Title: *Cancer Associated Kidney Alterations: Assessing Current and Identifying Novel Biomarkers*

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Abstract: Over 60% of cancer patients present with reduced kidney function at diagnosis, suggesting that remote cancer may alter renal function and induce kidney injury, with important implications for treatment. Accurate assessment of kidney function and injury in cancer patients is essential to optimize therapy and reduce acute kidney injury (AKI). Our lab has established the concept of cancer-kidney crosstalk, in which remote cancer alters kidney function, increases markers of kidney injury, and induces interstitial fibrosis through yet unidentified mechanisms. These alterations also increase susceptibility to cisplatin-induced AKI, highlighting the need to define both reliable biomarkers and mechanisms of cancer-associated kidney dysfunction. Here, we evaluated tumor effects on kidney function using transdermal glomerular filtration rate (tdGFR) and surrogate markers, serum creatinine (SCr) and blood urea nitrogen (BUN), in syngeneic mouse models of lung cancer. tdGFR declined early during tumor development, before detectable changes in SCr or BUN. Although tdGFR strongly correlated with tumor size, SCr and BUN did not. For kidney injury markers, lung tumors secreted NGAL and may falsely elevate serum and urinary NGAL; thus, urinary NGAL may be an unreliable marker of kidney injury in the setting of lung cancer. We performed targeted and unbiased serum proteomics in control and tumor-bearing mice to identify candidate biomarkers and mediators of tumor-induced kidney dysfunction. Cross-validation with cytokines and chemokines secreted by lung cancer cells in vitro identified several candidates, of which GDF15, CCL8, and osteoprotegerin have been validated thus far. Serum levels positively correlate with tumor size and tdGFR, supporting their potential as biomarkers of cancer-induced kidney dysfunction. Future studies will determine the clinical relevance of GDF15, CCL8, and osteoprotegerin and test whether they mediate remote cancer-induced kidney dysfunction.