Association Between *IL6R* Polymorphisms and Cachexia Phenotype in Patients with Pancreatic Ductal Adenocarcinoma

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Background: Cachexia, manifested as progressive adipose and muscle wasting, affects up to 80% of patients with pancreatic ductal adenocarcinoma (PDAC) and significantly increases morbidity and mortality. Increased inflammation is an underlying mechanism in almost all cases of cachexia. Trans-signaling of Interleukin-6 (IL-6) via the soluble form of its receptor (sIL6R) has been shown to promote inflammation. Certain polymorphisms of the *IL6R* gene such as rs2228145 (Asp358Ala substitution) are associated with increased levels of sIL6R. We hypothesize that patients with PDAC possessing *IL6R* alleles correlated with higher levels of circulating sIL6R will have increased systematic inflammation manifested as increased cachexia prevalence or severity.

Methods: DNA was extracted from prospectively collected blood samples acquired from patients with PDAC and from non-cancer controls. Genotype at the rs2228145 polymorphism was determined by TaqMan qPCR genotyping. The resulting genotypes (A/A, A/C, C/C) were compared against cachexia-related metrics, including presence of cachexia (>5% body weight loss in the prior 6-months), body mass index (BMI), BMI-adjusted weight loss grade (BMI-WLG), and muscle and adipose volumes calculated from height-adjusted surface areas obtained from CT scans at the level of the third lumbar vertebra.

Results: 83.3% of patients with PDAC heterozygous (A/C) and 84.6% of the patients homozygous for the rs2228145 polymorphism (C/C) exhibited cachexia, versus 57.9% of patients homozygous for the reference allele (A/A), ($P = 0.0364$, Chi-square test). No significant difference was found among genotypes for BMI, 6-month weight loss, BMI-WL grade, or muscle and adipose tissue indices.

Conclusion: Patients with PDAC who are possess at least one copy of the rs2228145 polymorphism have a higher incidence of cachexia than those who are homozygous for the reference allele. This association suggests a causal role for sIL6R in cancer cachexia.