Abstract

Pancreatic ductal adenocarcinoma (PDAC) is often refractory to treatment with gemcitabine (GEM) and immune checkpoint inhibitors (ICIs), including anti–programmed cell death ligand 1 (PD-L1) antibody. However, the precise relationship between GEM-resistant PDAC and development of an immunosuppressive tumor microenvironment (TME) remains unclear. In this study, we investigated the immunosuppressive TME in parental and GEM-resistant PDAC tumors and assessed the therapeutic potential of combination therapy with the telomerase-specific replication-competent oncolytic adenovirus OBP-702, which induces tumor suppressor p53 protein and PD-L1 blockade against GEM-resistant PDAC tumors. Mouse PDAC cells (PAN02) and human PDAC cells (MIA PaCa-2, BxPC-3) were used to establish GEM-resistant PDAC lines. PD-L1 expression and the immunosuppressive TME were analyzed using parental and GEM-resistant PDAC cells. A cytokine array was used to investigate the underlying mechanism of immunosuppressive TME induction by GEM-resistant PAN02 cells. The GEM-resistant PAN02 tumor model was used to evaluate the antitumor effect of combination therapy with OBP-702 and PD-L1 blockade. GEM-resistant PDAC cells exhibited higher PD-L1 expression and produced higher granulocyte-macrophage colony-stimulating factor (GM-CSF) levels compared with parental cells, inducing an immunosuppressive TME and the accumulation of myeloid-derived suppressor cells (MDSCs). OBP-702 significantly inhibited GEM-resistant PAN02 tumor growth by suppressing GM-CSF–mediated MDSC accumulation. Moreover, combination treatment with OBP-702 significantly enhanced the antitumor efficacy of PD-L1 blockade against GEM-resistant PAN02 tumors. The present results suggest that combination therapy involving OBP-702 and PD-L1 blockade is a

promising antitumor strategy for treating GEM-resistant PDAC with GM-CSF–induced immunosuppressive TME formation.