Discoidin Domain Receptor 1 expression is associated with stroma 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 Transforming Growth Factor beta (TGFβ)-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 TGFβ pathway activation signature [3] and *DDR1* gene expression in all tumors and by individual histologic types.
- To further understand the role of the DDR1/TGFβ relationship, expression of TGFβ isoforms (*TGFβ1, TGFβ2, TGFβ3*) and binding proteins (*LTBP1, LTBP3, LRRC32, NRROS*) was compared to *DDR1* expression for indications with a strong/moderate relationship between TGFβ signature and DDR1 compared to those with a weak relationship or no relationship between the two.
- Relationships between indications were included if statically significant with a p-value <0.05 with Bonferroni correction (p<0.0015 for indication comparisons).

References

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, et al. Tumour DDR1 promotes collagen fibre alignment to instigate immune exclusion. Nature. 2021; 599: 673-678.
3. Teschendorff AE, Gomez S, Arenas A, et al. Improved prognostic classification of breast cancer defined by antagonistic activation patterns of immune response pathway modules. BMC Cancer. 2010; 604:1-20.

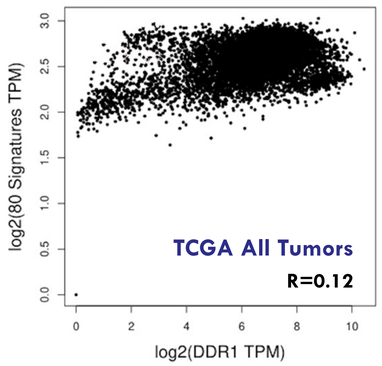
Disclosures

- All authors are employees of Parthenon Therapeutics, Inc.

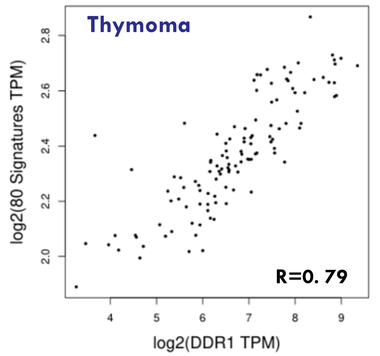
Results

- A pan tumor analysis of TCGA revealed no relationship between *DDR1* gene expression and TGFβ pathway activation signature (R=0.12). However, a subset of individual indications showed a strong (R>0.75), moderate (R<0.75, >0.5), or weak (R<0.5, R>0.25) relationship (see below).
- Additionally, no relationship (R<0.25 or adjusted p-value >0.0015) between TGFβ signature and *DDR1* gene expression was observed in cholangiocarcinoma (R=0.36, p= 0.03), cutaneous melanoma (R=0.23), gastric adenocarcinoma (R=0.22), pheochromocytoma (R=0.21), pancreatic adenocarcinoma (R=0.19), mesothelioma (R=0.16), clear cell renal cell carcinoma (R=0.12), urothelial carcinoma (R=0.12), breast cancer (R=0.12), uveal melanoma (R=0.05), or sarcoma (R=0.02).
- There was a strong relationship (R=0.76) between *LTBP3* and *DDR1* gene expression in indications with a strong/moderate correlation between TGFβ signaling signature and *DDR1* gene expression, but no *LTBP3*/*DDR1* association (r=0.17) in those indications with a weak or no relationship between *DDR1* and TGFβ signaling.
- No relationship (R<0.25) was seen between *DDR1* and the other genes examined (*TGFβ2, TGFβ3, LTBP1, LRRC32, NRROS*) in any of the indications.

