

DISCOIDIN DOMAIN RECEPTOR 1 EXPRESSION IS ASSOCIATED WITH STROMAL TGF BETA SIGNALING IN SELECTED CANCERS

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Background Discoidin Domain Receptor 1 (DDR1) has been implicated in cancer prognosis, invasion, and metastases in multiple tumor types.¹ More recently, DDR1 has also been implicated in immune exclusion.² However, the relationship between DDR1 and TGF beta-mediated immunomodulatory pathways is less clear and may vary by tumor type.

Methods The Cancer Genome Atlas (TCGA) was queried for the association between an 80-gene TGF beta pathway activation signature³ and DDR1 gene expression in all tumors and by individual histologic types. To further understand role of the DDR1/TGF beta interaction, TGF beta isoforms (TGFB1, TGFB2, TGFB3) and binding proteins (LTBP1, LTBP3, LRRC32, NRROS) were compared to DDR1 expression by indications with a strong/moderate relationship between TGF beta signature and DDR1 compared to those with a weak or no relationship between the two.

Results DDR1 gene expression and TGF beta signaling expression are not correlated in a pan-tumor analysis ($r=0.12$). In individual indications, there is a strong relationship ($r>0.75$) in thymoma ($r=0.79$); moderate relationship ($0.75>r>0.5$) in papillary renal cell carcinoma ($r=0.57$), and thyroid cancer (0.52); a weak relationship ($0.5>r>0.25$) in testicular ($r=0.49$), prostate ($r=0.49$), hepatocellular carcinoma ($r=0.47$), endometrial ($r=0.44$), ovarian, lung squamous cell carcinoma ($r=0.27$), lung adenocarcinoma ($r=0.29$), rectal ($r=0.32$), cholangiocarcinoma ($r=0.36$), cervical ($r=0.36$), head and neck ($r=0.30$), esophageal cancers ($r=0.30$), glioblastoma ($r=0.27$); No relationship (<0.25) in all others. There was a strong, direct relationship ($r=0.76$, figure 1) between LTBP3 expression and DDR1 expression in indications with a strong/moderate correlation between TGF beta signaling signature and DDR1 and no relationship ($r=0.17$) in those with a weak or no relationship. All other correlations between DDR1 and TGF beta isoforms or binding proteins were weak or nonexistent ($r<0.5$).

Conclusions DDR1 expression is correlated with TGF beta signaling expression in multiple cancer types, but with varying strength of correlation. In indications with a strong or moderate relationship, DDR1 is also strongly correlated with latent-transforming growth factor beta-binding protein 3 (LTBP3) gene expression, suggesting a common stromal-mediated interaction.

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