Phosphatidylserine-dependent efferocytosis and entosis

S. Nagata

Laboratory of Biochemistry and Immunology, WPI Immunology Frontier Research Center, Osaka University

Phosphatidylserine (PtdSer) is confined to the inner leaflet by the action of flippases that translocate PtdSer from the outer to inner leaflet. When cells undergo apoptosis, PtdSer is exposed to the cell surface, and is recognized as an “eat me” signal by macrophages for “efferocytosis” or "engulfment of apoptotic cells". Two P4-type ATPases (ATP11A and 11C) function as the flippase, and are inactivated by the caspase-cleavage during apoptosis. This flippase-inactivation is necessary but not sufficient for the apoptotic PtdSer exposure. To quickly expose PtdSer to the surface, scramblases of the XKR family containing 10 transmembrane regions must be activated by caspase to non-specifically and bi-directionally translocate phospholipids between the inner and outer leaflets. Among the 9 XKR members, XKR8 is ubiquitously expressed, and the apoptotic PtdSer exposure and efferocytosis was strongly delayed in Xkr8-/- hematopoietic cells. The two plasma membrane flippases (ATP11A and 11C) were ubiquitously expressed except for B cell progenitors, in which only ATP11C was present. ATP11C-/- mice suffered from B cell lymphopenia, which could be rescued by double deficiency of Axl and MerTK genes coding for tyrosine-kinase receptors involving PtdSer-dependent efferocytosis. The ATP11C-/- B cell progenitors in Axl-/- MerTK-/- background constitutively exposed PtdSer, and were efficiently engulfed by resident macrophages in vitro. These results indicate that PtdSer is sufficient for cells to be engulfed, and plays an important role in "entosis" or "engulfment of living cells". We recently found that PtdSer-exposure is regulated not only by caspase-mediated cleavage of flippase and scramblase, but also kinase-mediated their phosphorylation. I will discuss the PtdSer-exposure in various cell death processes, and other biological processes.

(References)

Nagata S (2018) Apoptosis and the clearance of apoptotic cells. Annu. Rev. Immunol. 36:489-517.

Nagata S, and Tanaka M (2017) Programmed cell death and the immune system. Nat. Rev. Immunol. 17:333-340.