Evaluation of driver mutations involving in RAS-RAF/PI3K-mToR pathway in gastric signet ring cell carcinoma

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ABSTRACT

Background: Signet ring cell carcinoma (SRCC) accounts for one thirds of gastric cancer (GC). Previous studies have confirmed that SRCC has a worse prognosis than other forms of GC. Trastuzumab was recently approved for the treatment of advanced HER2-positive GC patients as the encouraging result of ToGA study. However, the incidence of HER2 positivity in SRCC was merely 1%, leaving a significant proportion of patients whose clinical options can only limited to chemotherapy. Furthermore, no molecular profiling specific to SRCC has been explored until now.

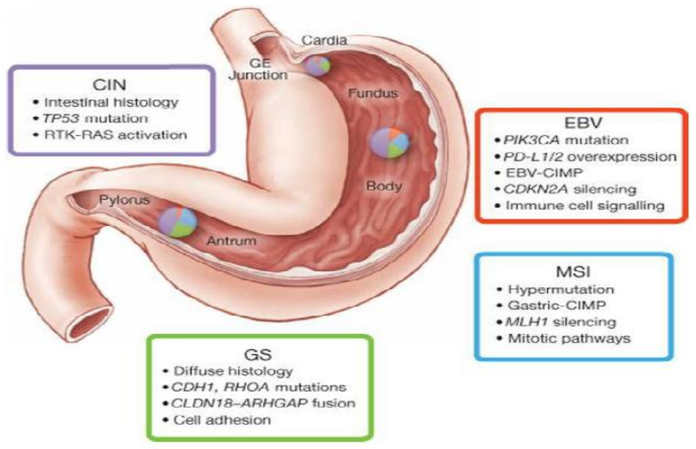
Methods: We assessed the mutation status of driver mutations in KRAS, NRAS, BRAF, PIK3CA by sanger sequencing in 5 GC cell lines and 400 SRCC samples. Correlation between drug sensitivity of MEK and mTOR inhibitors and gene mutations status was evaluated in 5 GC cell lines. Gene mutations status was also analyzed for association with patients' overall survival.

Results: The frequency of KRAS mutations in codon 12, 13 and 61 was 15%. G12V and G12D mutant KRAS alleles account for 80% of all KRAS mutant alleles. No mutant KRAS allele in codon 61 was observed. NRAS mutations of codon 12 or 13 were detected in1.75% of samples. Frequency of BRAF mutation in codon 15 was 1.73%, PIK3CA mutations in exon 9 or exon 20 was 2.27%, respectively. No correlation was found between patients' overall survival and gene status. GC cell line AGS with KRAS mutation was hypersensitive to MEK inhibitor compared with other four wild-type GC cell lines.

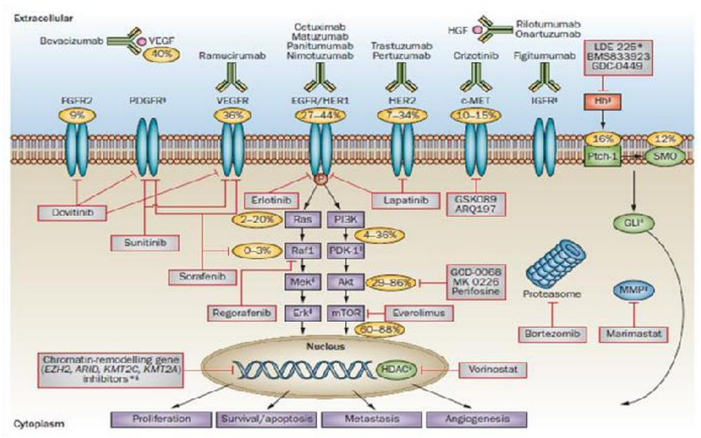
Conclusions: KRAS mutation rate is higher in SRCC than other types of GC. GC with such oncogenic KRAS mutations might be suitable for targeted therapy with MEK inhibitors.

BACKGROUD

- molecular characterization of gastric adenocarcinom

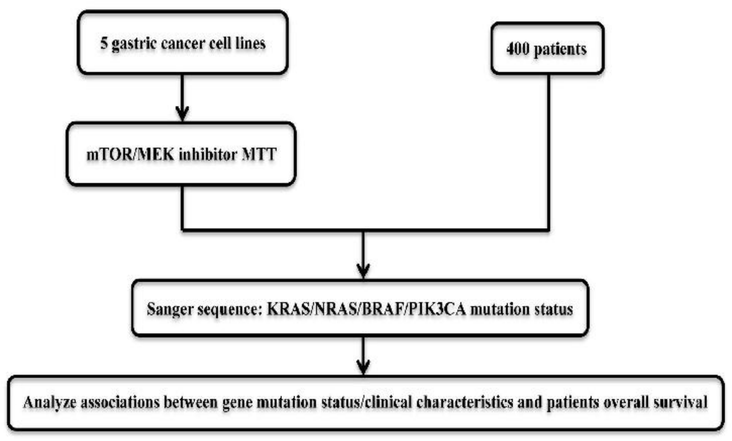


- Important pathways involving in gastric cancer



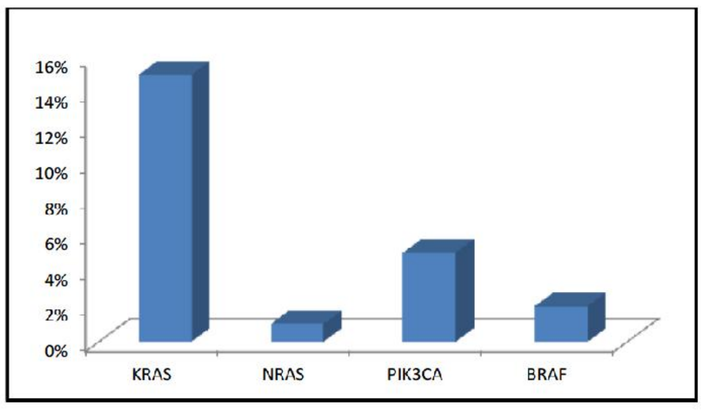
- However, no molecular profiling specific to SRCC has been explored until now.

