DDR1 expression is associated with a worse prognosis in intrahepatic cholangiocarcinoma

Amy Mueller1, Laura A. Dillon1, Xinwei Sher1, Joseph P. Eder1, Thomas Schürpf1, Lawrence N. Kwong2, G. Travis Clifton1

1Incendia Therapeutics, Boston, MA, USA; 2MD Anderson Cancer Center, Houston, TX, USA

Background

- Discoidin Domain Receptor 1 (DDR1) is a receptor tyrosine kinase expressed on cancer cells that binds to collagen.
- DDR1 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 immunohistochemistry (IHC) in a tissue microarray [3].
- IHC and mIF values across multiple samples from the same tumor were averaged for each of the patients.
- H score was determined from the DDR1 IHC. 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 tumor cells in 25% (20/80) of iCCA (H score = 300) (Figure 1).
- 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) (Figure 2).
- Patients with perineural invasion (n=15) had higher DDR1 H scores (median 292.5, IQR 52.5) than patients without (n=65, median 240, IQR 105; p = 0.011) (Figure 3).
- High DDR1 expression was associated with worse overall survival (p = 0.048) and a trend towards worse disease-free survival (p = 0.059), independent of stage (Figures 4, 5).

Conclusions

- 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 associated poor survival outcomes make iCCA a relevant tumor type for evaluating novel DDR1-targeted therapies.