Apoptosis and Autoimmunity

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ABSTRACT
To maintain homeostasis in animals, many cells die via process called apoptosis. In this process, caspases are activated upon a death signal(s), and cleave more than 400 cellular substrates, leading to cell blebbing, DNA fragmentation, and exposure of phosphatidylserine (PS). A defect in the death system causes cancer, and autoimmune diseases such as systemic lupus erythematosus (SLE). Dead cells are quickly engulfed by phagocytes, and are transferred to lysosomes, where the dead cell components are degraded into their building units such as nucleotides and amino acid, for re-use. Phagocytes recognize PS exposed on the dead cell surface as an “eat me” signal. We have identified molecules (receptor and opsonin) that are involved in recognizing the PS on apoptotic cells, and showed that if these molecules can not work properly, the mice develop SLE-type autoimmune diseases. It seems that unengulfed apoptotic cells undergo secondary necrosis, and their intracellular contents are released. These materials activate the immune system to produce various cytokines such as interferon and tumor necrosis factor, leading to severe anemia and chronic arthritis.

Phospholipids are distributed asymmetrically in plasma membrane, with PS and phosphatidylethanolamine (PE) in the inner leaflet and phosphatidylcholine (PC) and sphingomyelin (SM) mainly in the outer leaflet. This asymmetrical distribution is disrupted in various processes, including apoptotic cell death as described above, platelets activation, and the fusion of macrophages and myocytes. We identified an 8-transmembrane protein (TMEM16F) as a phospholipid scramblase. A deficiency of this molecule causes a defect in the PS-exposure in the activated platelets leading a human disease called Scott Syndrome, whereas its deficiency did not have any effect on the apoptotic PS exposure. TMEM16F belongs to a large family (TMEM16) consisting of 10 members. I will discuss the phospholipid scramblase activity of this family members, and their physiological roles.