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Identification of a novel mediator of lysosomal fusion in macrophages

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Abstract

During inflammation, macrophages phagocytose many dead cells and/or bacteria into phagosomes and digest them into a series of peptides by the fusion of phagosomes with lysosomes. These peptides bind to MHC molecules and are transported to the surface of macrophages by the fusion of phago-lysosomes with cell plasma membrane. Using a similar mechanism, undigested debris in phago-lysosomes can be released from macrophages. During these processes, lysosomal enzymes are also secreted, causing the degradation of the surrounding tissues. This process is called heterolysis, but its molecular mechanisms as well as its relevance to the development of chronic inflammation have been unclear.

We have recently identified a novel protein that can be a mediator of lysosomal fusion in macrophages. It is a type II transmembrane protein, carrying multiple C2 domains in the cytoplasmic region. It is highly expressed in various types of phagocytes, particularly inflammatory macrophages, but not in T and B lymphocytes. We found that this protein is specifically localized to lysosomes and mediates lysosomal fusion upon calcium stimuli, raising the possibility that it mediates fusion between lysosomes and endosomes, phagosomes or autophagosomes.

In addition, we found that it is also expressed at the cell plasma membrane and mediates fusion between the membrane and lysosomes upon calcium stimuli, causing the release of undigested debris and the secretion of lysosomal enzymes. Our findings would help to elucidate the molecular mechanisms of heterolysis that can be a critical process for the development of chronic inflammation.