[13-I] Targeting LAP: LC3-associated phagocytosis of dying cells in autoinflammation and anti-cancer immunity

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Two ancient processes, phagocytosis and macroautophagy, arose as mechanisms of meeting the energy demands of the cell. Both also evolved into mechanisms of host defense. We have described a process we term “LC3-Associated Phagocytosis” (LAP), in which signals that are generated upon engulfment of particles by phagocytic cells induce components of the autophagy machinery to associate with the phagosome, promoting its fusion to lysosomes (phagosome maturation). While engulfment of latex beads (for example) does not induce LAP, particles that engage TLR1/2, TLR2/6, TLR4, FcR, or receptors for engulfment of dying cells, cause recruitment of LC3 (ATG8) to the phagosome membrane. Like macroautophagy, this LC3 association depends on Beclin1, PI3P generation, ATG5, and ATG7, but unlike autophagy, LC3 associates with the single phagosome membrane (rather than the double membrane of autophagosomes). Further, unlike macroautophagy, LAP proceeds in the absence of elements of the autophagic pre-initiation complex, ULK1, ATG13, and FIP200, and involves a novel PI3K complex. This raises an intriguing possibility: It is now well established that defects in some components of the autophagy machinery, promote inflammatory disease and compromise host defense to intracellular infections. While such effects are generally interpreted as consequences of defective macroautophagy, the existence of LAP as a discrete phenomenon suggests that at least some such effects may specifically relate to LAP. I will discuss LAP and its relationship to phagosome maturation, and its roles in tumor associated macrophages and anti-cancer immunity.