EDITORIAL

# Immunology of cell death in cancer and infection



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A significant amount of research investigations, spanning several decades, has unequivocally determined that cell death pathways, and their multi-faceted immunomodulatory activity, has major implications for health and disease [1, 2]. The role of cell death immunology is particularly impactful in the context of cancer or infection [3, 4]. Harsh conditions, resulting from infection orchestrated by pathogenic microbes (especially bacteria or viruses) or due to physicochemical stressors within tumour microenvironment (TME), induce cell death in specific target cells [5, 6]. In case of infections, such target cells predominantly consist of cells against which pathogenic microbes show specific tropism (e.g., epithelial, or immune cells) [7], or cells that die during host level-responses against the infection (e.g., neutrophils, macrophages, or T cells) [8]. In case of cancer, such target cells predominantly consist of cancer cells unable to cope with genetic instability or TME-associated stressors (e.g., hypoxia, acidosis, or nutrient-deprivation), followed by immune cells that die due to TME-associated stressors (e.g., neutrophils, dendritic cells) or cancer-driven direct induction of dysfunction or exhaustion (e.g., $CD8^{+}$T cells) [6, 9, 10]. Such cell death induced due to the progression of infection or a tumour, largely supports rather than suppress, the severity of disease and patient mortality [11]. Therapeutic interventions aimed at disease amelioration also operate via induction of cell death, especially in the case of cancer, e.g., conventional cytotoxic therapies (like chemotherapy, targeted therapy, radiotherapy) [12, 13], and immunotherapies (like immune checkpoint blockers [ICBs], T cell-based therapies, dendritic cell [DC] vaccines, and oncolytic viruses) [14–16]. Although the primary aim of therapies against infection is not orientated toward cell death induction per se, yet this could be a potential side-effect of several such modalities e.g., antibiotics or anti-viral medications [17].

Cell death has a major influence on the TME and the infected tissue, because dying/dead cells secrete or passively release an overabundance of immunomodulatory factors [18]; e.g., small metabolites including extracellular ATP or other nucleic acids and lipids [19]; cytokines like interleukin 1 beta (IL1β), tumour necrosis factor (TNF), type I interferon (IFN), IL6, IL33, and transforming growth factor beta 1 (TGF-β) [20, 21]; mitochondria-associated factors like mitochondrial DNA (mitDNA) [22, 23]; chemokines like C-X-C motif chemokine ligand 1 (CXCL1), CXCL11, CXCL2, CXCL8, CXCL10, CXCL3, CXCL9, C-X3-C motif chemokine ligand 1 (CX3CL1), and C-C motif chemokine ligand 2 (CCL2) [24]; and a series of danger signals or damage-associated molecular patterns (DAMPs), like surface-exposed calreticulin (CALR) or extracellular high mobility group box 1 (HMGB1) [25]. Together with the cancer-relevant or microbes-derived antigens that associate with the dying cells, and the immunological composition of the TME or site of infection, above immunomodulatory factors regulate the immunological impact of cell death on disease progression or inhibition [26]. Interestingly, a spatiotemporally defined combination of danger signals or DAMPs, cytokines or chemokines, and metabolites, emitted by dying cells can drive antigen-specific T cell immunity [16, 26]. Such immune responses can pave way for tumour regression or resolution of infection, accompanied by establishment of immunological memory against cancer or microbial antigens. This immunologically peculiar subtype of cell death has been termed either immunogenic cell death (ICD) or inflammatory cell death [16].

In recent years, substantial research has been dedicated to revealing the molecular as well as cellular pathways operating during the sensing and decoding of dying cells-associated immunomodulatory signals by innate and adaptive immune cells [27]. In "Immunology of Cell Death in Cancer and Infection" (a special issue of *Genes & Immunity*), a panel of leading scientists investigating immunology of cell death contributed to a discussion on mechanisms behind cell death immunology and its clinical implications.

