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### **Clinical Relevance of VM-M3 in Modeling Cancer Cachexia**

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Cancer cachexia has been redefined since the early 20<sup>th</sup> century. The current consensus is that cancer cachexia involves loss of skeletal muscle and body fat, accompanied by inflammation, anorexia, metabolic dysfunction, anemia, and hypoalbuminemia. Cachexia has been further defined through progressive staging of the disease from pre-cachexia, cachexia, and refractory cachexia based on both weight and biochemical changes, and metastasis has been associated with higher incidence of cachexia. To date, no model system encapsulates all aspects of the cachexia condition. The VM-M3 model of systemic metastasis presents progressive loss of skeletal muscle and adipose tissue. It also exhibits elevated levels of proinflammatory cytokines by 2 weeks, and elevated spleen weight, white blood cells counts, and pro-inflammatory cytokines at end-of-life, indicating a progressive and prolonged inflammatory state as is seen in cachexic patients. The VM-M3 model develops a primary tumor at the site of implantation followed by systemic metastasis to all major organ systems, replicating the metastatic process seen in metastatic disease. Additionally, aerobic fermentation is present in VM-M3 cells matching the metabolic phenotype often seen in tumors prone to metastasis. VM-M3 mice develop anemia, hypoalbuminemia, and reduced total protein, all characteristics commonly reported in cachexic patients. VM-M3 mice also have elevated lactate levels indicating potential metabolic dysfunction which is reported in cachexia patients. Additionally, the VM-M3 model provides a repeatable and logistically feasible model for assessing cachexia therapeutics against a phenotype that replicates many hallmark characteristics of cancer cachexia. This recent evidence indicates that the VM-M3 model of systemic metastasis may present an ideal system for evaluating the multifactorial cachexia syndrome and testing emerging therapeutic interventions.

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