Abstract

Dendritic cells (DCs) are crucial in cancer immunity, because they activate cytotoxic T cells by presenting tumor antigens. Recently, oncolytic virus therapy has been recognized as a systemic immune stimulator. We previously developed a telomerase-specific oncolytic adenovirus (OBP-301) and a p53-armed OBP-301 (OBP-702), demonstrating that these viruses strongly activate systemic antitumor immunity. However, their effects on DCs remained unclear. In the present study, the aim was to elucidate the mechanisms of DC activation by OBP-702, focusing particularly on tumor-derived exosomes. Exosomes (Exo53, Exo301, or Exo702) were isolated from conditioned media of human or murine pancreatic cancer cell lines (Panc-1, MiaPaCa-2, and PAN02) after treatment with Ad-p53, OBP-301, or OBP-702. Exo702 derived from Panc-1 and MiaPaCa-2 cells significantly upregulated CD86, CD80, CD83 (markers of DC maturation), and IFN-γ in DCs in vitro. Similarly, Exo702 derived from PAN02 cells upregulated CD86 and IFN-γ in bone marrow-derived DCs in a bilateral PAN02 subcutaneous tumor model. This DC maturation was inhibited by GW4869, an inhibitor of exosome release, and anti-CD63, an antibody targeting the exosome marker. Intratumoral injection of OBP-702 into PAN02 subcutaneous tumors significantly increased the presence of mature DCs and CD8-positive T cells in draining lymph nodes, leading to long-lasting antitumor effects through the durable activation of systemic antitumor immunity. In conclusion, tumor-derived exosomes play a significant role in DC maturation following OBP-702 treatment and are critical for the systemic activation of antitumor immunity, leading to the abscopal effect.