Abstract

Cancer-associated fibroblasts are a critical component of the tumor microenvironment and play a central role in tumor progression. Previously, we reported that cancer-associated fibroblasts might induce tumor immunosuppression via interleukin-6 and promote tumor progression by blocking local interleukin-6 in the tumor microenvironment with neutralizing antibody. Here, we explore whether an anti-interleukin-6 receptor antibody could be used as systemic therapy to treat cancer, and further investigate the mechanisms by which interleukin-6 induces tumor immunosuppression.

In clinical samples, interleukin-6 expression was significantly correlated with α-smooth muscle actin expression, and high interleukin-6 cases showed tumor immunosuppression. Multivariate analysis showed that interleukin-6 expression was an independent prognostic factor. In vitro, interleukin-6 contributes to cell proliferation and differentiation into cancer-associated fibroblasts. Moreover, interleukin-6 increased hypoxia inducible factor-1α expression and induced tumor immunosuppression by enhancing glucose uptake by cancer cells and competing for glucose with immune cells. MR16-1, a rodent analog of anti-interleukin-6 receptor antibody, overcame cancer-associated fibroblast-induced immunosuppression and suppressed tumor progression in immunocompetent murine cancer models by regulating hypoxia inducible factor-1α activation in vivo. The anti-interleukin-6 receptor antibody could be systemically employed to overcome tumor immunosuppression and improve patient survival with various cancers. Furthermore, the tumor immunosuppression is thought to be induced by interleukin-6 via hypoxia inducible factor-1α activation.