1. Lung Cancer: KRAS mutant NSCLC is an area of unmet clinical need

- KRAS G12C mutations are present in approximately 15% of all lung cancer cases.
- A phase I study in NSCLC of Sotorasib (KRAS G12C GDP inhibitor) revealed a disease control rate of 80.1% with a median progression free survival of 6.3 months; unfortunately, all patients developed progressive disease.
- A diverse range of resistance mechanisms have been identified but analysis of clinical cohorts failed to find putative resistance mechanisms in approximately 40% of cases.

2. Aims

- Develop a panel of KRAS-G12C GDP inhibitor (Sotorasib) resistant NSCLC cell lines.
- Identify therapeutic vulnerabilities inherent to resistant cells or that delay the onset of acquired resistance.

3. Generating resistant cell lines

KRAS G12C mutant NSCLC lines were treated with Sotorasib for 9-12 months and changes in sensitivity were demonstrated by changes in IC50 (A-D) and downstream signaling (E).

4. KRAS GDP G12C inhibitor resistant cell lines demonstrate heterogeneous resistant mechanisms

Multiple different KRAS G12C GDP inhibitor resistant cell lines were treated with either a KRAS G12C GTPi or a Pan-RAS-GTPi inhibitor. All cell lines were sensitive to Pan-RAS-GTPi inhibition (A-C). 1/3 cell lines show increased expression of KRAS (A-D).

5. G12C GDP inhibitor resistant cell lines remain sensitive to Pan-RAS-GTP inhibitors suggesting persistent RAS addiction

As different KRAS G12C GDP inhibitor resistant cell lines were treated with either a KRAS G12C GTPi or a Pan-RAS-GTPi inhibitor. All cell lines were sensitive to Pan-RAS-GTPi inhibition (A-C). 1/3 cell lines show increased expression of KRAS (A-D).

6. Using a scRNA-seq experiment to understand heterogeneity of RAS signalling amongst different transcriptomic clusters

A scRNA-seq experiment using H1792 cells treated for 2 weeks or 9 months with a G12C inhibitor demonstrated transcriptomic heterogeneity (A-E). More work is needed to understand the functional role of this heterogeneity. Interestingly pseudo-bulk analysis suggests that the H1792 resistant cells have lower levels of KRAS signaling (D) while there is heterogeneity of RAS signaling amongst clusters comprising of intermediate cell (C).

7. Conclusions and future directions

Acquired resistance to KRAS G12C GDP inhibitors can be overcome with Pan-RAS GTP inhibitors.

References:


Persisting RAS Addiction- a therapeutic vulnerability in the context of KRAS G12C inhibitor resistance

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