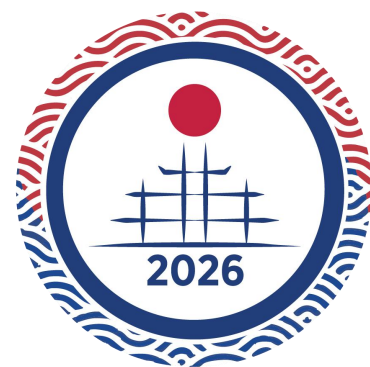




P2.019: CAF derived VTN Drives Radioresistance in NSCLC through TOPBP1 mediated ATR-CHK1 Pathway

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INTRODUCTION

Vitronectin (VTN) is a glycoprotein distributed in extracellular matrix and plasma, involved in cell differentiation, invasion, and metastasis. Its cellular origin and function in NSCLC remain unclear. Radiotherapy is a major treatment for NSCLC, while radioresistance limits its efficacy. This study investigates the role of VTN in radioresistance and its mechanisms.

METHODS

This study prospectively collected blood samples of 121 NSCLC patients who underwent radical thoracic radiotherapy at our center, and plasma VTN levels were quantified by ELISA. Radiation resistance of NSCLC cells was assessed by co-culture model or upon exogenous recombinant human VTN treatment using colony formation, γH2AX foci, and apoptosis assays. In vivo validation was evaluated by a subcutaneous tumor model. RNA-sequencing was performed to analyze transcriptomic alterations in control and rhVTN-treated groups at multiple time points post-irradiation. Rescue experiments were conducted to validate that VTN modulates radiosensitivity through the TOPBP1/ATR/CHK1 pathway. Dual-luciferase and ChIP assays were used to identify the transcriptional regulation of TOPBP1 by p-STAT3.

RESULTS

Figure1. High VTN expression correlated with inferior OS , PFS and poorer tumor response.