A large volume of work on DAMPs-driven immune responses has been done in the context of cancer [28]. Just like dying cancer cells, microbes-infected stressed or dying cells can also release DAMPs that can modulate immune sensing of infected cells. However, cytokines or chemokines have received more attention in the context of infection-associated cell death rather than DAMPs [29]. In his review article [30], W.G. Land surveyed the current literature on respiratory viruses (including, coronavirus disease-19 [COVID-19]) and found that DAMPs-driven immune responses also dominated respiratory virus pathology together with cytokine-associated responses. This review concludes that DAMPs might have an underappreciated role in the pathogenesis of acute respiratory distress syndrome and systemic inflammatory response syndrome (including COVID-19). The review also highlights how DAMPs might serve the purpose of diagnostic or prognostic biomarkers for such infections. This review is very timely because, a recent single-cell resolution analyses of lung-associated bronchoalveolar fluid from patients with severe COVID-19, found that COVID-19 associated lung pathology was associated with considerable release of extracellular ATP [31]. Accordingly, genetic signatures of purinergic and inflammasome signalling (that is downstream of extracellular ATP) were enriched across various lung-associated immune compartments [31].

In the context of cancer, DAMPs form the cornerstone of the ICD concept. Over the past decade, while ICBs have worked really well against T cell-infiltrated tumours yet they have repeatedly failed against various T cell-depleted tumours like glioblastoma (GBM). Such failures have fuelled an interest in exploiting ICD to overcome cancers like GBM. In their review article [32], Decraene and co-authors (Steven De Vleeschouwer's lab) discuss how GBM can benefit from ICD-based therapies capable of stimulating anti-GBM immunity. The authors describe the major mechanisms behind ICD and its preclinical as well as clinical implications for GBM. Notwithstanding such remarkable advancements accomplished over the past decade, the clinical translation of ICD-based immunotherapy still remains a major challenge. In their original contribution [33], Van Gool, and co-workers (Wilfried Steucker-led

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clinical center) describe interesting clinical observations pertaining to an immunotherapy regimen combining IO-Vac® vaccine (tumour lysate-pulsed DCs, matured via IL-6, TNF, and IL-1β, as well as Newcastle Disease Virus (NDV)), with ICD-induced NDV therapy, and local electro-hyperthermia, administered to the GBM patients. They observed that their multi-modal immunotherapy regimen by itself had similar clinical performance as standard-of-care therapy involving temozolomide (TMZ). However, the combination of both TMZ as well as the multi-modal immunotherapy significantly improved overall survival of the GBM patients. This observation deserves more clinical validation in better designed clinical trials.

Beyond DAMPs and ICD, there is an urgent need to identify novel regulators of other danger signalling pathways [34]. In their original contribution [35], Liang and colleagues (Buzukela Abuduaini's lab) reported that overexpression of RALY, a multi-functional RNA-binding protein, induced upregulation of genes relevant for NOD-like receptor signalling while causing inhibition of type I IFN signalling, which ultimately associated with decrease in proliferation of cancer cells. Further research is required in the future to reveal translational impact of signalling proteins like RALY for cell death immunology.

Finally, in the context of a tumour, induction of cancer cell death is obviously a top priority from the perspective of disease amelioration [36]. However with the clinical success of cancer immunotherapy, cell death of $CD8^+$T cells has also come into focus since this can be debilitating for the success of immunotherapies that rely on their activation for anti-cancer efficacy [37]. However, while this concept is pre-clinically well established yet its clinical existence is not always demonstrated. In their original contribution [38], Vanmeerbeek and co-authors (Abhishek D. Garg's lab) applied integrated computational immunology approaches to bulk-tumour transcriptomic and single-cell (sc) RNAseq data from melanoma patients in clinical studies applying ICBs. They found that stem-like memory $CD8^+$/$CD4^+$T cells that predicted superior patient response to ICB-treatment, also enriched for signatures of cell death/apoptosis resistance. In fact, these distinguishing characteristics were together necessary for predicting clinical responses to anti-PD1 ICB, after the melanoma patients had previously progressed on anti-CTLA4 ICB.

In summary, this special issue of *Genes & Immunity* emphasizes the importance of exploring cell death immunology from multiple perspectives (e.g., target cells vs. immune cells, disease subtypes, type of therapies), and highlights the importance of context behind the disease promoting or inhibiting impacts of cell death pathways. One area that still needs more attention than it is currently getting, is biomarkers related to cell death immunology that are still largely lacking for most diseases.

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## DATA AVAILABILITY

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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## ADDITIONAL INFORMATION

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