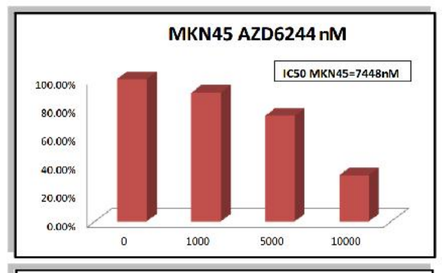
PATIENTS AND METHODS

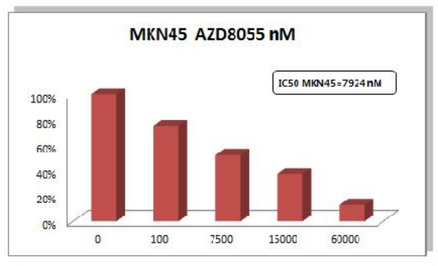


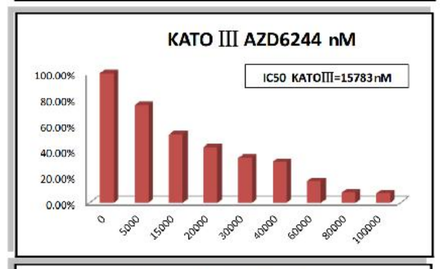
RESULTS

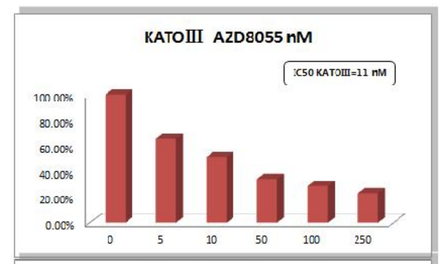
Sanger sequencing results

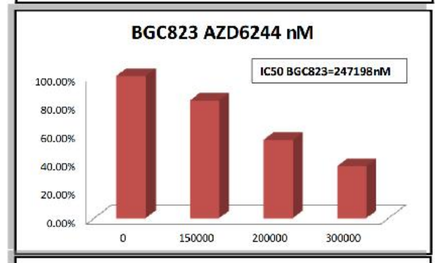


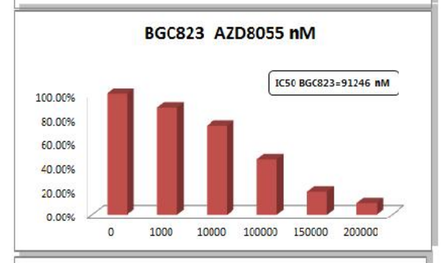


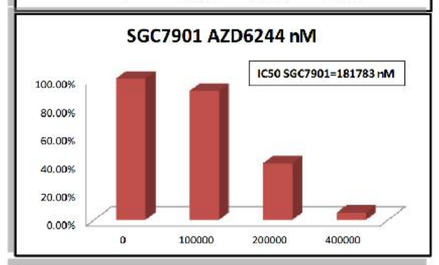


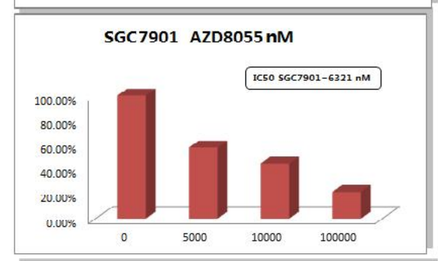


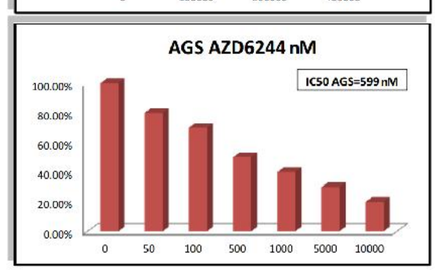


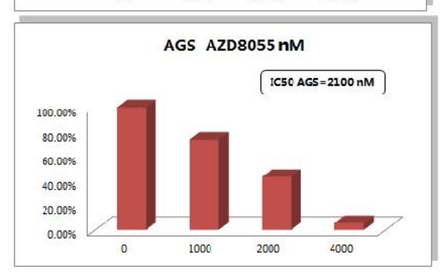












Cell lines	AZD6244 IC 50 (nM)	AZD8055 IC 50 (nM)	KRAS status
KATOIII	15783	11	Wide type
MKN45	7448	7924	Wide type
BGC823	247198	91246	Wide type
SGC7901	181783	6321	Wide type
AGS	599	2100	p.G12D

CONCLUSIONS

- KRAS mutation rate is higher in SRCC than other types of GC.
- GC with such oncogenic KRAS mutations might be suitable for targeted therapy with MEK inhibitors.

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