

Eosinophil cytolysis and release of cell-free granules

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We are grateful for an excellent opportunity to expand on our recent Review (Eosinophils: changing perspectives in health and disease. *Nature Rev. Immunol.* **13**, 9–22 (2013))¹ that has been provided by the correspondence from Carl Persson and Lena Uller (Primary lysis of eosinophils as a major mode of activation of eosinophils in human diseased tissues. *Nature Rev. Immunol.* <http://dx.doi.org/10.1038/nri3341-c1> (2013))². To recap: researchers in the eosinophil field have defined three main mechanisms of degranulation. The first, exocytosis, in which cytoplasmic granules fuse with the plasma membrane and release all of their contents into the extracellular space *en masse*, is not typically observed *in vivo*. A second type of degranulation, piecemeal degranulation, is a process that was first defined by the electron microscopic observations of Dvorak and colleagues³, who noted that, similarly to what had been observed for basophils, eosinophil granules do not empty as completely or as explosively as would be anticipated if exocytosis were taking place⁴. As discussed in detail in the original Review¹, recent studies by Spencer, Melo, Weller and colleagues^{5,6} have identified tubulovesicular subcellular structures and have elucidated receptor–chaperone systems that are the among the important features underlying piecemeal degranulation.

However, a third mechanism, which was covered more briefly, is cytolysis. Cytolysis is classified as a form of degranulation because, as was recently shown, it is not purely ‘death’ but a way for eosinophils to live on functionally and to have an important and ongoing immunomodulatory impact on eosinophil-enriched organs and tissues.

The results of eosinophil cytolysis — specifically, the release of intact granules — are not new findings. There have been many reports of free granules in tissues found in conjunction with eosinophil-associated diseases, including allergic rhinitis, bronchial asthma, atopic dermatitis, urticaria and eosinophilic esophagitis⁷. However, it was not clear what role these granules had, if any, in promoting health or disease. This issue was addressed by the recent work of Neves, Moqbel, Weller and colleagues⁷, who made a substantial step forward by showing us that granules could function in a cell-free state and could secrete immunomodulatory mediators. Specifically, granules isolated by subcellular fractionation express the interferon- γ (IFN γ) receptor and CC-chemokine receptor 3 (CCR3) on their membranes and release the cationic ribonuclease eosinophil cationic protein (ECP) in a dose-dependent fashion in response to either IFN γ - or CC-chemokine ligand 11 (CCL11; also known as eotaxin 1)-mediated stimulation via a p38 mitogen-activated protein kinase (MAPK)-dependent signalling pathway⁷. Other receptors that have been identified on cell-free eosinophil granules include cysteinyl leukotriene receptor 1 (CYSLTR1), CYSLTR2 and P2Y purinoceptor 12 (P2RY12)⁸. Likewise, as noted by Uller and Persson, Ueki and colleagues⁹ have reported (since the publication of our Review) that the release of mitochondrial DNA ‘nets’, which is another form of cytolysis, is also accompanied by the release of intact granules.

Among the important questions that remain to be explored, it is not clear whether the mechanisms of protein trafficking found in intact cells also take place in granules, and/or if individual proteins can be selectively mobilized. Equally interesting, it will be important

to determine what conditions *in vivo* favour piecemeal degranulation and what conditions promote cytolysis (with or without ‘net’ formation) and release of intact granules. There are several strong recent reviews covering mechanisms of degranulation, including those written by Neves and Weller¹⁰, and Lacy and Moqbel¹¹, for those seeking greater insight into this important and evolving field.

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Competing interests statement

The authors declare no competing financial interests.