Title: *Effects of Myeloid-Cell-Specific ZEB1 Deletion in a Repeated Low-Dose Cisplatin Remote Tumor Model*

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Abstract:

Cisplatin, a widely used chemotherapeutic for the treatment of solid tumors is limited by dose-dependent nephrotoxicity. Approximately 30% of patients develop acute kidney injury (AKI), increasing their risk of chronic kidney disease (CKD). In a model of repeated low-dose cisplatin (RLDC), the kidney undergoes proximal tubule failed repair, partial epithelial-to-mesenchymal transition (EMT), increased infiltration of M2-like and resident macrophages (MΦ) impaired kidney function and fibrosis. To identify potential therapeutic targets, we investigated the Zinc-finger-E-box-binding-homeobox-1 (ZEB1), a transcription factor known to drive EMT and promote MΦ polarization. Unpublished data from our group demonstrated that ZEB1 is upregulated in kidneys following RLDC treatment and that global heterozygous knockout (ZEB1+/−) conferred protection against cisplatin-induced kidney injury, EMT, macrophage infiltration and fibrosis. We hypothesized that ZEB1 drives RLDC-induced nephrotoxicity through MΦ polarization.

Male and female 8-week-old C57BL/6 mice with myeloid cell-specific ZEB1 knockout (ZEB1F/F; LysM-Cre) and littermate controls bearing remote lung tumors were subjected to weekly cisplatin (7 mg/kg, i.p.) or vehicle for four weeks. Kidney function was assessed via transdermal glomerular filtration rate (GFR) one day prior to euthanasia. BUN, KIM-1, and NGAL were measured as markers of renal injury. Kidney and tumor immune cell populations were analyzed by flow cytometry. EMT, inflammatory, and fibrotic markers were assessed by Western blot, RT-qPCR, and immunohistochemistry. Two-way ANOVA was used for statistical analysis ($p < 0.05$).

ZEB1F/F; LysM-Cre mice were not protected from RLDC-induced kidney injury. Transdermal GFR, BUN, NGAL, and KIM-1 levels were not significantly different between genotypes following RLDC. Inflammation, EMT, fibrosis markers, and tumor immune composition were similarly unchanged.

These findings indicate myeloid ZEB1 is not the primary mediator of cisplatin-induced nephrotoxicity, suggesting renal protection in global knockout model is driven by ZEB1 deletion in a non-myeloid population. Future work will examine proximal tubule-specific ZEB1 deletion.