Myostatin is a novel tumoral factor that induces cancer cachexia.

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Abstract

Humoral and tumoral factors collectively promote cancer-induced skeletal muscle wasting by increasing protein degradation. While several humoral proteins, namely TNF-α and IL-6, have been shown to induce skeletal muscle wasting, there is dearth of information regarding the tumoral factors that contribute to the atrophy of muscle during cancer cachexia. Therefore, we have characterized the secretome of C26 colon cancer cells to identify the tumoral factors involved in cancer-induced skeletal muscle wasting. In this report, we show that Myostatin, a pro cachectic TGF-β superfamily member, is abundantly secreted by C26 cells. Consistent with Myostatin signaling during cachexia, treating differentiated C2C12 myotubes with C26 conditioned medium (CM) resulted in myotubular atrophy due to the up-regulation of muscle-specific E3 ligases, Atrogin-1 and MuRF1, and enhanced activity of the ubiquitin-proteasome pathway. Furthermore, the C26 CM also activated ActRIIB/Smad and NF-κB signaling, and reduced activity of the IGF-1/PI3K/Akt pathway, three salient molecular features of Myostatin action in skeletal muscles. Antagonists to Myostatin prevented C26 CM-induced wasting in muscle cell cultures, further confirming that tumoral Myostatin may be a key contributor in the pathogenesis of cancer cachexia. Finally, we show that treatment with C26 CM induced the autophagy-lysosome pathway and reduced mitochondria number in myotubes. These two previously unreported observations were recapitulated in skeletal muscles collected from C26 tumor-bearing mice.