcones, short-term fasting or caloric restriction mimetics, thereby boosting ATP release and enhancing anticancer immunosurveillance.[10–14]

In a recent article, Annamaria Gulla and colleagues showed that the loss of GABA type A receptor-associated protein (GABARAP) expression, which is often found in high-risk multiple myeloma (MM) patients, leads to a malfunction in autophagy and also disrupts surface exposure of calreticulin (CALR) via Golgi-mediated vesicular transport during bortezomib-induced ICD.[15] Consequently, GABARAP deficiency diminishes DC-mediated phagocytosis of MM cells, in turn limiting antigen processing and hampering

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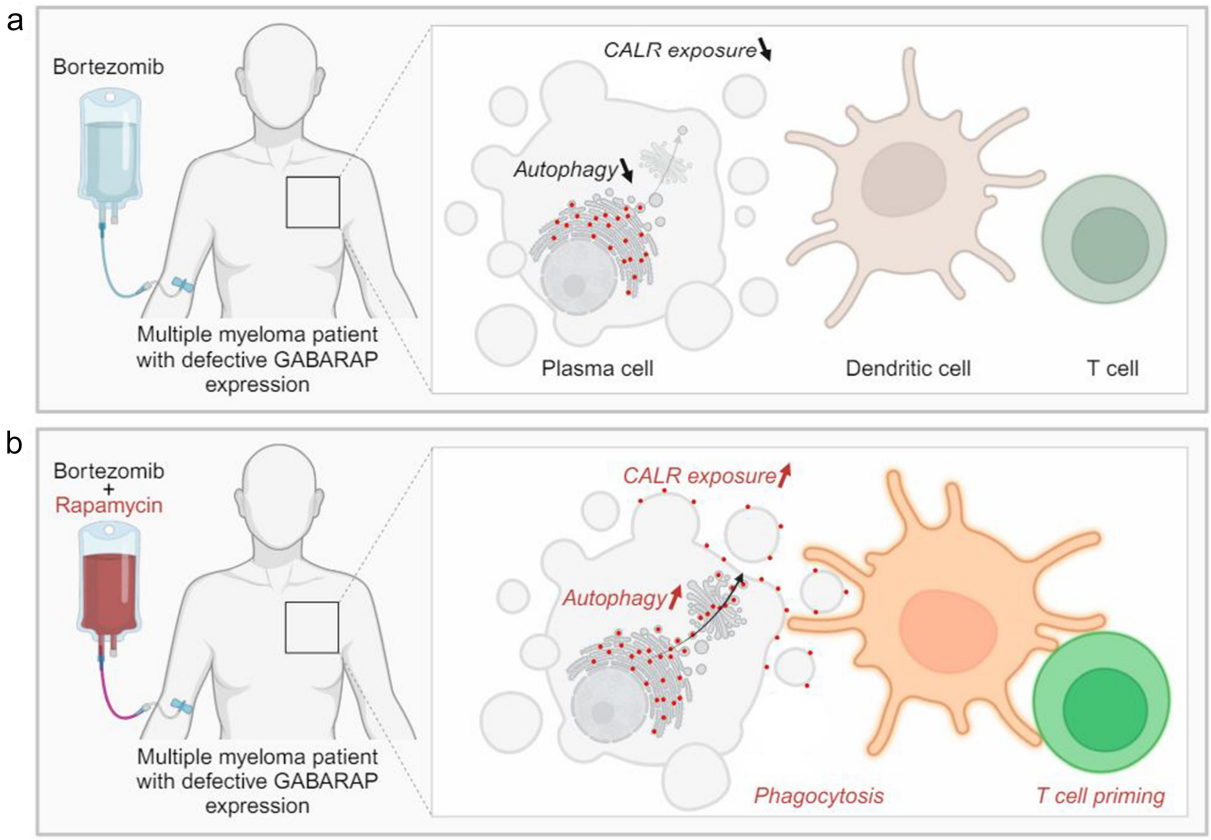

Figure 1. (a) Induction of autophagy in cells with defective GABARAP expression restores Golgi-mediated calreticulin exposure in multiple myeloma. The absence of GABA type a receptor-associated protein (GABARAP) in high-risk multiple myeloma impairs autophagy and interferes with bortezomib-induced immunogenic cell death (ICD) by disrupting calreticulin (CALR) relocation, reducing dendritic cell phagocytosis and limiting anti-tumor T cell responses (A). Rapamycin restores autophagy, facilitates Golgi vesicular transport and reinstates CALR exposure, thus enhancing ICD in GABARAP-deficient cells treated with bortezomib (b). Combining bortezomib with rapamycin may overcome ICD resistance in MM patients with defective GABARAP expression.

immunosurveillance by T lymphocytes. Accordingly, MM patients with low levels of GABARAP exhibit decreased tumor immune cell infiltration and dismal prognosis. In GABARAP-deficient MM cells cultured in vitro, the autophagy inducer rapamycin restored Golgi morphology while facilitating CALR exposure. In summary, combination of bortezomib with rapamycin might constitute a promising approach to overcome ICD resistance in MM patients lacking GABARAP (Figure 1).

The exact mechanism of autophagy-mediated Golgi restoration and CALR exposure remains elusive and future experiments should focus on elucidating the molecular mechanisms of this intriguing crosstalk. Furthermore, clinical studies must evaluate the feasibility to combine bortezomib or other ICD inducers with rapamycin or other autophagy enhancers including rapalogs to stimulate anticancer immunosurveillance.

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Disclosure statement

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Author contributions

LZ and ZS summarized data, designed display items and edited the manuscript. OK and GK wrote the manuscript.

Data availability statement

All data that led to the conclusions in this manuscript have been referenced and all sources have been described.

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