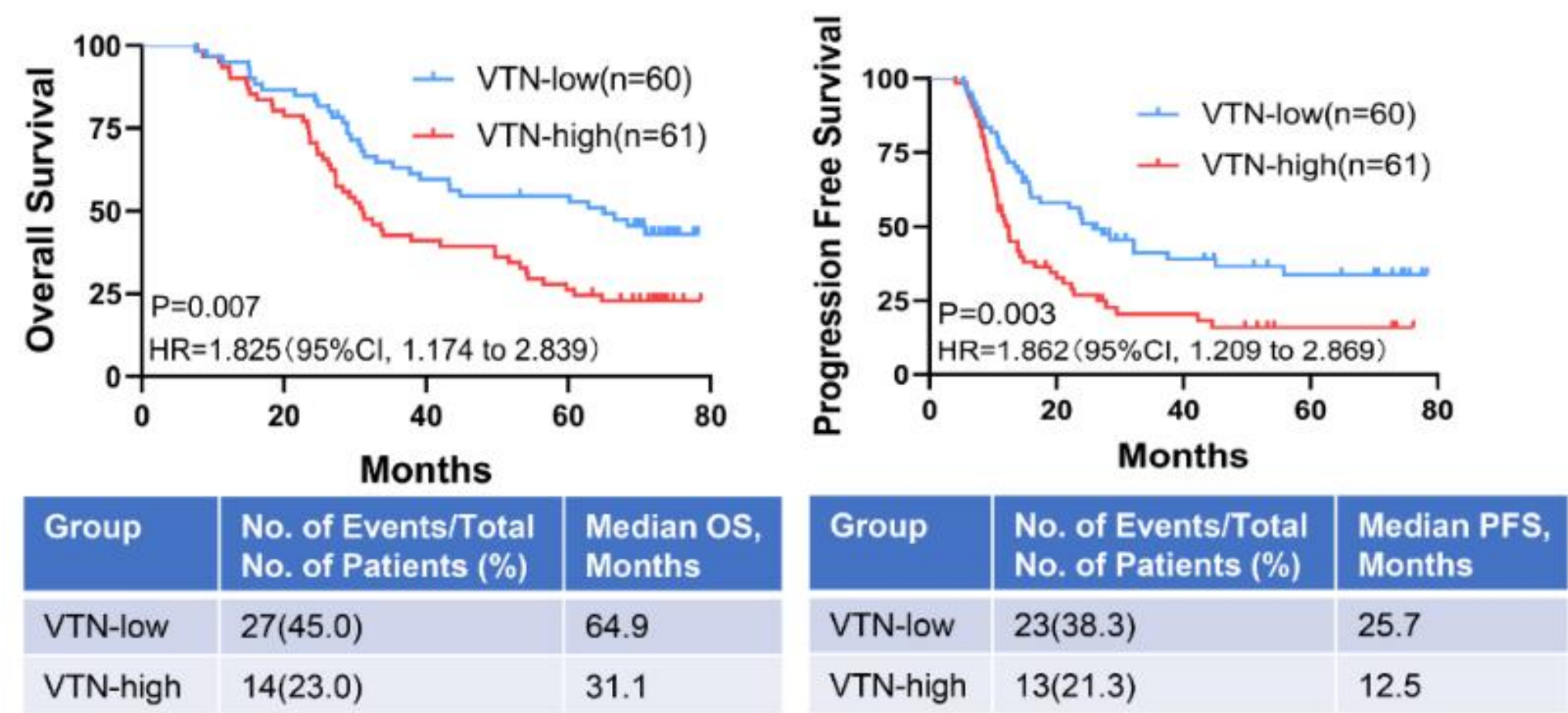


Figure2. VTN was predominantly localized to the NSCLC stroma and co-localized with CAF markers

