DDR1 expression is associated with a worse prognosis in intrahepatic cholangiocarcinoma

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Background
Discoidin Domain Receptor 1 (DDR1) is a tyrosine kinase expressed on cancer cells that binds to collagen, is associated with T-cell exclusion and poor outcomes in several cancer types and is the target of investigational drug therapy PRTH-101.[1,2] DDR1 mRNA expression is known to be high in intrahepatic cholangiocarcinoma (iCCA). We evaluated the correlation of DDR1 protein expression with histologic and clinicopathologic factors and outcomes in iCCA.

Methods
Surgical samples from 80 patients with iCCA who underwent resection at a single institution from 2004-2016 were evaluated by multiplexed immunofluorescence (mIF) and DDR1 immunohistochemisty (IHC) in a tissue microarray.[3] IHC and mIF values across multiple samples from the same tumor were averaged for each of the patients. DDR1 was classified as high for an H score >150. Correlations between DDR1 H-score and clinicopathologic features and outcomes were compared using Spearman correlation (continuous variables), Wilcoxon Rank sum (binary features), or Kruskal-Wallis tests (categorical features).

Results
DDR1 expression was high in 87.7% (71/81) of iCCA. There was IHC 3+ expression on 100% of cells in 25% (20/80) of iCCA. The DDR1 H score was positively correlated with the percentage of the tumor bed that was comprised of stroma (R=0.27, p=0.014). Patients with perineural invasion (n=15) had higher DDR1 H scores (median 292.5, interquartile range 52.5) than patients without (n=65, median 240, interquartile range 105; p=0.011). High DDR1 expression was associated with worse overall survival (0.048) and a trend towards worse disease-free survival (p=0.059), independent of stage. There was no association between DDR1 H-score and CD3+ or CD8+ density within the tumor stroma or parenchyma. There was no association between DDR1 H-score and tumor mutation status, including FGFR and IDH1.

Conclusion
DDR1 is highly expressed in the majority of iCCAs. DDR1 expression is associated with higher levels of stroma, which contains collagen, the ligand of DDR1. The prevalence of high DDR1 expression and poor survival outcomes associated with this make iCCA a relevant tumor type for evaluating novel DDR1-targeted therapies.

References
1. Sun X et al. Tumour DDR1 promotes collagen fibre alignment to instigate immune exclusion. Nature. 2021 Nov;599(7886):673-678. doi: 10.1038/s41586-021-04057-2. Epub 2021 Nov 3. PMID: 34732895; PMCID: PMC8839149.

2. Liu J et al. A highly selective humanized DDR1 mAb reverses immune exclusion by disrupting collagen fiber alignment in breast cancer. J Immunother Cancer. 2023 Jun;11(6):e006720. doi: 10.1136/jitc-2023-006720. PMID: 37328286; PMCID: PMC10277525.

3. Carapeto F et al. The immunogenomic landscape of resected intrahepatic cholangiocarcinoma. Hepatology. 2022 Feb;75(2):297-308. doi: 10.1002/hep.32150. Epub 2021 Dec 6. PMID: 34510503; PMCID: PMC8766948.