Analyzing the Effects of MG132 on Tumor Xenografts, the Ras pathway, and HPK1 function

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Background

- Pancreatic cancer has a 5-year survival rate of only 9%.[1]
- The RAS pathway, which regulates cell growth, is mutated in nearly 100% of pancreatic ductal adenocarcinoma cases (PDA), making it a critical therapeutic target.[2]

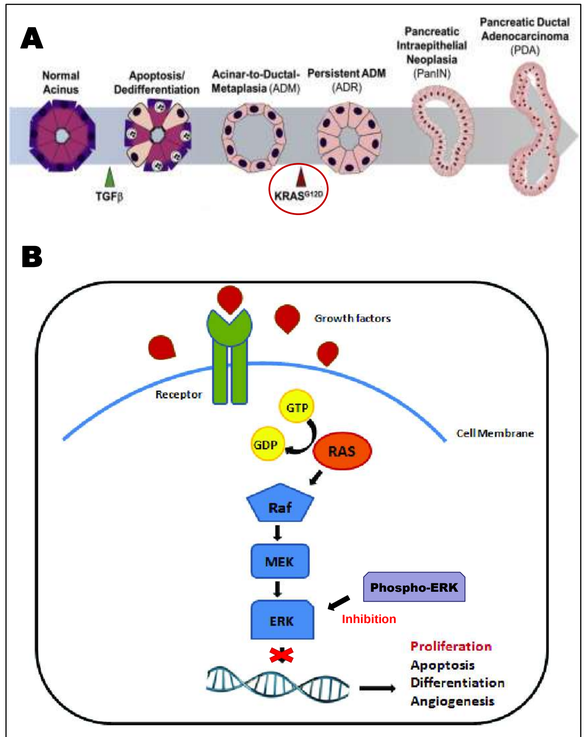

Figure 1. **(A)** KRAS mutations are highly correlated with PDAC.[2] Figure modified from (3). **(B)** Active phospho-ERK (p-ERK) has been shown to potentially downregulate the Ras pathway, reducing the rate of cell proliferation.[4] Figure modified from (5).

Background (continued)

- Hematopoietic progenitor kinase (HPK1) is a regulator of cellular response to stress, proliferation, and apoptosis.[6]
- HPK1 loss is present in >95% of pancreatic cases and is correlated to PDA.[6]
- MG132 is a proteasome inhibitor, which blocks the degradation of proteins. However, a comprehensive mechanism of action is still unclear.

Figure 2. Proteasome inhibitors block protein degradation, causing an accumulation of misfolded proteins and ER stress, ultimately leading to apoptosis.[7]

Hypothesis

It is hypothesized that a decrease in tumor size is due to MG132 stabilizing HPK1 levels and influencing the Ras pathway.

Methods

- Tumor cells were grafted through subcutaneous injection.
- Mice were injected with MG132 twice over the span of two days.
- Tumor growth was assessed via measurements performed every three days for two weeks.
- HPK1 and ERK levels were analyzed through Western blot analysis.

Results

Figure 4. MG132 treatment appears to suppress tumor growth and increase phospho-ERK and HPK1 levels.

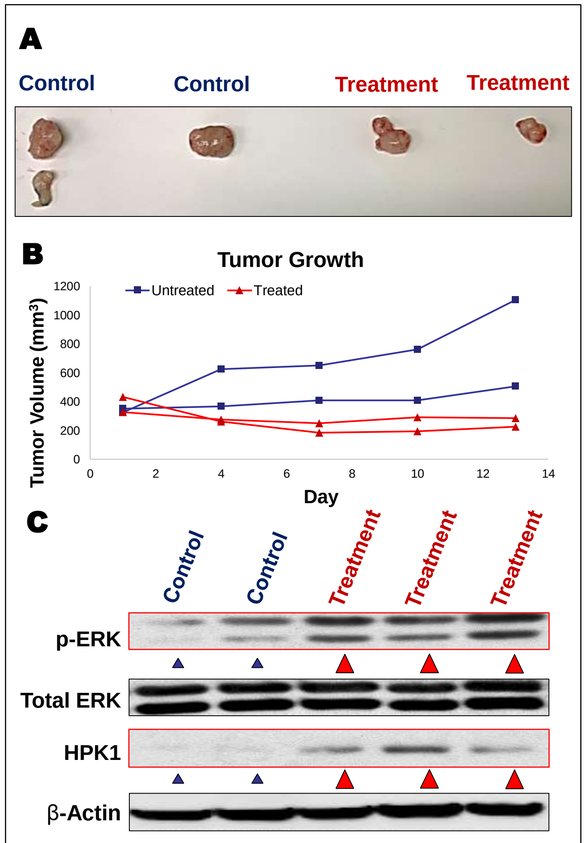

Figure 3. **(A)** and **(B)** Tumor growth appears to decrease in mice treated with MG132. **(C)** Levels of p-ERK and HPK1 appear to increase in untreated control tumor tissue compared to tissue treated with MG132, with total ERK and β-Actin levels to ensure equal loading.

Conclusions

- MG132 appears to suppress tumor xenograft growth in mice.

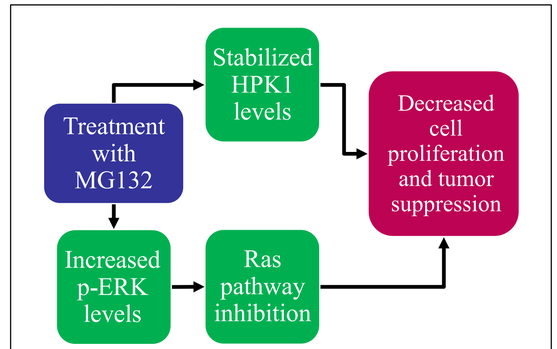

Figure 4. MG132 may interact with Ras pathway inhibitors, such as p-ERK to slow cell proliferation, and stabilize HPK1 levels in tumor tissue.

- If MG132 inhibits the Ras pathway, it could be applied to tumor suppression treatments in pancreatic cancer and other malignancies.
- Further study could include comparison of how different Ras mutant cell lines respond to treatment with MG132.

References

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