TNF α triggers release of extracellular vesicles containing TNFR1 and TRADD, which can modulate TNF α responses of the parental cells.

Abstract

Tumor necrosis factor-α (TNF α)-induced reactions are effective to maintain homeostasis; however, excessive responses play progressive roles in the pathogenesis of various chronic inflammatory diseases. We demonstrate that TNF α triggered the release of its receptor TNFR1 as a content of extracellular vesicles (EVs) from the human bronchial epithelial cell, BEAS-2b. The TNFR1 cytoplasmic domain binding partner, TNFR-associated death domain (TRADD), was released by TNF α treatment along with TNFR1. TNF α-triggered release of EVs was decreased in the presence of amitriptyline, an inhibitor of acid sphingomyelinase (A-SMase), or of GW4869, an inhibitor of neutral sphingomyelinase (N-SMase), indicating that EVs containing TNFR1 and TRADD are released through A-SMase and N-SMase dependent manners. From sucrose density gradient analysis, each sphingomyelinase is involved in the generation of distinct populations of EVs. Inhibition of A-SMase or N-SMase resulted in significantly increased responses to TNF α in parental cells. Given that TRADD serves as a platform for the assembly of subsequent signaling molecules, the TNF α triggered release of TNFR1 and TRADD might be an effective strategy for down regulation of the TNF α responses of parental cells.