High Fat Diet worsens Ovarian Cancer Cachexia in mice

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Ovarian cancer (OC) is a leading cause of cancer-related deaths in women. Obesity is a major comorbidity of OC, with recent meta-analysis demonstrating that obese women are at a higher risk for developing OC and experience higher rates of mortality and worse response to treatment. It is of clinical importance to incorporate models of obesity into the preclinical research to ensure our investigations best represent the patient population we hope to develop treatments for. Most OC patients, especially in their most advanced stages, also experience the development of *'cancer-associated cachexia'*, a comorbidity characterized by unintentional weight loss and accompanied by skeletal muscle loss, metabolic derangements and inflammation. Nevertheless, preclinical OC cachexia is understudied and research on this topic often uses young, lean animals to assess the disease. In the current study, we aimed to understand how diet-induced obesity (DIO) impacts the development of cachexia in OC hosts.

10-week-old female NSG mice were placed on a high-fat diet (HFD; 60% kcal from fat) or low-fat diet (LFD; 10% kcal from fat) for 7-weeks (n=10) prior to implantation with ES2 OC cells for 2-weeks. Body weight (BW) was monitored throughout the study, and at endpoint tissue masses were recorded, flash-frozen or fixed for analyses. To profile skeletal muscle response to DIO and/or cancer, RNA-sequencing and western blotting analyses were performed on quadricep muscles (n=4-5 per group). To determine how DIO and/or cancer impact other metabolic organs, livers were sectioned and blinded scoring was performed by a pathologist (n=5 per group).

Animals fed HFD for up to 7 weeks gained on average 33% BW and 2 grams of fat compared to the mice fed LFD. After 2-weeks from ES2 implantation, LFD-fed mice lost 9.7%, whereas HFD-fed mice lost 14.6% BW. HFD-fed mice lost more gastrocnemius, quadricep, and heart mass relative to both LFD-fed tumor hosts and HFD-fed controls, thus suggesting exacerbated cachexia. RNA-seq analysis of ES2 mice versus controls revealed a total of 2,248 differentially expressed genes in both HFD- and LFD-fed mice, with 371 genes uniquely differentially expressed in mice receiving HFD, with pathway analysis of this gene subset revealing significant alterations in ROS, NO, phagocytosis, and cytoskeletal organization. Western blotting analysis displayed significant activation in catabolic signaling (STAT3, FOXO3, LC3b) and depletion of mitochondrial proteins (OPA1, VDAC, Cytochrome-C) in both LFD- and HFD-fed ES2 muscles. Cox-IV and PPAR-alpha were significantly depleted in HFD-fed ES2 animals relative to controls. Liver histophathology scoring revealed ES2 tumor burden increases hepatic inflammation in both LFD- and HFD-fed animals, with the latter demonstrating greater inflammation and hepatic pathology.

Overall, our data demonstrates that cachexia and skeletal muscle wasting in OC hosts is worsened by DIO, potentially due to mechanisms caused by metabolic stress and increased hepatic inflammation.