MUTANT P53 (MUTP53)-DRIVEN HMGA1 SECRETION PROMOTES PANCREATIC DUCTAL ADENOCARCINOMA (PDAC) PROLIFERATION AND CHEMORESISTANCE

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Pancreatic ductal adenocarcinoma (PDAC) is among the most lethal cancers. In this tumor type mutant p53 (mutp53) has a key role in altering the secretion of many signaling molecules, thus manipulating the tumor microenvironment (TME) to drive tumorigenesis. Since an extensive characterization of cancer secretome may lead to the identification of druggable targets for tumor treatments, we focused our study on the roles of mutp53-dependent secretome in PDAC cells.
Through mass-spectrometry analysis, we detected secreted proteins modulated by mutp53 and, among them, we selected the nuclear high mobility group A1 (HMGA1) for further studies. HMGA1 is an architectural transcription factor involved in several cellular processes and found to be upregulated in several tumors, but its function in cancer remains unclear. We demonstrated that mutp53-dependent secretion of HMGA1 promotes PDAC cells hyperproliferation and resistance to gemcitabine (GEM) treatment in vitro suggesting a critical role of this protein in tumor aggressiveness. This observation is also confirmed by our in vivo data showing that HMGA1 deficiency significantly affects tumor progression. Moreover, we showed that chemotherapy increases HMGA1 secretion only in cells harboring mutp53 with a mechanism that fully relies on the activity of the Casein kinase 2 (CK2). Lastly, since our preliminary data suggest that mutp53-driven secretion of HMGA1 may act in an autocrine/paracrine manner stimulating crucial anabolic and oncogenic pathways, we analyzed which pathways are activated by the secreted HMGA1 by performing phosphoproteomic analysis.
Overall, our study links the secretome of PDAC cells to hyperproliferation and chemoresistance highlighting HMGA1 as a promising secreted target in aggressive PDAC with mutations in TP53 gene thus confirming that the alteration of TME might provide new therapeutic opportunities counteracting chemoresistance in mutp53-PDAC patients.