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**Targeting MXD1 sensitises pancreatic cancer to trametinib**

Zhang S, Deng S, Liu J, *et al.* Targeting MXD1 sensitises pancreatic cancer to trametinib. *Gut* 2025; 74(8): 1262-1278. doi: 10.1136/gutjnl-2024-333408.

Trametinib is an orally bioavailable mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2 inhibitor. It was first approved for the treatment of melanoma, but its therapeutic potential is now being explored in other cancers, including pancreatic cancer. Initial trials for its use in Pancreatic ductal adenocarcinoma (PDAC) have not met with much success due to the development of drug resistance, which is considered multifactorial. In the present study, Zhang *et al.,* aimed to address this issue using patient-derived xenograft models and multiomic analysis.

They found that trametinib-treated PDAC cells demonstrate resistance through viral mimicry. Many transposable elements (TEs) are overexpressed in PDAC cells treated with trametinib. Additionally, trametinib treatment leads to overexpression of MXD1 (MAX dimerisation protein 1) RNA and protein levels in trametinib-resistant PDAC cell lines. These results show that trametinib-induced MXD1 upregulation promotes TE transcription and dsRNA production, which activates viral mimicry in PDAC cells.

When MXD1 was depleted, PDAC proliferation decreased compared to control, and this effect was more pronounced when PDAC cells were treated with trametinib. These findings confirm that MXD1 may play a protumourigenic role, and its inhibition could help resolve the issue of trametinib resistance in PDAC. Further investigation revealed that PDAC xenografts (PDXs) treated with trametinib and MXD1 inhibitor showed sustained growth suppression, while those treated with trametinib plus control initially responded but later regrew due to resistance.

The targeted therapeutic response of PDAC to trametinib has been limited by drug resistance. The Zhang *et al.,* discovered a potential mechanism for this resistance that could be exploited therapeutically. Hyperregulated viral mimicry, secondary to MXD1 upregulation, causes chromatin remodelling at TE loci, leading to trametinib resistance. The study also shows that inhibiting MXD1 restores trametinib-induced sustained tumour suppression. Moreover, MXD1 appears to act as a tumour promoter in PDAC, contrary to its previously assumed tumour-suppressive role.