

Gemcitabine Treatment Causes Dereglulation of Epithelial to Mesenchymal Transition Transcription Factors Transcription and Translation in Pancreatic Ductal Adenocarcinoma Cells

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Context Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease, characterised by limited response to chemotherapeutic treatment and early metastasis, leading to very poor prognosis. Epithelial to mesenchymal transition (EMT), a process finely regulated both at transcription and splicing level, contributes to PDAC invasion and affects the response to chemotherapeutic drugs. The expression of the EMT transcription factor ZEB1 is inversely related to sensitivity cells to gemcitabine treatment. Notably, ZEB1 encodes multiple splice variants that mainly differ in the 5' untranslated region (UTR). However, the biological role of these splice variants in EMT and drug resistance is currently unknown. **Objective** Characterization of the molecular events involved in the acquisition of gemcitabine resistance in PDAC cells. **Methods** PCR analysis of EMT genes; Western blot analysis of proteins of the mTOR pathway; 7-mGTP cap assay of cap-dependent translation; polysomal-RNPs fractioning for analysis of mRNA translation.

Results PDAC cells exposed to gemcitabine for 72 hours up-regulated mesenchymal genes, including ZEB1, which is known to confer chemoresistance. This response is accompanied by inhibition of mTOR pathway and cap-dependent translation, as confirmed by reduced assembly of the translation initiation complex eIF4F. Conversely, cap-independent translation is not impaired by the drug. In this context, ZEB1 splice variants containing different 5' UTRs are differentially loaded on polysomes, suggesting that expression of specific variants allows ZEB1 translation during drug treatment. **Conclusion** Our results show that treatment with gemcitabine alters the expression of EMT genes and that these events are concomitant to important alteration in the translational program. Together, these processes can drive to different translational patterns in presence of gemcitabine, as shown for the ZEB1 variants, which may take part to the mechanisms leading to chemoresistance of PDAC cells.