LINK TO ORIGINAL ARTICLE

The pros and cons of dying tumour cells in adaptive immune responses

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Therapeutics based upon using the adaptive immune system to fight against tumours have become the most promising in the field. Increasing evidence has shown that multiform cell death-mediated events play vital roles in regulating adaptive immune responses within tumours, thus providing potential antitumour therapeutic targets. In their recent Review article (Dying cells actively regulate adaptive immune responses. *Nat. Rev. Immunol.* **17**, 262–275; 2017)[1], Albert *et al.* discussed the active signals generated during cell death processes and their roles in facilitating the priming of antigen-specific $CD8^+$ T cells. These immunogenic processes represent an ideal tumour–immune interaction and offer a favourable immune basis for conventional therapeutics such as chemotherapy and radiotherapy.

However, Albert *et al.* neglected the fact that dying tumour cells may also regulate adaptive immune responses in another way: namely, by prompting T cell exhaustion. Previous studies have shown that dying tumour cells can release tumour antigens, which can serve as damage-associated molecular patterns (DAMPs), into the tumour microenvironment[2,3]. These tumour antigens persistently stimulate adaptive immune cells such as $CD8^+$ and $CD4^+$ T cells and induce the latter to acquire a dysfunctional state called T cell exhaustion[4]. Unlike tolerance to a self-antigen, T cell exhaustion is a dysfunctional state characterized by reduced cytokine production and compromised cell-killing ability[5]. Mounting evidence has shown that T cell exhaustion contributes significantly to tumorigenesis and may induce failure of antitumour therapeutics[6]. Therefore, besides actively regulating antitumour adaptive immune responses, dying tumour cells may also compromise antitumour immunity by inducing T cell exhaustion.

The authors highlighted the importance of type I interferons (IFNs), which can be released by dying cells as a type of 'inducible DAMP (iDAMP)' in treatment-associated immunogenic cell death. However, several studies have suggested that type I IFN signalling has contradictory roles in adaptive immune response. For example, Wang *et al.* showed that the upregulation of IFNβ expression in dendritic cells promoted antigen presentation but compromised T cell priming[7]. Another study showed that elevated levels of type I IFNs during type 1 diabetes triggered lymphocyte exhaustion and disabled lymphocyte-mediated immune responses[8]. In a tumour-bearing mouse model, IFNα augmented programmed cell death 1 (PD1) expression on antigen-specific $CD8^+$ T cells and thus significantly inhibited T cell-mediated immunity[9]. In a chronic infection model, blocking type I IFN signalling decreased T cell exhaustion and viral replication[10]. Therefore, type I IFNs might also impair adaptive immunity by inducing T cell exhaustion in tumours.

In summary, besides the effects of dying cells on adaptive immunity that are detailed by Albert *et al.*, dying cells might have another effect on adaptive immunity: that is, inducing T cell exhaustion.

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Competing interests statement
The authors declare no competing interests.