Inhibition of TWEAK/Fn14 signaling prevents cachexia in cancer

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The cytokine TWEAK and its cognate receptor Fn14 are members of the TNF Superfamily that are upregulated in tumors. Because they can promote angiogenesis, we developed specific antibodies against Fn14 that inhibit TWEAK/Fn14 signaling and tested them in mouse tumor models. Surprisingly, these antibodies were poor inhibitors of tumor growth but extended life span dramatically by inhibiting tumor induced weight loss. This weight loss was cachectic and anti-Fn14 antibodies prevented tumor induced inflammation and loss of fat and muscle mass. TWEAK-Fn14 signaling in the tumor, rather than in the environment, is important for cachexia because tumors that express Fn14 promote cachexia and tumors with Fn14 knock-down are less potent at promoting cachexia. These results extend the role of TWEAK-Fn14 in muscle development and indicate that Fn14 antibodies may be a promising approach to treat cachexia thereby extending lifespan and improving quality of life of cancer patients.