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Immunosuppressive cell death in cancer

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Harnessing the fundamental machinery of the immune system provides an opportunity to cure cancer, and this has led oncologists to turn their attention to the interface between therapeutic strategies, cancer cell death and the immunological consequences. In their recent Review article (Immunogenic cell death in cancer and infectious disease. *Nat. Rev. Immunol.* **17**, 97–111 (2017))[1], Galluzzi *et al.* discussed the molecular mechanisms underlying immune activation in response to dying cells in the context of cancer and infection, which was termed immunogenic cell death. This immunogenic outcome provides the ideal basis to treat malignant cancers with conventional therapeutics — such as chemotherapy and radiotherapy — that induce cancer cell death. However, accumulating clinical and experimental data have revealed that dying cancer cells can also have immunosuppressive effects.

Upon oxidative stress, nutrient deprivation or therapy-induced events, cancer cell death is often necrotic, leading to rapid membrane destruction and the release of damage-associated molecular patterns (DAMPs). Cancer cell necrosis has been shown to be associated with the development of advanced cancer and a poor prognosis[2]. One of the most well-known DAMPs, interleukin-1α (IL-1α), can be released rapidly by necrotic cells and may promote malignant cell transformation and proliferation[3]. IL-1α is also involved in cancer angiogenesis and metastasis through its interaction with platelets[4]. Importantly, IL-1α release also leads to the production of IL-6 by other cell types, which typically links inflammation to cancer progression. Accordingly, a therapeutic monoclonal antibody targeting IL-1α has been generated to treat patients with metastatic cancer[4] and is currently being evaluated in phase III clinical trials (see ClinicalTrials.gov identifiers NCT02138422 and NCT01767857). The canonical DAMP high-mobility group protein B1 (HMGB1) and downstream Toll-like receptor (TLR) signalling are generally considered to be required for the anticancer effects of immunogenic cell death, but there is also evidence that this signalling pathway can promote (not inhibit) cancer[5,6]. Furthermore, S100 family proteins released by necrotic cells contribute to myeloid cell migration and cancer metastasis[7,8]. In addition, cancer cell death contributes to a local ionic imbalance, as exemplified by increased potassium concentrations. Elevated extracellular potassium levels impair T cell receptor signalling and therefore may limit effector T cell responses against the cancer[9].

With regard to treatment-associated immunity, there are several lines of evidence that conflict with this Review. First, chemotherapeutics have been shown to induce the secretion of CXC-chemokine ligand 1 (CXCL1) by some cancer cells, in addition to the induction of CXCL10 described by Galluzzi and co-workers. CXCL1 attracts $CD11b^{+}GR1^{+}$ myeloid cells, which promote chemoresistance and metastasis[10,11]. Second, the drug gemcitabine can trigger necrosome formation, resulting in immunosuppression via the production of CXCL1 and SIN3-associated polypeptide p130 (SAP130)[12]. Third, different therapeutic approaches can trigger the recruitment of immunosuppressive cell types: oxaliplatin can induce tumour infiltration by immunosuppressive plasma cells[13]; ionizing irradiation can stimulate the accumulation of regulatory T cells in malignant lesions[14]; and, remarkably, even immunotherapy such as checkpoint blockade can fail owing to the presence of immunosuppressive myeloid cells — only when these cells are eliminated or inhibited are cytotoxic T cells susceptible to checkpoint blockade[15].

Given that various therapeutic strategies suffer clinical failure or resistance, appropriate animal models or clinical validation are needed to re-examine the immunological consequences described above. Despite the induction of opposing functions and mechanisms by tumour cell necrosis, the consensus in the field could be shifted in favour of improving the efficiency of anticancer therapeutics. To this end, we need a better understanding of how tumour cell necrosis influences the immune system, which depends not only on intracellular signals and constituents but also on the extracellular context and systemic crosstalk. Therefore, precision or combination therapies should be considered for refractory cancer.

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1. Galluzzi, L., Buque, A., Kepp, O., Zitvogel, L. & Kroemer, G. Immunogenic cell death in cancer and infectious disease. *Nat. Rev. Immunol.* **17**, 97–111 (2017).
2. Richards, C. H., Mohammed, Z., Qayyum, T., Horgan, P. G. & McMillan, D. C. The prognostic value of histological tumor necrosis in solid organ malignant disease: a systematic review. *Future Oncol.* **7**, 1223–1235 (2011).
3. Di Paolo, N. C. & Shayakhmetov, D. M. Interleukin 1α and the inflammatory process. *Nat. Immunol.* **17**, 906–913 (2016).
4. Hong, D. S. *et al.* MABp1, a first-in-class true human antibody targeting interleukin-1α in refractory cancers: an open-label, phase 1 dose-escalation and expansion study. *Lancet Oncol.* **15**, 656–666 (2014).
5. Kang, R., Zhang, Q., Zeh, H. J. III, Lotze, M. T. & Tang, D. HMGB1 in cancer: good, bad, or both? *Clin. Cancer Res.* **19**, 4046–4057 (2013).
6. Liu, Y. *et al.* Hypoxia induced HMGB1 and mitochondrial DNA interactions mediate tumor growth in hepatocellular carcinoma through Toll-like receptor 9. *J. Hepatol.* **63**, 114–121 (2015).
7. Hiratsuka, S., Watanabe, A., Aburatani, H. & Maru, Y. Tumour-mediated upregulation of chemoattractants and recruitment of myeloid cells predetermines lung metastasis. *Nat. Cell Biol.* **8**, 1369–1375 (2006).
8. Coffelt, S. B. *et al.* IL-17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis. *Nature* **522**, 345–348 (2015).
9. Eil, R. *et al.* Ionic immune suppression within the tumour microenvironment limits T cell effector function. *Nature* **537**, 539–543 (2016).
10. Sistigu, A. *et al.* Cancer cell-autonomous contribution of type I interferon signaling to the efficacy of chemotherapy. *Nat. Med.* **20**, 1301–1309 (2014).
11. Acharyya, S. *et al.* A CXCL1 paracrine network links cancer chemoresistance and metastasis. *Cell* **150**, 165–178 (2012).
12. Seifert, L. *et al.* The necrosome promotes pancreatic oncogenesis via CXCL1 and Mincle-induced immune suppression. *Nature* **532**, 245–249 (2016).
13. Shalapour, S. *et al.* Immunosuppressive plasma cells impede T-cell-dependent immunogenic chemotherapy. *Nature* **521**, 94–98 (2015).
14. Price, J. G. *et al.* CDKN1A regulates Langerhans cell survival and promotes T_{reg} cell generation upon exposure to ionizing irradiation. *Nat. Immunol.* **16**, 1060–1068 (2015).
15. De Henau, O. *et al.* Overcoming resistance to checkpoint blockade therapy by targeting PI3Kγ in myeloid cells. *Nature* **539**, 443–447 (2016).

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Competing interests statement
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