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Vav1 and mutant k-Ras synergize in pancreatic ductal adenocarcinoma development: Lessons from mouse models

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Pancreatic Ductal AdenoCarcinoma (PDAC), the predominant form of pancreatic cancer, develops via Acinar-Ductal Metaplasia (ADM) and neoplastic precursor lesions, such as Pancreatic Intraepithelial Neoplasia (PanIN). Mutant K-Ras is present in >90% of PDAC and represents the most frequent and the earliest genetic alteration found in low-grade PanIN1A lesions. Identification of additional molecular lesions that affect PDAC is of cardinal importance. One such potential protein is Vav1, a hematopoietic specific signal transducer. Overexpression of Vav1 is implicated in human PDAC and is indicative of a worse survival rate. We generated transgenic mice that express Vav1, K-Ras^{G12D}, or both Vav1 and K-Ras^{G12D} (K-Ras^{G12D}, Vav1) in the pancreas. The number of lesions in the pancreata of K-Ras^{G12D}, Vav1 mice exceeded at least three times the number obtained in K-RasG12 mice already at three months post transgene induction. Also, the number of Ki-67 (indicative of proliferation) positive cells in K-Ras^{G12D}, Vav1 mice was significantly higher than in Vav1 or K-Ras^{G12D} transgenic mice. Thus, expression of Vav1 together with K-Ras^{G12D} in the pancreas has a dramatic synergistic effect enhancing ADM formation. Also, continuous Vav1 expression is needed for maintenance of the ADM lesions formed. Interestingly, a dramatic increase in phosphorylation of EGFR and activation of Rac1 was noted in pancreatic malignant lesions of K-Ras^{G12D}, Vav1 mice compared to the pancreas of the control transgenic mice. These results suggest that Vav1 regulates a cross-talk between tumor cells and the microenvironment resulting in up-regulation of signal transduction pathways. Identification of Vav1 as a protein that synergizes with mutant K-Ras in PDAC development might pave the way to choosing good candidates for therapeutic drug design.

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