Modulating amino acid cross-talk between the Tumor and the Host to improve cancer diagnosis and therapy

S-04.5-1

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Cancer-associated cachexia (CAC) is an incurable, pervasive clinical challenge. All cancer types can present with CAC, which contributes to up to 30% of cancer-related deaths, either directly or by fostering therapy resistance. Addressing CAC requires the dissection of intricate interactions between multiple physiological systems contributing to CAC pathogenesis. Despite extensive investigations into how tumors rewire their metabolism and that of their microenvironment, the broader impact of tumors on whole-body metabolism, i.e., tumor MACRO-Environment, and conversely, remains largely unexplored.

We recently demonstrated that cancer-induced inflammation alters liver metabolism by reducing levels of HNF4a, impacting tumor proliferation and weight loss in human cancer patients and animal models. Interestingly, we now find that HNF4a is also regulated by the autonomic nervous system (ANS), which innervates the liver. Furthermore, we find that neuromodulation of the ANS preserves liver and muscle aminoacid metabolism and alleviates CAC manifestations independent of tumor burden. We hence hypothesize that liver metabolism is pivotal in promoting CAC in extrahepatic cancers.

Undoubtedly, gaining knowledge on the contribution of host metabolism to tumor progression to CAC holds immense potential to interrupt the cascade of deteriorating events and ultimately enhance outcomes for cancer patients.