Key Findings

Ion transporters in MAPK-dependent haematological malignancies are potential therapeutic targets:

1. Combined inhibition of SERCA channel with MEK results in synergistic toxicity in human leukaemia cell lines through upregulation of apoptosis.

2. Combined inhibition of Na/K ATPase with MEK significantly slowed the progression of murine xenograft model of human acute myeloid leukaemia (AML).

Introduction + Aim

- There is gathering evidence supporting roles for ion transporters in vital cellular processes in cancer.
- Our group recently showed therapeutic synergy from combined inhibition of Na/K ATPase by digitoxin and the MAPK signalling pathway by the MEK inhibitor trametinib in cancers dependent on the MAPK pathway.

I wanted to investigate ion transporters that interact with the MAPK pathway in haematological malignancies by screening transporter ligand libraries to identify inhibitors that are selective toxic, and is enhanced when combined with MEK inhibitor trametinib.

Materials / Methods

Leukaemia cell lines used in experiments are grown in table below, with mutation status of components of MAPK pathway, and sensitivity to MEK inhibitor trametinib. All cell lines were cultured and maintained according to ATCC guidelines. NCBi = human umbilical cord blood cells.

Discussion

- Screening ion transporter inhibitor libraries identified candidates selectively toxic to leukaemia cells, of which SERCA inhibitor thapsigargin; and Na/K ATPase inhibitor digitoxin were the most potent (lowest IC50).
- Toxicity against leukaemia cells in vitro was enhanced when thapsigargin was combined with MEK inhibitor trametinib through increased apoptosis.
- Trametinib likely enhances thapsigargin toxicity by downregulating the chaperone protein GRP78. Similar findings were also observed in melanoma and breast cancer.
- Combining digitoxin with trametinib treatment significantly slowed the growth of human AML cells when grafted into mice.

Conclusion

The combined inhibition of SERCA or Na/K ATPase ion transporters with the MAPK pathway in MAPK-dependent leukaemias offers a novel therapeutic strategy.

Future Work

- Therapeutic potential of combining thapsigargin with trametinib in vivo using human leukaemia models.
- Assess the efficacy of digitoxin and trametinib in other MAPK-dependent cancers.
- Investigating the functional role of SERCA and Na/K ATPase in MAPK-dependent leukaemia.

References


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