AB073. P045. Mutant GNAS drives pancreatic tumorigenesis via PKA-SIK signaling and reprogramming lipid metabolism

Krushna Patra[1], Yasutaka Kato[1], Yusuke Mizukami[1], Andrew S. Liss[1], Robert A. Screaton[2], Wilhelm Haas[1], Mari Mino-Kenudson[1], Carlos Fernandez-Del Castillo[1], Nabeel Bardeesy[1]

[1]Harvard Medical School, Boston, MA, USA; [2]University of Toronto, Toronto, Ontario, Canada

Abstract: G-protein α_s (GNAS) mediates receptor-stimulated cAMP signaling, a conserved pathway that integrates nutritional and hormonal cues with regulation of cellular metabolism. GNAS is mutationally activated in many human tumors, yet its oncogenic functions remain elusive. We investigated the functions of activated $GNAS^{R201C}$ in pancreatic tumorigenesis where concurrent *GNAS* and *KRAS* mutations define an important pancreatic ductal adenocarcinoma (PDA) subset arising from intraductal papillary mucinous neoplasms (IPMNs). By developing genetically engineered mouse models (GEMMs), we show that $GNAS^{R201C}$ cooperates with $KRAS^{G12D}$ to drive initiation of IPMN, which progress to invasive PDA following Tp53 loss. Moreover, continued expression of mutant GNAS remains critical for tumor maintenance in both GEMMs and human PDA cells. Additionally, we demonstrate that tumor maintenance requires $GNAS^{R201C}$-mediated activation of protein kinase A (PKA) and resulting inhibition of the salt-inducible kinases (SIK1-3). This pathway reprograms cellular metabolism, potentiating lipid remodeling and fatty acid oxidation. Furthermore, comparison of *KRAS* mutant pancreatic cancer cells with and without *GNAS* mutations reveals striking differences in the circuitry and functional impact of this network. Thus, our studies uncover GNAS-driven oncogenic mechanisms, identify SIK kinases as potent tumor suppressors, and demonstrate unanticipated metabolic heterogeneity among KRAS-mutant pancreatic neoplasms.

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