RNA Sequencing of Intrahepatic Cholangiocarcinoma Reveals Two Prognostic Subclasses

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INTRODUCTION

Cholangiocarcinoma (CCA), the second most common primary liver cancer, has heterogeneous features and a generally poor outcome with limited treatment options. Recent molecular analysis on CCA revealed that KRAS mutation, KRAS mutations and multiple aberrantly regulated oncogenic pathways, including activation of HER2 and epidermal growth factor receptor (EGFR) signaling are characterized as a poor prognostic factors in CCA and these markers can be potential molecular treatment target.

However, integrative analysis between molecular and clinical characterization has not been known yet. If each molecular subtype has specific clinical feature, we can predict molecular subtype based on clinical feature and can approach to distinguished treatment.

Our hypothesis are that intrahepatic CCA can be subclassified according to the specific clinical and pathological features with different outcomes, and different treatment option may be applied according to the subtype of intrahepatic CCA.

METHOD

Experimental group : 30 patients of intrahepatic CCA, Keimyung University Dongsan Medical Center
Validation group : 32 patients of intrahepatic CCA, Mayo clinic
Next generation sequencing
• mRNA expression, RNA variant
• qPCR of 6 CCA cell lines for evaluating expression of 8 genes
  • Gemcitabine sensitivity test with 6 CCA cell lines

RESULTS

1) 2 DISTINCT CLUSTER BETWEEN TUMOR AND NORMAL SAMPLES

Figure 1. Cluster between tumor and normal sample

2)2 subclass of intrahepatic CCA

- With 2,048 differential expressed genes (DEGs) between tumor and normal tissues, further subsequent analysis was performed within 30 tumor tissues and showed 2 distinct subclasses within tumor with significant difference in the overall survival rates (Figure 2)

Figure 2. Two subclass within tumor – Korea data

- We applied 148 DEGs between 2 tumor subclasses to validation group, 2 distinct subclass with different overall survival rates was observed (Figure 3)

Figure 3. Two subclass within tumor – USA data

CONCLUSIONS

1) We used an integrative genomic analysis to identify two subclasses of intrahepatic CCA, characterized by tumor and non-tumor genomics as the driver of CCA. We identified 2 subclasses of intrahepatic CCA with different clinical and pathological features.

2) The 2 subclasses of intrahepatic CCA were significantly different in overall survival rates. The subclass A had better overall survival rates than the subclass B.

3) Pathway analysis by Gene set enrichment analysis (GSEA)