Mol Cancer Res. 2019 Sep;17(9):1787-1800.

AKT1^{E17K} Activates Focal Adhesion Kinase and Promotes Melanoma Brain Metastasis

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Abstract

Alterations in the PI3K/AKT pathway occur in up to 70% of melanomas and are associated with disease progression. The three AKT paralogs are highly conserved but data suggest they have distinct functions. Activating mutations of AKT1 and AKT3 occur in human melanoma but their role in melanoma formation and metastasis remains unclear. Using an established melanoma mouse model, we evaluated E17K, E40K, and Q79K mutations in AKT1, AKT2, and AKT3 and show that mice harboring tumors expressing AKT1E17K had the highest incidence of brain metastasis and lowest mean survival. Tumors expressing AKT1E17K displayed elevated levels of focal adhesion factors and enhanced phosphorylation of focal adhesion kinase (FAK). AKT1E17K expression in melanoma cells increased invasion and this was reduced by pharmacologic inhibition of either AKT or FAK. These data suggest that the different AKT paralogs have distinct roles in melanoma brain metastasis and that AKT and FAK may be promising therapeutic targets. IMPLICATIONS: This study suggests that AKT1E17K promotes melanoma brain metastasis through activation of FAK and provides a rationale for the therapeutic targeting of AKT and/or FAK to reduce melanoma metastasis.