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THE TUMOR-INTRINSIC NLRP3 INFLAMMASOME ESTABLISHES A PULMONARY METASTATIC NICHE VIA TYPE II EPITHELIAL HSP70/TLR4 SIGNALING AND FACILITATES DISEASE HYPERPROGRESSION IN RESPONSE TO IMMUNOTHERAPY

Balamayooran Theivanthiran*, Fang Liu, Nicholas DeVito, Michael Plebanek, Brent Hanks.
Duke University, Durham, NC, USA

Background Our understanding of those underlying mechanisms that contribute to metastatic progression in melanoma remains limited. While uncommon, melanoma hyperprogression in response to immunotherapy is likely to be an extreme form of acquired resistance. Therefore, studies that define the underlying mechanisms of these processes are expected to provide insight into the discovery of novel therapeutic targets and predictive biomarkers. We previously demonstrated that tumor-intrinsic NLRP3 drives adaptive resistance to anti-PD-1 immunotherapy (anti-PD-1) by inducing the recruitment of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) via the upregulation of CXCL5. Gain-of-function polymorphisms in the TLR4 gene have been associated with pulmonary metastases in melanoma patients. We have shown HSP70 to promote PMN-MDSC chemotaxis via the stimulation of TLR4 signaling. As a result, we hypothesized that the tumor NLRP3 inflammasome may also contribute to distant metastatic progression and disease hyperprogression during immunotherapy by establishing a long-distance signaling axis mediated by HSP70-TLR4 signaling in the lung.

Methods We pharmacologically and genetically inhibited the NLRP3 inflammasome and HSP70 in a transgenic BRAFV600E mouse model to examine their role in distant metastatic progression before and during anti-PD-1. An inducible type II pulmonary epithelial cell-specific TLR4 knock-out mouse model was engineered to examine the role of distant HSP70-TLR4 signaling in the recruitment of PMN-MDSCs and subsequent metastatic progression to the lung. Plasma HSP70 levels were monitored in melanoma patients undergoing anti-PD-1

Results Anti-PD-1 significantly increases CXCL2/CXCL5 expression and PMN-MDSC accumulation in the lungs of the transgenic BRAFV600E model. This effect is reversed by 1) tumor-targeted ablation and pharmacologic inhibition of NLRP3 but not systemic host knock-out of NLRP3, 2) Pharmacologic Wnt5a ligand inhibition, 3) tumor-specific ablation and inhibition of HSP70. Inducible knock-out of TLR4 in type II epithelial cells suppressed Wnt5a and CXCL5 expression and inhibited the recruitment of PMN-MDSCs to the lung in response to anti-PD-1. Tumor-specific inhibition of NLRP3/HSP70 and lung-specific ablation of TLR4 suppressed metastatic progression following anti-PD-1 in the BRAFV600E melanoma model. Combination anti-PD-1 and NLRP3 inhibition suppressed primary melanoma progression and distant melanoma metastases versus anti-PD-1 monotherapy. Elevated plasma levels of HSP70 were associated with disease hyperprogression in metastatic melanoma patients undergoing anti-PD-1

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Conclusions Together, these results describe a novel cross-talk mechanism between the primary tumor and the lung that mediates distant metastatic progression that is accentuated following anti-PD-1 (figure 1). Future clinical studies are needed to evaluate the pharmacologic inhibition of this tumor-lung NLRP3/HSP70/TLR4/Wnt5a/CXCL5 axis on melanoma metastasis and disease hyperprogression during checkpoint inhibitor immunotherapy

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