# Discoidin Domain Receptor 1 expression is associated with stroma TGF beta signaling in selected cancers.

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## Introduction

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 TFGb pathway activation signature [3] 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).

## Conclusion

*DDR1* expression is correlated with TGF-B 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.

1. Gao Y, Zhou J, Li Jin. Discoidin domain receptors orchestrate cancer progression: A focus on cancer therapies. Cancer Sci. 2021; 112: 962-969.

2. Sun X, Wu B, Chiang HC, Deng H, Zhang X, Xiong W, Liu J, Rozeboom AM, Harris BT, Blommaert E, Gomez A, Garcia RE, Zhou Y, Mitra P, Prevost M, Zhang D, Banik D, Isaacs C, Berry D, Lai C, Chaldekas K, Latham PS, Brantner CA, Popratiloff A, Jin VX, Zhang N, Hu Y, Pujana MA, Curiel TJ, An Z, Li R. Tumour DDR1 promotes collagen fibre alignment to instigate immune exclusion. Nature. 2021; 599: 673-678.
3. Teschendorff AE, Gomez S, Arenas A, El-Ashry D, Schmidt M, Gehrmann M, Caldas C. Improved prognostic classification of breast cancer defined by antagonistic activation patterns of immune response pathway modules. BMC Cancer. 2010;604:1-20.