IRAK4 Inhibitor Is a Potential Target for the Treatment of Biliary Tract Cancer

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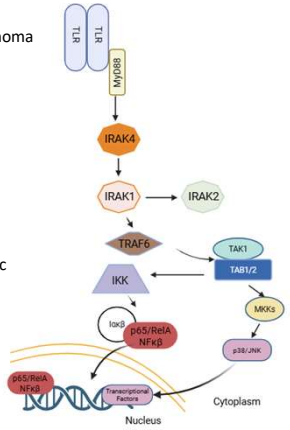
Introduction

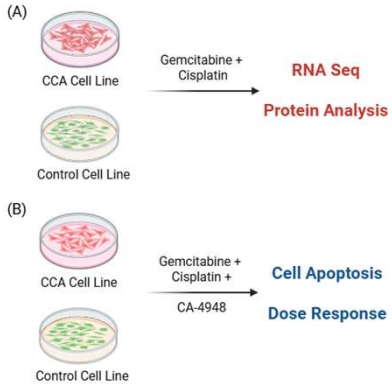
Biliary tract cancers (BTC) BTC is the second most common hepatic malignancy after hepatocellular carcinoma with 5-year survival ranging from 2–23%.[1] The combination of cisplatin and gemcitabine (CG) with an immune checkpoint inhibitor (ICI) such as pembrolizumab or durvalumab is the current first-line treatment for BTC patients. However, this regimen is palliative and associated with significant toxicity.[2]

Aberrant activation of the NF-κB pathway is a well-established mechanism driving the malignant behavior of multiple gastrointestinal cancers, including colorectal, gastroesophageal, BTC, and pancreatic ductal adenocarcinoma (PDAC), leading to therapeutic resistance and poor survival.[3-4] IRAK4 inhibitor CA-4948 is an orally bioavailable small molecule that has shown promise in hematologic malignancies and PDAC mouse models.[4]

Inhibition of IRAK4 in pancreatic adenocarcinoma (PDAC) mouse models sensitized tumors to gemcitabine and ICIs by enhancing NF-κB activity, increasing $CD4^+$ and $CD8^+$ T-cell infiltration, and attenuating tumor fibrosis.[5-6] Understanding the similarities that PDAC shares with BTC as evidenced by their dense desmoplastic environment,[7] I hypothesize that IRAK4 inhibitor CA-4948 may also have synergistic effect and increase therapeutic effect of current chemotherapy regimen CG.[11]



Methods



Results

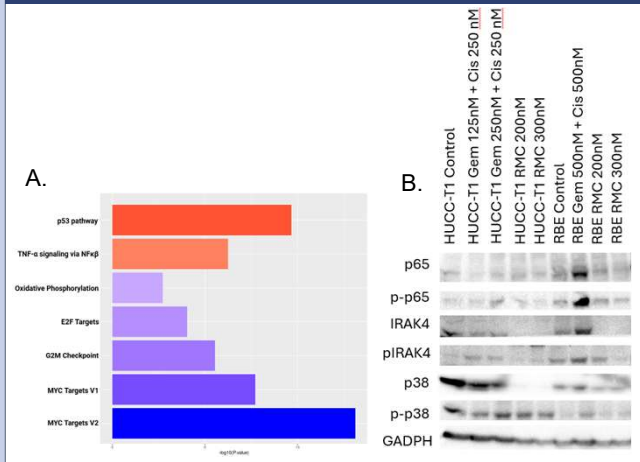


Figure 3. Upregulation of NFκβ pathway in RNA (A) and protein expression (B) compared to control. IRAK4 protein upregulation following treatment with Gemcitabine and Cisplatin in human cholangiocarcinoma cell lines (B) compared to control.

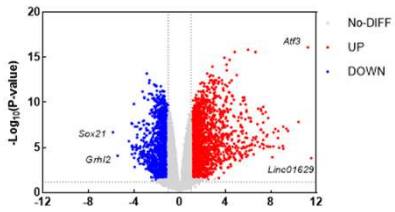


Figure 1. Differential expression of human cholangiocarcinoma cell line after treatment with gemcitabine and cisplatin compared to control.

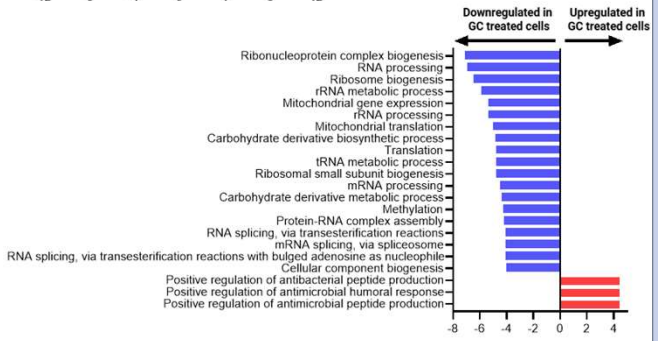


Figure 2. (A) Biological process of human cholangiocarcinoma cells lines treated with Gemcitabine and Cisplatin compared to control.

Discussion

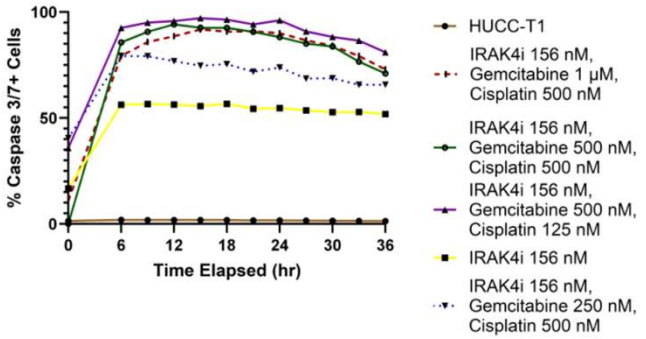


Figure 4. IRAK4 inhibitor CA-4948 activates Caspase 3/7 apoptotic pathway when treating human cholangiocarcinoma cell line in combination with Gemcitabine and Cisplatin. Effect is possible at lower drug concentration.

Conclusion

New therapies are needed to prolong survival in patients with this Biliary Tract Cancer. We believe that this new IRAK4 inhibitor can add substantial therapeutic response to overcome these challenges and expand therapeutic armamentarium.

Further in vitro work is underway to define therapeutic mechanism of acting using human and mouse knockout cell lines. In vivo studies are also underway to assess additive effect of IRAK4 inhibitor in tumor response and tumor microenvironment in orthotopic mouse models.

References

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