

Efferocytosis: the Removal of Apoptotic Cells by Phagocytes

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The term 'efferocytosis' is new, but it is one of the oldest fundamental cellular processes in multicellular organisms. Efferocytosis is the process of removal or clearance of apoptotic cells by professional and non-professional phagocytes. The process is continuously going on in human body, in all animals and multicellular organisms, and is crucial for development, tissue homeostasis and resolution of inflammation¹. The importance of apoptosis and associated removal of apoptotic cells is so high that it has been speculated that without apoptosis a human body by the age of 80 would probably accumulate 2 tons of bone marrow and lymph nodes and a 16-kilometer intestine². In fact, inefficient or defective clearance of dead or dying cells results in developmental failure, autoimmunity, accumulation of toxic cell debris and chronic inflammation. Recent studies have clearly demonstrated the involvement of defective efferocytosis in the pathogenesis of inflammatory diseases including autoimmune diseases, atherosclerosis, chronic inflammatory pulmonary diseases and cystic fibrosis³.

The efferocytosis is a multi-step process involving recognition, binding, ingestion and digestion of dying cells by phagocytes. Apoptotic cells send 'find-me' signal by releasing diffusible extracellular factors that attract phagocytes. Although, the lipids lysophosphatidylcholine and sphingosine-1-phosphate and the nucleotides (such as ATP and UTP) released by apoptotic cells have been demonstrated to attract phagocytes, details of the mechanisms and the other molecules involved in this process are not yet clear. In addition to 'find me' signal, apoptotic cells also express 'eat-me' signals on their surface. Apoptotic cells expose phosphatidylserine on the outer leaflet of plasma

membrane, which normally resides on the inner leaflet in live cells. The phosphatidylserine is the best-characterized among the 'eat-me' signals identified so far. The phagocytes, being attracted by 'find-me' signals, recognize and bind to apoptotic cells directly through interaction between specific phagocytic receptor and the 'eat-me' signal molecule on apoptotic cells, or indirectly through bridging molecules. Subsequent phagocytosis of apoptotic cells is accomplished by cytoskeletal rearrangement within the phagocytes and is regulated by the action of small GTPase protein Rac^{3,4}. After engulfment by phagocytes apoptotic cells are rapidly degraded, within 30 to 60 minutes, by lysosomal enzymes. However, unlike phagocytosis of pathogens which usually induces a pro-inflammatory response, efferocytosis is anti-inflammatory or at least immunologically silent³. The intricate cellular, molecular and biochemical signaling events that regulate efferocytosis are still not clear. A multidisciplinary approach with expertise from biochemistry, immunology, pathology and molecular biology is needed to decipher the mechanisms of efferocytosis and to identify the factors that regulate efferocytosis.

References

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