GENETIC SILENCING OF AKT INDUCES MELANOMA CELL DEATH

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BRAF-mutant melanoma: A therapeutically challenging malignancy

- Melanoma is the 5th most common cancer for men & women in the U.S. (Cancer Facts & Figures 2022).
- Approximately 50% of all melanomas harbor an activating BRAF mutation.
- Targeted therapy options for BRAF-mutant melanoma exist, but most patients will experience primary or secondary resistance.
- The five-year survival rate of stage IV melanoma remains at 30%, highlighting the need for new therapeutics to treat this disease.

MAPK and PI3K pathway alterations co-occur and play a significant role in melanoma

- Approximately 50% of all melanomas harbor an activating BRAF mutation.
- Staurosporine, siCtrl, siAKT123, and siAKT123 + WT Akt1.
- MAPK and PI3K pathway alterations co-occur and play a primary or secondary resistance.
- Rescue of melanoma cells from siRNA-mediated knockdown of AKT1,2,3 is dependent on Akt kinase activity and T308 phosphorylation.

Discover of melanoma cells from siRNA-mediated knockdown of AKT123 is dependent on Akt kinase activity and T308 phosphorylation

- Absorbance
- Normalized Absorbance

Conclusions and Future Directions

- Genetic silencing of AKT induces melanoma cell death through suppression of downstream mTOR signaling and is dependent on functional kinase activity.
- Genetic silencing is superior to pharmacological inhibition as it prevents reactivation of the PI3K-AKT pathway following withdrawal of negative feedback.
- Activated SGK1 can rescue lethal effects of siAKT123 knockdown.
- Combined inhibition of AKT and SGK suppresses melanoma cell proliferation and increases overall survival of BRAF-mutant melanoma in vivo

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