REPLY

Immunosuppressive cell death in cancer

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In our recent Review (Immunogenic cell death in cancer and infectious disease. *Nat. Rev. Immunol.* **17**, 97–111 (2017))[1], we discussed the molecular and cellular processes through which the death of infected and malignant cells can initiate an adaptive immune response against dead cell-associated antigens (in immunocompetent syngeneic hosts). This process, which is commonly known as immunogenic cell death (ICD), involves: first, the timely release of danger signals from dying cells secondary to the activation of adaptive stress responses, which include the unfolded protein response[2] and autophagy[3]; and second, the proficient detection of such signals by innate and adaptive compartments of the immune system[4]. Preclinical and clinical data support the notion that ICD has prominent pathophysiological implications in the context of cancer therapy[1]. Indeed, molecular defects in the mechanisms that underlie the release or detection of ICD-associated danger signals have been associated with poor disease outcome in multiple cohorts of patients with cancer[5–7].

In their Correspondence (Immunosuppressive cell death in cancer. *Nat. Rev. Immunol.* doi: 10.1038/nri.2017.46 (2017)), Xia and collaborators correctly point out that the demise of malignant cells responding to chemotherapy or radiation therapy frequently fails to elicit anticancer immunity in preclinical and clinical scenarios. Indeed, far too often neoplasms progress as they harness strategies to evade or suppress potential ICD-driven immune responses[8–10]. Furthermore, chemotherapy and radiation therapy are often administered to patients at high doses, which have immunosuppressive rather than immunostimulatory effects[11–13]. Thus, cancer cell death — as elicited in patients by conventional chemotherapeutic and radiotherapeutic regimens — is intrinsically prone to be overlooked by the immune system or to stimulate immune tolerance. Based on this postulate, Xia and collaborators propose that combinatorial antineoplastic strategies should be aimed at maximizing the number of cancer cells that succumb to treatment.

We believe that — as long as anticancer therapies are unable to eradicate 100% of malignant cells (which is obviously a utopian goal) — our efforts should instead concentrate on the development of combinatorial therapeutic regimens that render cancer cell death immunogenic and revert immune exhaustion or suppression. Indeed, accumulating preclinical and clinical data support the notion that the way in which cancer cells succumb in response to treatment may be far more important for long-term disease outcome — which is almost always determined by immunosurveillance — than the actual fraction of cells that die[14].

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Competing interests statement
The authors declare no competing interests.