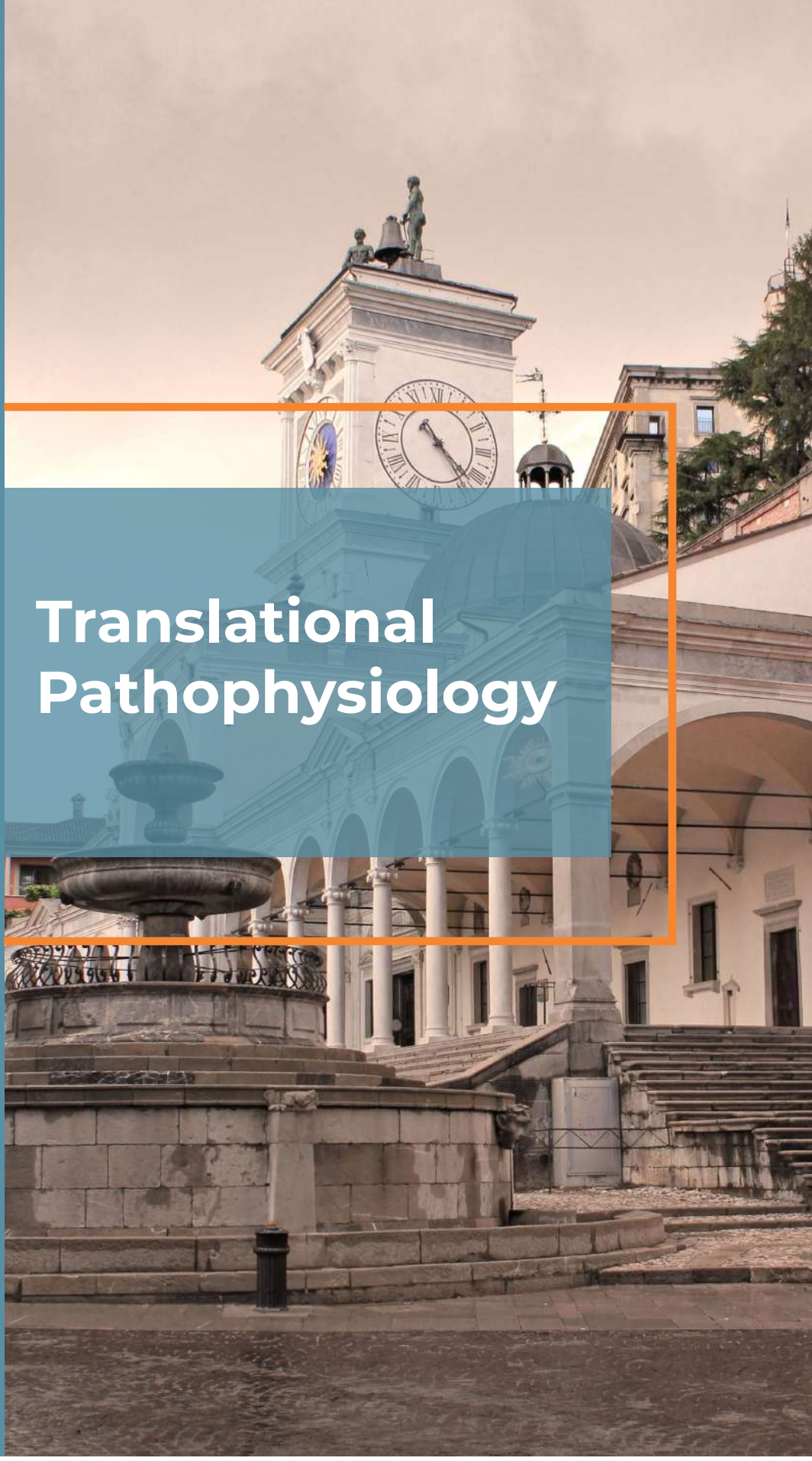


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ABSTRACT BOOK

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TRKAIII PROMOTES PD-L1 EXPRESSION IN SH-SY5Y NEUROBLASTOMA CELLS.

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BACKGROUND-AIM

Neuroblastomas (NBs) are heterogeneous, aggressive, therapy-resistant embryonal tumours of neural crest origin. Alternative TrkAIII splicing of the TrkA neurotrophin receptor in NBs correlates with post-therapeutic relapse and advanced stage metastatic disease, is characterized by exons 6 and 7 skipping and expression of a variant receptor devoid of the extracellular D4 domain that accumulates in pre-Golgi membranes and exhibits ligand-independent activation. In NB cell models, intracellular TrkAIII activation induces pro-survival PI3K-AKT signaling, enhances stress and drug-resistance and augments primary and metastatic tumorigenicity. Immune evasion is an additional hallmark of tumor progression and PD-L1/PD1 immune checkpoint activation has been identified as a potential target in NBs. Considering this, and the correlation between alternative TrkAIII splicing and NB progression, we evaluated whether TrkAIII may also regulate PD-L1 expression, in an SH-SY5Y NB cell model.

METHODS

PD-L1 mRNA and protein expression were evaluated by RT-qPCR, RT-PCR, Western blotting and indirect immunofluorescence in stable pcDNA, TrkA and TrkAIII SH-SY5Y transfectants, under untreated conditions (all cell lines), following treatment with NGF (TrkA SH-SY5Y), treatment with DTT (TrkAIII SH-SY5Y) and in all cell lines following treatments with Trk, PI3K and MEK inhibitors. PD-L1 function was assessed by IL-2 ELISA in Jurkat/TrkAIII SH-SY5Y cell co-cultures.

RESULTS

Control and TrkA-SH-SY5Y transfectants exhibit similar PD-L1 expression. NGF enhances PD-L1 expression in TrkA-SH-SY5Y transfectants, which is prevented by Trk and PI3K but not MAPK inhibitors. TrkAIII SH-SY5Y transfectants exhibit elevated PD-L1 expression, which is also reduced by Trk and PI3K but not MAPK inhibitors and by TrkAIII siRNA. TrkAIII SH-SY5Y PD-L1 inhibits Jurkat cell IL-2 production in co-cultures.

CONCLUSIONS

The data confirm that NGF-activated TrkA and TrkAIII promote PD-L1 expression in SH-SY5Y NB cells via PI3K but not MAPK and confirm PD-L1 function in preventing T cells IL2 production. We propose, therefore, that promotion of PD-L1 expression in NB cell can be added to the oncogenic repertoire of TrkAIII and targeted by Trk and PI3K inhibitors.