623 NOTCH ORCHESTRATES A MULTIFACETED IMMUNE EVASION PROGRAM IN HEPATOCELLULAR CARCINOMA

Katherine Lindblad*, Marina Ruiz de Galarreta, Romain Donne, Marina Bárcena-Varela, Ian Liebling, David Repáraz, Melissa Yao, Maxime Dhainaut, Brian Brown, Alice Kamphorst, Amaia Lujambio. *Icahn School of Medicine at Mount Sinai, New York, NY, USA*

Background Hepatocellular carcinoma (HCC) is a major global health concern, causing over 700,000 deaths annually [1]. For decades, treatment for advanced HCC was restricted to broad-acting tyrosine kinase inhibitors that conferred limited survival benefits [2]. Recently, immunotherapies have revolutionized treatment of advanced HCC with objective response rates of around 30% [3]. However, with 70% of patients remaining insensitive, there is an urgent need to identify biomarkers of resistance and response and to design novel combination therapies that restore sensitivity in the resistant patients.

Methods To understand mechanisms of HCC immune evasion, we performed transcriptomic analysis on a collection of immune-escaped murine tumors harboring MYC overexpression and loss of p53 (MYC;p53-/-) [4]. The immune-escaped tumors could be categorized into ”immune-inflamed” and ”immune-desert” through single sample gene set enrichment analysis. We further identified an enrichment signature of Notch signaling in immune-inflamed tumors that was associated with a specific deficit of CD8+ T cells – a result validated in HCC patient samples. To test the role of Notch in immune escape, we generated a novel murine model of HCC based on MYC overexpression, activated Notch1 Intracellular Domain (MYC;NICD1), and customized expression of tumor antigens.

Results Expression of tumor antigens in MYC;p53-/- mice led to enhanced survival and active immune surveillance/tumor clearance by antigen-specific CD8+ T cells compared to control MYC;p53-/- mice without tumor antigens. However, this survival advantage conferred by tumor antigen expression was abrogated in MYC;NICD1 mice, demonstrating that Notch activation drives immune evasion in HCC in the presence of antigen expression. Mechanistically, Notch activation in the liver led to a reduced number of tumor antigen-specific CD8 + T cells within the tumor microenvironment compared to the MYC;p53-/- mice while the presence of dendritic cells was similar. Adoptive transfer experiments have revealed a potential impairment of CD8+ T cell priming and activation. Further, Notch1-driven tumors were resistant to anti-PD1 monotherapy as well as anti-PDL1/anti-VEGFR2 and anti-PDL1/anti-TGFB1 combination therapies, indicating a multifaceted immune resistance mechanism mediated in part by VEGF and TGFB1. Resistance to anti-PDL1/anti-VEGF combination therapy has been confirmed in HCC patients.

Conclusions Together, Notch activation promotes a multifaceted immune escape program in HCC. Additionally, it promotes resistance to currently approved immunotherapies, establishing the Notch pathway as a putative biomarker for HCC patient stratification.

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Ethics Approval All mouse experiments were approved by the ISMMS Animal Care and Use Committee (protocol number IACUC-2014–0229).

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