

Neuromuscular dysfunction precedes muscle atrophy in C26 tumor-bearing mice

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Background: Cancer patients frequently develop skeletal muscle wasting and weakness, which are hallmarks of cachexia, a wasting disease which worsens quality of life and is directly responsible for up to 30% of all cancer-related deaths. While advancements in detection and treatment have increased the population of cancer survivors, skeletal muscle dysfunction can persist for years following cancer remission. We previously demonstrated that late-stage cachexia is associated with impaired skeletal muscle innervation, linking loss of motor unit (MU) connectivity to cancer-induced wasting and weakness. In the present study, we investigated the onset of neuromuscular dysfunction in a preclinical model of cancer cachexia. **Methods:** CD2F1 male mice (8-week-old) were subcutaneously injected with C26 colorectal cancer cells (1.0×10^6) or saline and randomized into one the following timepoint groups: day 6, day 8, or day 10 (n=8-10). Animals were assessed for indices of MU connectivity and muscle function at each timepoint. Following functional assessment, skeletal muscles were harvested, weighed, and processed for molecular analyses. **Results:** 6 days post tumor injection, C26 hosts displayed reductions in neuromuscular junction (NMJ) transmission and motor unit connectivity, while muscle torque and mass were preserved. Specific torque was reduced in C26 hosts at day 8, while reductions in muscle mass or cross-sectional area did not occur until day 10. Molecular analysis revealed alterations of NMJ components as early as day 6 in C26 hosts, further suggesting that neuromuscular dysfunction precedes muscle atrophy. **Conclusions:** Altogether our data demonstrate that cancer-induced neuromuscular dysfunction precedes cancer-induced muscle atrophy, identifying impaired innervation as an early prognosticator of cachexia progression. Our work supports strategies to counteract impaired neuromuscular function in the treatment of cancer cachexia, in hopes of sustaining quality of life in cancer patients and the growing population of cancer survivors.