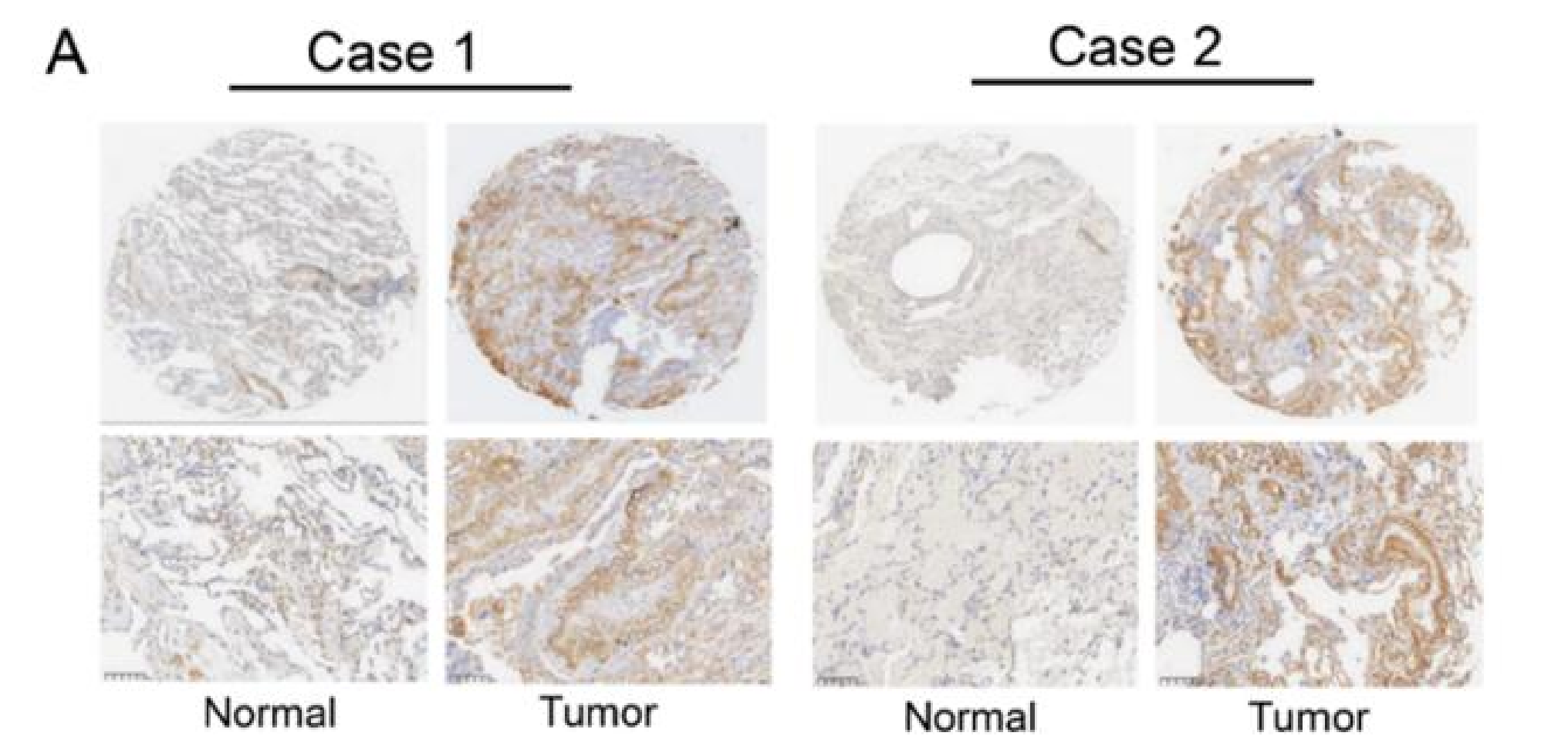


Figure3. In vitro and in vivo evidence confirms VTN promotes NSCLC cell radioresistance

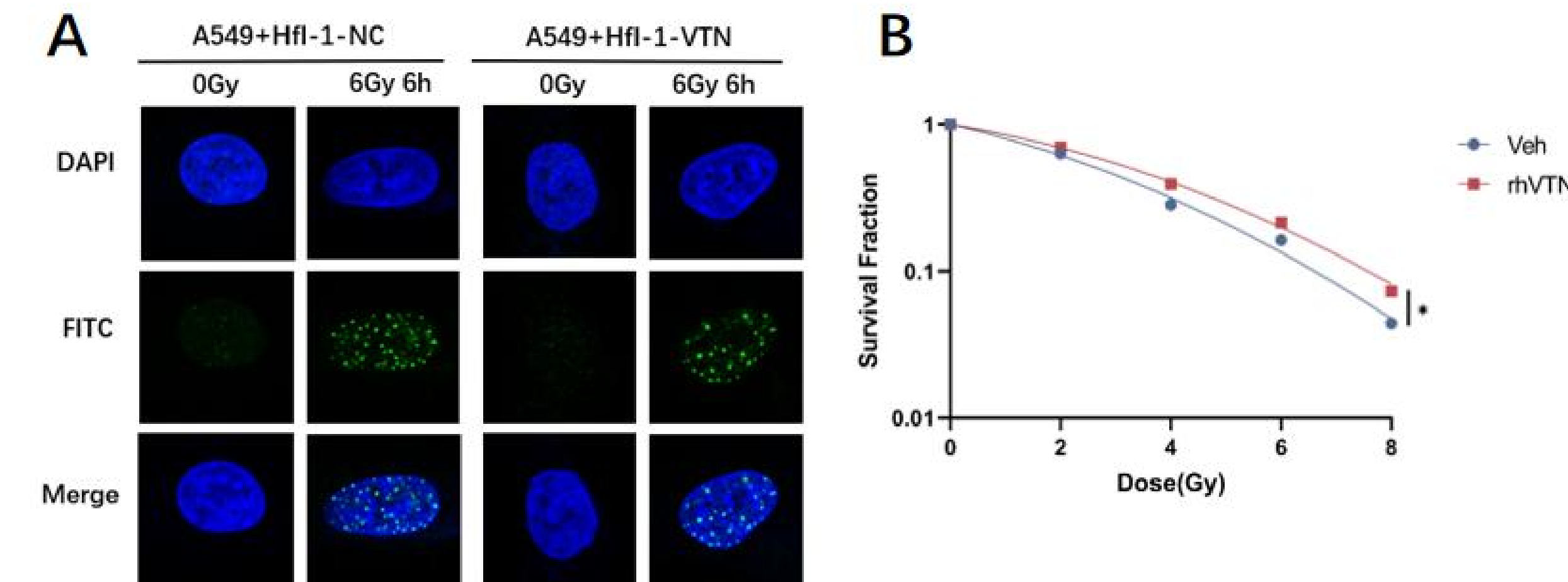


Figure4. VTN upregulates TOPBP1 via activating the FAK pathway to promote ATR/CHK1 activation

