Abstract:

The programmed cell death 1 protein (PD-1)/programmed cell death ligand 1 (PD-L1) axis plays a crucial role in tumor immune suppression, while the cancer-associated fibroblasts (CAFs) have various tumor-promoting functions. To determine the advantage of immunotherapy, the relationship between the cancer cells and the CAFs was evaluated in terms of the PD-1/PD-L1 axis. Overall, 140 cases of esophageal cancer underwent an immunohistochemical analysis of the PD-L1 expression and its association with the expression of the α smooth muscle actin (SMA), fibroblast activation protein (FAP), and the CD8, and forkhead box P3 (FoxP3) cells. The relationship between the cancer cells and the CAFs was evaluated in vitro, and the effect of the anti-PD-L1 antibody was evaluated using a syngeneic mouse model. A survival analysis showed that the PD-L1^{+} CAF group had worse survival than the PD-L1- group. In vitro and in vivo, direct interaction between the cancer cells and the CAFs showed a mutually upregulated PD-L1 expression. In vivo, the anti-PD-L1 antibody increased the number of dead CAFs and cancer cells, resulting in increased CD8^{+} T cells and decreased FoxP3+ regulatory T cells. We demonstrated that the PD-L1-expressing CAFs lead to poor outcomes in patients with esophageal cancer. The cancer cells and the CAFs mutually enhanced the PD-L1 expression and induced tumor immunosuppression. Therefore, the PD-L1-expressing CAFs may be good target**s** for cancer therapy, inhibiting tumor progression and improving host tumor immunity.