Correspondence

Extracellular ATP and P2X7 receptor exert context-specific immunogenic effects after immunogenic cancer cell death

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Cell Death and Disease (2016) 7, e2097; doi:10.1038/cddis.2015.411; published online 18 February 2016

Dear Editor,

Immunogenic cell death (ICD) facilitates danger signalling-driven trafficking of damage-associated molecular patterns (DAMPs) like extracellular ATP (eATP).1,2 The binding of eATP to P2X7 receptor triggers immunogenic signalling,3 which (along with other factors) converts the dying cancer cells into an effective anticancer vaccine.3

Endoplasmic reticulum (ER) stress is central to ICD,1 on the basis of which ICD inducers are subdivided into two types,1 that is, Type I (e.g., some chemotherapies), which elicit danger signalling through ‘collateral’ non-lethal ER stress,1 and Type II (e.g., hypericin-photodynamic therapy (Hyp-PDT)), which elicit danger signalling via ‘focused’ lethal ER stress.1,4 Type II and Type I ICD inducers differ on several levels, for example, plasticity of danger signalling and the trafficking mechanisms of DAMPs.4 In fact, eATP was found to be absent during Newcastle disease virus (NDV)-induced Type II ICD despite the induction of macroautophagy (a Type I ICD-associated, eATP-trafficking mechanism).2,3 Moreover, we have established that Hyp-PDT-induced eATP is PERK and secretory pathway-dependent,4 while being independent of macroautophagy2 or chaperone-mediated autophagy.8 This raised an important question – like in the case of NDV-induced ICD, could eATP be dispensable or a partial immunogenic signal for Hyp-PDT-induced ICD?

To this end, we decided to gain further insights into the eATP-trafficking mechanism and its immunogenic potential following Hyp-PDT. To address the contribution of the pannexin/connexin-caspase axes2 that elicits eATP following Hyp-PDT. To address the contribution of the eATP-trafficking mechanism and its immunogenic potential induced ICD?

Moreover, we have established that Hyp-PDT-induced eATP is PERK and secretory pathway-dependent,4 while being independent of macroautophagy2 or chaperone-mediated autophagy.8 This raised an important question – like in the case of NDV-induced ICD, could eATP be dispensable or a partial immunogenic signal for Hyp-PDT-induced ICD?

These results are unprecedented because eATP and P2X7 receptor had been shown to act in a synergistic manner.1,2,3 Here, we rather observed a potentiating effect, that is, blockade of either eATP or P2X7 receptor did not, but combined blockade significantly reduced ICD’s immunogenic potential. Thus, our results suggest that the mere presence of eATP does not ensure the presence of corresponding immunogenic activity in all contexts. Moreover, a certain degree of redundancy exists on the level of purinergic receptor agonists, and thus these results

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may also point to the release of such (as-yet-uncharacterized) agonists from dying cells. Lastly, these observations are based on the heterotopic (subcutaneous) tumour model; it would be crucial to reanalyze the role of eATP in an orthotopic tumour model to overcome immunological variations stemming from incompatibility between the transplanted cancer type and the surrounding tissue.

Conflict of Interest
The authors declare no conflict of interest.

Acknowledgements. ADG is supported by the FWO postdoctoral fellowship 2013 from the Research Foundation Flanders (FWO-Vlaanderen). This work is supported by FWO (G0584.12N and K202313N to PA; G.0607.13N to PA, PV/DVK; G.0A54.13N to DVK) and C16/15/073 grant of the KU Leuven to PA and BOF14/GOA/019 of Ghent University to DVK. PV holds a Methusalem grant (BOF09/01M00709) from
the Flemish Government. This paper represents research results of the IAP7/32 funded by the Interuniversity Attraction Poles Programme, initiated by the Belgian State.

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