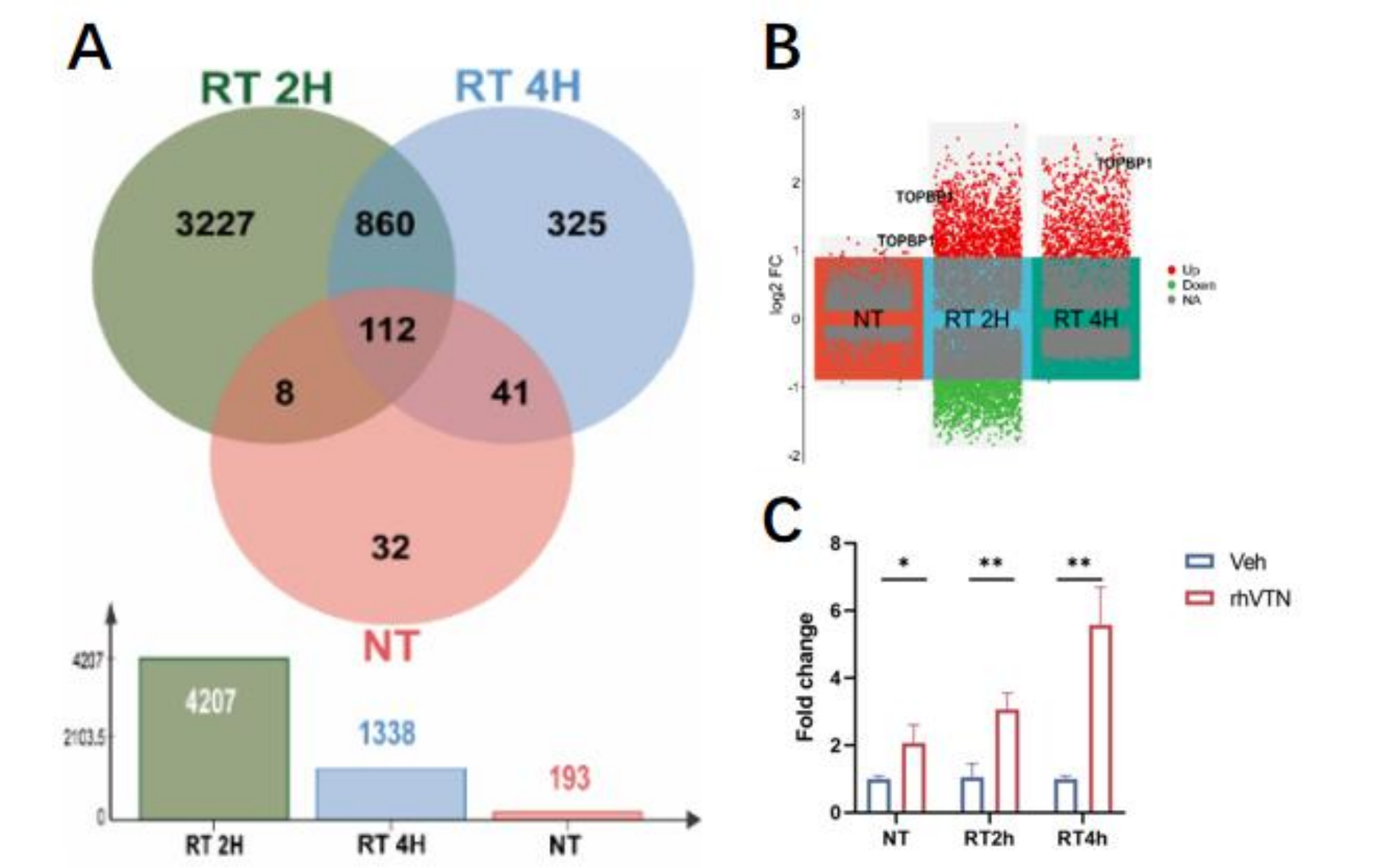
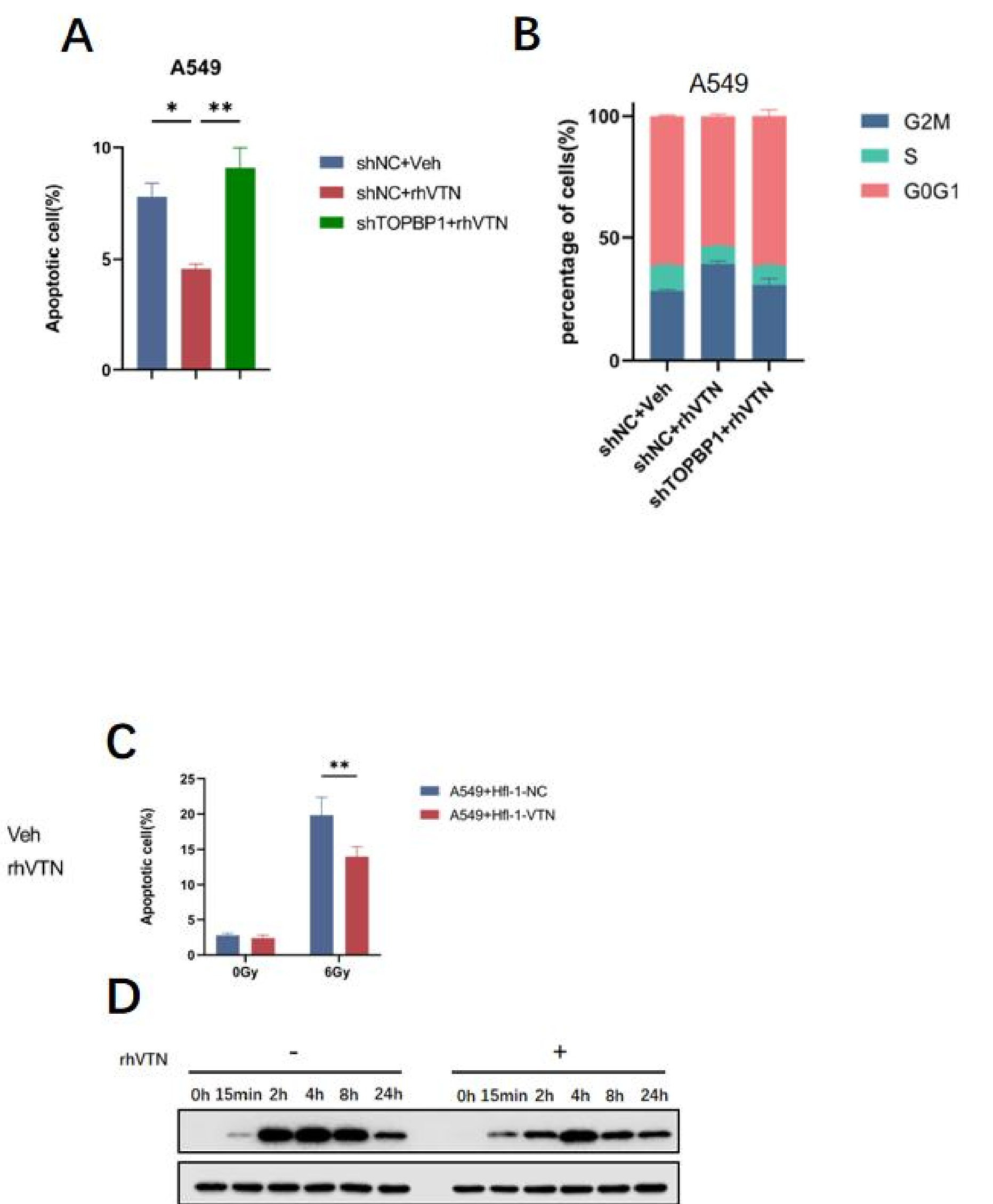


Figure5. TOPBP1 knockdown abolishes VTN-mediated radioresistance



DISCUSSION AND CONCLUSION

Elevated plasma VTN levels at baseline predicts inferior radiotherapy outcomes in patients with NSCLC. CAF-derived VTN drives radioresistance in NSCLC by activating the integrin-FAK pathway, which induces p-STAT3-mediated TOPBP1 upregulation and subsequently enhances ATR-CHK1 signaling and homologous recombination repair.

REFERENCES & ACKNOWLEDGEMENTS

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