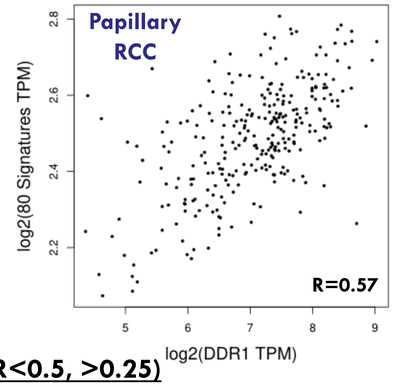
Pan tumor analysis

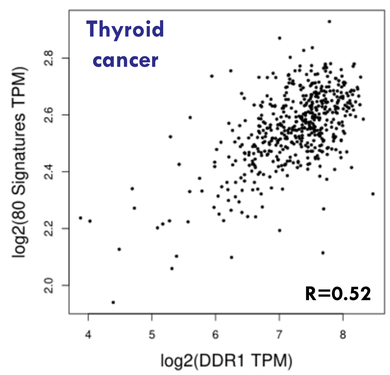


Strong Relationship (R>0.75)

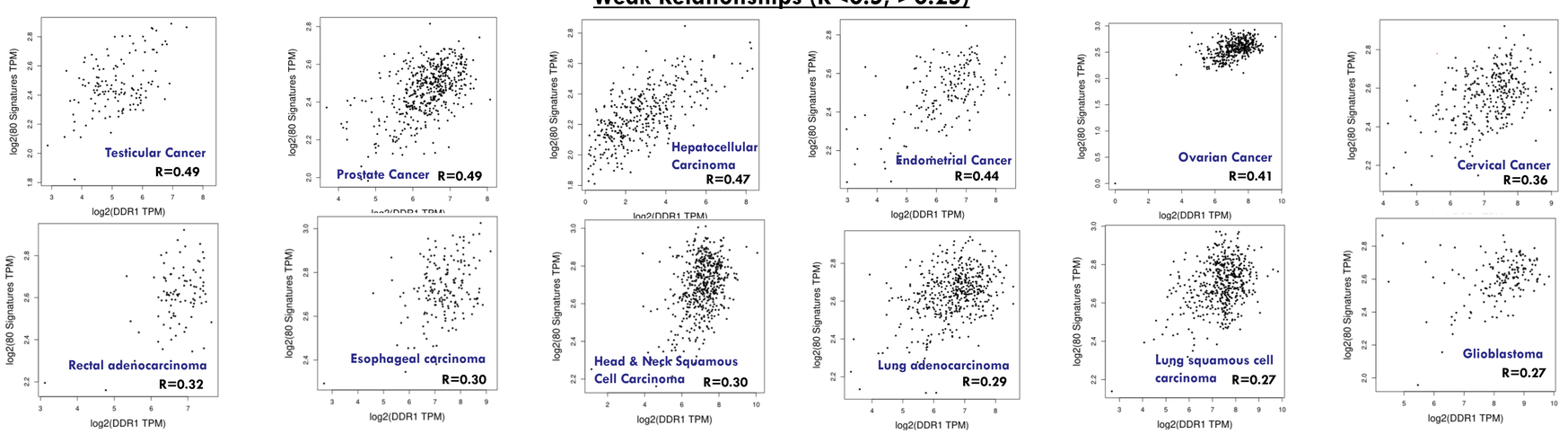


Moderate Relationships (R<0.75, >0.5)

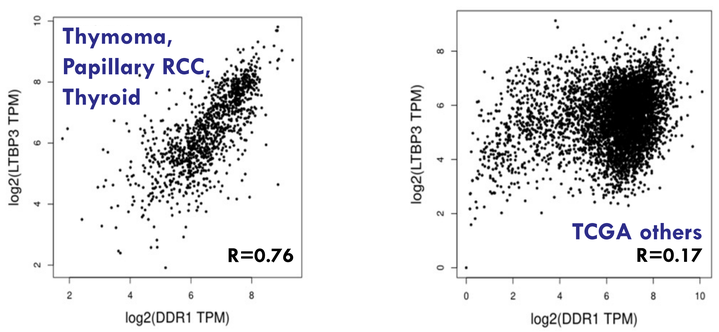




Weak Relationships (R<0.5, >0.25)



Correlation between DDR1 and LTBP3



Conclusions

- *DDR1* mRNA expression is correlated with TGFβ pathway activation signature in multiple cancer types, but with varying strength of correlation.
- In indications with a strong or moderate relationship between *DDR1* and TGFβ signature, *DDR1* is also strongly correlated with latent transforming growth factor beta-binding protein 3 (*LTBP3*) gene expression, suggesting a common stromal-mediated interaction.