Abstract: Cachexia is the unintentional loss of body weight secondary to chronic disease and is prevalent in roughly 50% of cancer patients. The loss of body weight, specifically skeletal muscle mass, is associated with reduced functional independence and life quality resulting in increased morbidity and mortality. The etiology of cachexia is multimodal and complex; however, cachexia has been linked to several systemic (e.g. chronic inflammation, hypogonadism, anemia, insulin resistance) and behavioral (e.g. anorexia, inactivity) changes that compound to accelerate muscle mass and body weight loss. While several inflammatory cytokines are associated with cachexia’s disease progression, our laboratory has established that Interleukin-6 (IL-6) is necessary and sufficient to induce skeletal muscle wasting in tumor-bearing ApcMin/+ (MIN) mice. Additionally, we have shown that reduced volitional activity and increased skeletal muscle fatigue occurs prior to significant wasting and exercise training is able to prevent IL-6-induced cachexia in the MIN without affecting muscle inflammatory signaling. Furthermore, repeated muscle contractions were able to attenuate myofibrillar atrophy, and increase muscle oxidative metabolism without effecting the tumor environment. While the efficacy of exercise to improve skeletal muscle’s metabolic health during aging and disease has been well described, the effects of volitional activity on cancer-induced skeletal muscle fatigue, oxidative metabolism, and muscle inflammatory signaling is not well understood. The overall purpose of this study is to determine the regulation of skeletal muscle fatigue by activity and muscle inflammatory signaling during the progression of cachexia. Our central hypothesis is that cancer-induced skeletal muscle fatigue develops prior to significant weight loss concomitant with decreased muscle use and disrupted muscle oxidative metabolism which occurs through chronically activated muscle gp130 signaling. Our results suggest that the onset of skeletal muscle fatigue developed prior to significant weight loss in MIN mice. Furthermore, elevated circulating IL-6 accelerated skeletal muscle fatigue and reduced muscle oxidative metabolism through muscle gp130 signaling; however, loss of muscle gp130 signaling was unable to improve skeletal muscle fatigue in MIN mice. Last, we demonstrate that there is a direct relationship between activity and skeletal muscle fatigue in healthy and tumor-bearing mice. Together, these results suggest that inactivity and chronic inflammation together disrupt oxidative metabolism and accelerate skeletal muscle fatigue and increasing muscle use through exercise may alleviate the onset of cancer-induced fatigue.