The Role of MYC in RET Fusion Tumorigenesis and RET Inhibitor Resistance

Background & Review of Literature

Non-Small-Cell Lung Cancer

- Lung cancer is the leading cause of cancer deaths worldwide
  - Non-small-cell lung cancer (NSCLC) accounts for 85% of all diagnoses
- 5-year survival rate of 15.6%
  - ~1,180,000 deaths per year
- NSCLC mainly treated with surgery and chemotherapy,
  - Only ~20-30% of disease respond

1,180,000 NSCLC deaths each year

70-80% of treatments are ineffective

Personalized Medicine

- Standard treatments only effective for subset of the population
  - Patients diagnosed with the same subtype have different genetic causes
- Identifying driving mechanisms opens avenues for targeted therapies
  - Greater efficacy and safety compared to standard approach

Treatment Resistance in RET Fusion NSCLC

- RET encodes for a transmembrane receptor associated with cell proliferation, migration, & differentiation
- RET-fusions can be treated with RET inhibitors
  - Selpercatinib, pralsetinib, and cabozantinib
- Resistance to RET inhibitors frequently occurs but mechanisms of resistance are poorly defined
- RET inhibitor application decreases MYC levels

RET inhibitor application decreases MYC levels

MYC is a family of ‘master regulator’ transcription factors
  - Regulates ~15% of all genes and is dysregulated in >70% of all cancers

Our objective was to determine the role of MYC in RET fusion NSCLC tumorigenesis and treatment resistance

Methodology, Results, and Discussion

Hypotheses were supported
1) RET fusions increase MYC levels by stabilizing the MYC protein
2) MYC overexpression is a mechanism of resistance to RET inhibitors in NSCLC

MYC plays a key role in RET fusion tumorigenesis and resistance to current therapies

Global Impact

- Connection between MYC and RET allows for development of new therapeutic approaches
- New personalized approaches will have improved effectiveness
- RET fusions present in ~3% of NSCLC
  - Based on an estimated 1.87 million NSCLC cases, this has potential to benefit 56,100 patients per year

RET fusion NSCLC is usually seen in young, never-smokers
  - Particularly benefits these groups

Applications to other cancers
  - Thyroid, medullary, breast

Future Focuses

- Develop & test combined anti-RET anti-MYC therapy in mice
- Determine more comprehensive model of MYC upregulation with additional inhibitory approaches
  - MYC shRNA, dox-inducible MYC system, Omomyc
- Test more RET fusion variants
- Verify MYC stabilizing mechanism

Student and Mentor Roles

Student Role

- Idea for the study
- Design of purposes and methods
- All data collection
- Determination of results, conclusions, implications, and future research

Mentor Role

- Consulting in design of methods
- Cell line generation
- Verification of results, conclusions, implications, and future research

Conclusion

- Determine the role of MYC in RET-fusion tumorigenesis and RET inhibitor resistance

Results

- Hypotheses were supported
  1) RET fusions increase MYC levels by stabilizing the MYC protein
  2) MYC overexpression is a mechanism of resistance to RET inhibitors in NSCLC
- MYC plays a key role in RET fusion tumorigenesis and resistance to current therapies

Future Focuses

- Benefits over 50,000 patients per year
- Benefits young, never-smokers
- Applications to other cancers

Global Impact

- Benefits young, never smokers
- Applications to other cancers