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1 Editorial

2 Immunogenic cell stress and death sensitize tumors to immu- 3 notherapy

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12 The efficacy of chemotherapy with cytotoxicants or that of targeted therapies with
13 more sophisticated agents is limited due to the plasticity of malignant cells that leads to
14 the inevitable development of resistance. Immune checkpoint inhibitors (ICI) that target
15 inhibitory cytotoxic T lymphocyte associated protein 4 (CTLA4) or T cell exhaustion
16 signals such as the programmed cell death-1 (PDCD1, better known as PD-1), and pro-
17 grammed cell death-1 ligand 1 (CD-274, better known as PD-L1) are occupying a central
18 stage in the first-line adjuvant and neoadjuvant treatment of advanced neoplasms (1, 2).
19 ICIs are now broadly used through the oncological spectrum.

20 Nevertheless, certain cytotoxic agents have the ability to induce durable disease
21 control exceeding the clinical treatment phase in many cancer patients. Retrospectively, it
22 appears that those agents that were empirically selected by clinicians over decades due to
23 their effectiveness, are particularly capable of triggering specific stress and death path-
24 ways in cancer cells rendering them recognizable to the immune system (3, 4). In pre-
25 clinical mouse models, treatment of tumors with drugs inducing immunogenic cell death
26 (ICD) is only efficient if functional dendritic cells (DCs) and T lymphocytes are available
27 (5-7). In patients, the induction of ICD correlates with the recruitment of antigen pre-
28 senting cells (APCs) as well as cytotoxic T lymphocytes (CTLs) into the tumor bed, and
29 tumor infiltration by DCs and CTLs is indeed a biomarker of favorable prognosis (8-10).
30 ICD inducers include conventional chemotherapeutic agents such as anthracyclines,
31 oxaliplatin, taxanes, as well as more disease-specific targeted agents from the group of
32 tyrosine kinase inhibitors (TKIs) (11, 12). Moreover, ionizing irradiation (13, 14), photo-
33 dynamic therapy (PDT) (15, 16), as well as oncolytic viruses (17, 18), have been shown to
34 induce ICD. In preclinical experimentation and in clinical routine, it appears that com-
35 binations of ICD inducers with immune checkpoint inhibitors (ICIs) are particularly
36 efficient in mediating their therapeutic potential (19, 20).

37 ICD facilitates the onset of anticancer immune responses via an increase in both the
38 antigenicity as well as the adjuvanticity of the malignant cells. Mechanistically, this in-
39 volves the onset of coordinated premortem stress responses that can affect the antigenic
40 makeup of cancer cells via genetic or epigenetic alterations of the transcriptome. More-
41 over, ICD-related cellular stress facilitates the emission of normally confined 'danger
42 associated molecular patterns' (DAMPs) that act on pattern recognition receptors (PRRs)
43 expressed on professional antigen DCs (21-24). Thus, immature DCs, which express the
44 ATP receptor P2Y2 are chemotactically attracted into the tumor bed by ATP secreted
45 from cancer cells undergoing ICD (15, 25). The final approximation of DCs towards dy-
46 ing cancer cells is facilitated by tumor-emitted annexin A1 (ANXA1) that acts on formyl
47 peptide receptor-1 (FPR1) present on DCs (24). Antigen transfer from tumor cells to DCs

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is mediated by an 'eat-me' signal, namely surface-exposed calreticulin that appears on the plasma membrane of malignant cells and then acts as on its receptor CD91 present on DCs (13). The maturation of DCs is ignited via the ligation of Toll like receptor 4 (TLR4) by high mobility group box 1 (HMGB1), emanating from the nuclear compartment of dying cancer cells. DC maturation further drives the production of type-1 interferons, which in turn amplifies the synthesis of the C-X-C motif chemokine ligand 10 (CXCL10), thus stimulating T cell priming. In sum, induction of ICD in malignant cells leads to a coordinated alteration of the cell surface and the local secretome, thereby facilitating the attraction, differentiation and maturation of DCs so that they present tumor-associated antigens to T cells and hence initiate adaptive anticancer immunity (22-24). Of note, malignant cells and pathogenic viruses can subvert ICD-associated DAMP emission, thus blunting the immune response. Moreover, inherited or acquired defects in the perception of ICD by the host immune system can undermine immunosurveillance and provoke failure of cancer treatments.

The concept of ICD has transcended the realm of preclinical experimentation and is now used for drug discovery (to identify novel ICD inducers) as well as for the design of clinical trials (to identify suitable drug combinations, in particular with ICIs). The present special issue "Immunogenic Cell Stress and Death", discusses different strategies for inducing anticancer immunity by facilitating the molecular crosstalk between cancer cells, DCs and T lymphocytes. The role of ICD is reviewed in the context of colorectal, gastric, pancreatic, and hepatocellular cancer as well as multiple myeloma. Moreover, it is revealed that combination treatment with cetuximab plus cisplatin for the treatment of head and neck cancer induced traits of ICD. Interestingly, high dose of the non-immunogenic cell death inducer cisplatin blunted antitumor immunity in this context. Additional aspects of immunogenic cell stress and death cover the role of ICD-associated chemokines and chemokine receptors in the activation of CD8 T-cells and clinical applications thereof. Furthermore, light is shed on the role of tumor-associated macrophages (TAMs) in the response to dying cancer cells. Finally, three-dimensional organ-on-chip technology is introduced for modeling the tumor microenvironment (TME). At the mechanistic level, evidence is presented that targeting the unfolded protein response (UPR) can increase the efficacy of anticancer therapy.

Altogether, in this special issue, ICD induction is discussed in different disease-relevant therapeutic approaches, novel immune signals are described, and the role of specific immune cell subtypes is elucidated. Advanced in vitro systems are helping to understand the apical targets of ICD, the organellar genesis of ICD signals, as well as the complex cellular interplay in the tumor microenvironment. Altogether, an ever more sophisticated pipeline of preclinical ICD-relevant exploration will prepare the bases for the clinical implementation of ICD-based anticancer therapies.

List of Contributions

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Conflicts of Interest: OK and GK have been holding research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Tollys, and Vascage. GK is on the Board of Directors of the Bristol Myers Squibb Foundation France. GK is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio. OK is a scientific co-founder of Samsara Therapeutics. GK is in the scientific advisory boards of Hevolution, Institut Servier and Longevity Vision Funds. GK is the inventor of patents covering therapeutic targeting of aging, cancer, cystic fibrosis and metabolic disorders. GK's brother, Romano Kroemer, was an employee of Sanofi and now consults for Boehringer-Ingelheim. LZ, has held research contracts with Glaxo Smyth Kline, Incyte, Lytix, Kaleido, Innovate Pharma, Daiichi Sankyo, Pilege, Merus, Transgene, 9 m, Tusk and Roche, was on the on the Board of Directors of Transgene, is a cofounder of everImmune, and holds patents covering the treatment of cancer and the therapeutic manipulation of the microbiota. The funders had no role in the design of the study; in the writing of the manuscript, or in the decision to publish the results.

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