Whole Exome Sequencing Analyses of Gastric Cancers Reveal Two Distinct Genomic Alteration Patterns with Implications in Drug Sensitivity


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Abstract

Gastric cancer is the fourth most common cause of cancer-related death worldwide. Multiple factors can contribute to the development of gastric cancer, including Helicobacter pylori, dietary behavior and lifestyle, possibly resulting in distinct cancer subtypes with different drug sensitivity profiles. In this present study, we analyzed for gastric cancer molecular alterations associated with the development and clinical outcome of patient derived xenografts (PDXs). In a recent report, we evaluated gene alteration patterns for their implication in drug sensitivity. In both TCGA and our PDX datasets, Whole exome sequencing (WES) analysis revealed two subtypes of gastric cancers (Figure 1A). One signature profile, with different types and numbers of genomic alterations. The first subset (22% of TCGA and 37% of tumors contained Ras/RAF mutations and was characterized by increased numbers of mutations in tumor suppressor genes, such as APC, MLH1, and others. The second subset of tumors (49%-60% of cases) possessed higher levels of mutations in tumor suppressor genes, such as TP53, PTEN, and others. In PDXs, gene alteration levels correlated with MSS tumors, with a lower number of mutations in tumor suppressor genes and a higher number of mutations in oncogenes, including KRAS or MET and a richer oncogenic profile, in both subtypes, the oncogenic signature was maintained with an increase in small subclonality in the subset of highly mutated tumors. At the gene level, for the first subtype, the most altered genes in our TCGA cohort were enriched with the mutation frequency greater than 30% compared with our PDX cohort, regarding the most frequent mutated genes in the first cohort, high levels of gene alteration were observed for genes involved in DNA synthesis and repair, genes involved in cell proliferation and cell cycle progression, mutations in genes of DDR, TP53 and INI1. In contrast, an increased frequency of mutations in oncogenes and tumor suppressors, including KRAS ( Coding DNA), PHKA2 (Missense) and PTEN (Missense), was found in the second cohort. The mutational profile of these tumors suggested the role of oncogenes and tumor suppressors in the development of gastric cancer. In particular, high tumor mutation numbers were found in TCGA panel but were not found in our PDX panel. By using a drug sensitivity profiling platform, we found that the survival rate of gastric cancer xenografts in vitro was high for selective drugs targeting PI3K, AKT, and mTOR. The correlation of gene alterations was observed with PDX drug sensitivity, tumors with high levels of mutations in PI3K, AKT, and mTOR were less sensitive to targeted PI3K, AKT, mTOR drugs. We conclude that gene alterations were informative for drug sensitivity, and that the mutational profiles of tumors are highly variable, with some tumors displaying a DNA repair signature, and others displaying inactivation of tumor suppressor genes. In conclusion, we identified two subtypes of gastric tumors both in the TCGA dataset and in our collection of PDX models, characterized by different genomic alteration profiles suggesting different therapeutic approaches, and we are currently performing drug sensitivity analyses within these subtypes.

Materials and Methods

Figure 1: Variants and gene mutation numbers.

Table 1: Oncogas / tumor suppressor gene alterations patterns.

Table 2: Table A shows the kind and number of mutations and gene alterations.

Table 3: Table B shows the kind and number of mutations and gene alterations.

Table 4: Table C shows the kind and number of mutations and gene alterations.

Table 5: Table D shows the kind and number of mutations and gene alterations.

Table 6: Table E shows the kind and number of mutations and gene alterations.

Table 7: Table F shows the kind and number of mutations and gene alterations.

Table 8: Table G shows the kind and number of mutations and gene alterations.

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Conclusions

- Gastric PDX models retained important genetic alteration patterns similar to those of patient tumors, including signatures of mutational processes, chromosomal rearrangements and mutational profiles.
- Both patient tumors and PDX models could be divided in two distinct subgroups, one with increased chromosomal rearrangements and the other with high mutation levels in PI3K/AKT/MTOR.
- Both subtypes appeared to have different response patterns towards standard chemotherapies and targeted therapies.

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