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The Role of a More Invasive Phenotype in Response to MAPK-Directed Therapies in Thyroid Cancer

Abstract

Hypothesis: BRAF inhibition increases the production and secretion of fibronectin to promote a pro-invasive secretome.

Fibronectin is required for BRAF inhibitor-induced invasion.

Collagen is increased in response to BRAFi in resistant cells and promotes formation of invasive protrusions.

MAPK pathway reactivation occurs in response to single agent BRAFi.

Dual inhibition of BRAF and ERK prevents MAPK reactivation, blocks invasion, and slows tumor growth.

Results

BRAF inhibition increases fibronectin, which promotes invasion in BRAFi-resistant thyroid cancer cells.

MAPK pathway reactivation occurs in response to single agent BRAFi.

Future Directions:

Conclusions:

- BRAF inhibition and FN1 treatment increases invasion in BRAFi-resistant cells.
- FN1 is necessary for BRAFi-induced invasion, but not reactivation of the MAPK pathway.
- Combined BRAFi and ERKi/2 inhibition prevents MAPK pathway reactivation, blocks invasion, and slows tumor growth.
- Resistant cell lines can exhibit a pro-invasive secretome in response to BRAFi.
- Collagen promotes spheroidal invasion in sensitive and resistant cells.

Future Directions:

- Characterizing the role of ERG1 in an invasive phenotype in response to BRAFi.
- Determine the role of a BRAFi-driven invasive phenotype in promoting invasion and metastasis in vivo, and whether ERK inhibition can block this phenotype.