Hepatic Autophagy Deficiency Leads to Exosome Overproduction and Pro-inflammatory Response

Gang Liu, Michelle Ma, Xiao-Ming Yin
Department of Pathology & Laboratory Medicine
Tulane University School of Medicine, New Orleans, LA

Autophagy is an evolutionarily conserved metabolic process and plays a homeostatic role to maintain a normal liver function. Autophagy deficiency induces a plethora of pathological changes including inflammation, fibrosis, metabolic disturbance, and tumorigenesis. We are interested in determining how the inflammation is induced under this condition. We hypothesized that exosomes could contribute to the process. Exosomes are defined as membrane-surrounded, nanometer-sized vesicles with an average size of 40 to 160 nm in diameter. Exosomes contain a serious of cargos including nucleic acids, proteins, and lipids, which can play critical role in cell-cell communications. In the present study, nanoparticle tracking analysis (NTA) showed an increased production of exosomes in circulation under the condition of hepatic autophagy deficiency. To understand the functional role of these exosomes, they were incubated with macrophages derived from the bone marrows (BMDM), which can be recruited to the liver and contribute to the hepatic inflammation. We found that BMDM could effectively internalize the exosomes. Notably, the expression of a number of pro-inflammatory genes were increased in BMDM co-cultured with exosomes isolated from autophagy deficient mice, but not in BMDM co-cultured with exosomes isolated from wild type mice. Systemic sequencing of miRNA carried by these exosomes identified miR-3072-3p that can target to the inflammatory pathways. Indeed, BMDM transfected with miR-3072-3p mimics expressed a higher level of pro-inflammatory genes, suggesting that these cells can be activated by the exosomes via miRNA mediated signaling. Thus, increased production of exosome with miRNA unique to the condition of autophagy deficiency can lead to the activation of inflammatory cells.