

## CANCER CACHEXIA ASSOCIATED FC RECEPTOR EXPRESSION ON LEUKOCYTES AS POTENTIAL MECHANISM OF CHECKPOINT INHIBITOR RESISTANCE IN PATIENTS AND IN MURINE CANCER MODELS

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**Background** Cancer cachexia is a multifactorial syndrome characterized by irreversible loss of skeletal muscle and adipose tissue resulting from increased catabolism and metabolic activity.<sup>1</sup> Patients with cachexia are generally resistant to immune checkpoint inhibitor (ICI) therapy while also displaying elevated monoclonal antibody (mAb) catabolic clearance (CL), and this increased CL serves as a prognostic indicator of overall survival, independent of dose received.<sup>2–3</sup> Increased ICI CL is also replicated in the murine Lewis lung carcinoma (LLC) model of cancer cachexia but is absent in the non-cachectic MC38 colon adenocarcinoma model.<sup>4</sup> Elevated ICI CL is independent of mAb variable region and target binding, suggesting an important role for the Fc constant region and Fc domain binding to Fc receptors (FcRs). FcRs (FcRn + FcγRs) also play a critical role in both the pharmacokinetics (PK) and efficacy of ICI therapy.<sup>5–6</sup> We sought to understand cachexia-associated changes in leukocyte FcR expression as it pertains to ICI PK and efficacy.

**Methods** Mass cytometry time-of-flight (CyTOF) was used to assess circulating immune cells and FcR expression in peripheral blood mononuclear cells (PBMCs) from cancer patients and in mouse splenocytes. Healthy C57BL/6 mice and mice with LLC or MC38 tumors were used to investigate the effect of cachexia on FcR expression. PBMCs were obtained from patients receiving either pembrolizumab, nivolumab, or combination nivolumab and ipilimumab for the treatment of non-small cell lung cancer or renal cell carcinoma. Cachexia in these patients was assessed using L3 CT image analysis of skeletal muscle index (SMI).<sup>7</sup>

**Results** Many cachexia associated changes in leukocyte FcR expression were observed. Both FcγRI<sup>8</sup> and FcγRIIb<sup>9,10</sup> play a role in ICI PK and efficacy, and both illustrate a general inverse trend between expression and cachexia severity with less expression in cachectic patients and animals. We also observed trends between FcR expression and ICI CL that could potentially explain observed differences in CL in clinical patients. Cachectic mice displayed decreased circulating CD8+ T cells, which was also supported in humans in which patients displaying low SMI had lower levels of CD8+ T cells at the time of ICI therapy initiation.

**Conclusions** Many studies have highlighted the importance of Fc and FcR interaction on the therapeutic activity and PK of ICIs, however no studies have characterized expressional changes in FcRs as a function of disease state. Here, we highlight how disease state can mediate FcR expressional changes in patterns that can potentially explain altered ICI PK and efficacy.

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**Ethics Approval** Animal experiments were conducted according to protocols approved by The Ohio State University Institutional Animal Care and Use Committee (protocol #2017A00000117). Human studies were approved by The Ohio State University Cancer Institutional Review Board, approval #2020C0048.

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