Background:
Cachexia is a debilitating consequence of a multitude of chronic diseases including cancer and endotoxemia. The defining characteristic of cachexia as a rapid loss of skeletal muscle mass. Recent clinical data has demonstrated that the presence of cachexia is an independent predictor of mortality in cancer. Despite this the molecular mechanisms underlying cachexia are incompletely understood, hindering the development of effective pharmacotherapy. While inflammatory cytokines are generally regarded as key mediators, the substrate on which they act to produce cachexia remains the subject of controversy.

Methods:
1. Muscle-specific MyD88 and GR knockout mice were generated by crossing mice harboring a MCK-Cre allele to MyD88Flox and GRFlox mice respectively.
2. Muscle-specific MyD88 and GR knockout mice were treated by irradiation on skeletal muscle mass.
3. MyD88 dependent signaling is necessary for muscle atrophy.
4. Expression of the muscle-specific E3 ubiquitin ligases MAFbx and MuRF1 along with the controlling transcription factor Foxo1 was evaluated by real-time PCR.

Cancer and LPS-Induced Cachexia Requires Glucocorticoid Signaling in Skeletal Muscle
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Figure 1. Proposed Mechanisms for Cancer Cachexia
1. Tumor growth results in the production of inflammatory cytokines
2. Cytokines act in the CNS to produce behavioral and neuroendocrine changes which impact muscle
3. Cytokines can also act directly on muscle to promote atrophy

Figure 2. Whole-Body but not Muscle-Specific MyD88KO Mice Resist LPS-Induced Cachexia

Figure 3. Muscle-Specific Deletion of the Glucocorticoid Receptor Abrogates LPS-Induced Cachexia

Figure 4. Muscle-Specific Deletion of the Glucocorticoid Receptor Prevents Cancer Cachexia

Conclusions:
1. MyD88 dependent signaling is necessary for muscle atrophy in response to inflammation, but it is not necessary in skeletal muscle.
2. Glucocorticoid signaling is requisite for inflammation-induced muscle atrophy.
4. Inflammation produces cachexia indirectly via activation of the HPA axis rather than by direct signaling on the skeletal myocyte.

Future Directions:
1. Establish the inflammatory profile occurring in response to irradiation
2. Establish the impact of irradiation on skeletal muscle mass

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