Background Pancreatic ductal Adenocarcinoma (PDAC) is an aggressive malignancy complicated by poor early diagnosis and a lack of response to traditional treatments. It is characterized by a desmoplastic stroma, a lack of infiltration and activation of T cells, and a low mutational burden. The genetic landscape of PDAC is defined by activating KRAS mutations (~90%) and p53 alterations (~70%), but the molecular switches perturbed by these genetic aberrations remain unclear. p53 missense mutations, unlike mutations resulting in the loss of p53, are considered to acquire tumor-supporting functions. But these novel functions remain uncharacterized. The majority of p53 mutations are missense mutations in the DNA binding domain. The repertoire of transcription factors (TFs) it can interact with and the vast regulatory landscape of each TF—composed of gene promoters and distal enhancers—present obstacles in understanding the molecular mechanisms promoting PDAC.

Methods In this study, we examined how a common p53 missense mutation in PDAC plays a role in weakening the Immune checkpoint Inhibitors (ICIs) efficacy. Using cells derived from a genetically engineered mouse model of PDAC with activating KRAS mutation (KrasG12D/+) and a p53 missense mutation (p53R172H/−), we found that the PDAC tumorigenesis and resistance to ICIs are dependent on the mutant-p53. We used isogenic p53-null PDAC cells and the restoration of p53R172H in p53-null cells to demonstrate the role of p53R172H in controlling the expression of immunosuppressive chemokine genes such as Cxcl1.

Results p53R172H deletion attenuated PDAC tumor growth, increased the influx of cytotoxic T-cells, and sensitized the tumor to ICIs. The p53R172H-mediated TME reprogramming was replicated by the deletion of the Cxcl1 gene, suggesting the anti-tumorigenic effect of p53R172H was mediated by the Cxcl1 gene. We probed the mechanism of Cxcl1 expression dependence on p53R172H. We found that in conjunction with NF-κB, p53R172H occupies the distal transcription regulatory elements (dTREs) of the Cxcl1 gene harboring NF-κB binding sites. Strikingly, deletion of the Cxcl1 dTREs in PDAC cells recapitulates the phenotypes of p53R172H deletion and Cxcl1 deletion in terms of tumor size, immune landscape of the TME, and ICI responsiveness. Furthermore, we examined the interplay between p53R172H and NF-κB and found that the p53R172H physically interacts with the NF-κB subunit RelA and facilitates its nuclear translocation.

Conclusions Overall, we characterize how a common p53 mutation in PDAC co-opts non-coding regulatory DNA to augment the expression of selective chemokine genes and establishes an immunosuppressive TME to shield the therapeutic benefits of ICIs.

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