The molecular determinants of sensitivity to HER2 targeted therapy in patient derived xenograft gastric tumor models from Caucasian and Eastern Asian patients

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Introduction

- HER2 gene amplification occurs in 10 to 20% of gastric cancers. Trastuzumab has been approved for treatment of this cancer, but resistance to treatment is frequently observed.
- Tumor models may aid in gaining a better understanding of how resistance to anti-HER2 therapies arises.
- In the present study we investigated whether our collection of Caucasian and East Asian patient-derived gastric cancer xenografts (PDX) is reflective of the clinical situation and the prevalence of HER2+ tumors in this histotype.
- HER2+ PDX were evaluated for Trastuzumab sensitivity and possible biomarkers.

Materials and Methods

Gastric tumors were xenografted into nude mice and characterized for gene copy number variation (Affymetrix SNP 6.0 array and qPCR), for mutations (Sanger sequencing and Sequenom MassARRAY OncoCarta panels 1, 2 and 3), for mRNA expression (Affymetrix Hu-133 plus 2.0) and for protein expression (immunohistochemistry, IHC). Response to HER2-targeted therapy was assessed in vivo by treating PDX with Trastuzumab at 10 mg/kg/day on days 0, 7, 14, and 21.

Results-HER2 expression

- A total of 26 gastric cancer PDX were established (6 PDXs from patients of Caucasian and 20 from patients of Eastern Asian origin, poster R. Krumbach, abs 2789).
- Based on transcriptomic profiles, gastric PDXs clustered in distinct groups. Caucasian PDGX clustered in a separate group.
- 5 Gastric PDGXs highly expressed HER2 mRNA with all except one cluster together.

Results-HER2 pathway

- Amphiregulin was the predominant growth factor in most of the HER2amp gastric PDGXs.
- HER2 and HER3 were predominantly expressed (not EGFR or HER4).
- 4 out of 5 HER2amp gastric PDGXs expressed Met mRNA.

Results-antiHER2 sensitivity

- 2 out 5 HER2amp models were resistant to Trastuzumab.

Conclusion

- In concordance with what is observed in clinical practice, we identified HER2+ Caucasian and Eastern Asian gastric tumors.
- The PDGXs from these tumors allowed the investigation of response to HER2 targeting therapy.
- These PDGX will aid in testing new HER2 targeted treatments and in identifying potential molecular determinants of resistance to Trastuzumab and other HER2 targeting agents.

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