Molecular mechanisms of apoptotic cell recognition and clearance by stabilins

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Rapid phagocytic clearance of apoptotic cells plays an important role during the embryonic development and tissue homeostasis and is crucial to prevent inflammation and autoimmune responses. Phosphatidylserine (PS) to the external surface of the plasma membrane has been suggested as a general 'eat me' signal for apoptotic cells. Current theory holds that phagocytic receptors recognize PS through direct interactions or secretory bridging molecules. Phagocytic clearance of apoptotic cells is characterized by the active production of anti-inflammatory cytokines, thus preventing inflammation and autoimmune responses. Although several soluble bridging molecules have been suggested in the recognition of PS—-the PS-specific membrane receptor that binds directly to the exposed PS and provides tickling signal has been just identified. Here, we provide evidence that stabilin-2 is a PS receptor, which performs a key function in the rapid clearance of cell corpses. It recognizes PS on the surface of apoptotic cells, mediates their engulfment and releases the anti-inflammatory cytokine, TGF-β. The adaptor protein, GULP, interacts with the NPXY motif of the stabilin-2 cytoplasmic tail and mediates downstream signaling for phagocytosis. Several adaptor molecules including integrin have been also identified in our laboratory. Spatio-temporal dynamics of small GTPase molecules during apoptotic cell clearance has been studied by using FRET technology with real-time live cell imaging system. Stabilin-1 & -2 in sinus endothelial cells also play a critical role in capturing aged RBCs and presenting them to macrophages for the efficient clearance of aged RBCs. Taken together, stabilin-1 & 2 are the membrane PS receptors to provide tethering and tickling signals for the phagocytosis of apoptotic cells and could be widely involved in inflammation, tumor microenvironment and autoimmune diseases.