Adaptive rewiring of oncogenic signaling in response to MTOR blockade in pancreatic cancer

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Background:
Pancreatic ductal adenocarcinoma (PDAC) still carries a dismal prognosis with overall five-year survival of 8% and currently used therapies need urgent improvement. Although preclinical data show that the PI3K-AKT-MTOR pathway is a relevant pathway for therapeutic intervention, clinical trials have failed so far. Therefore, detailed molecular knowledge on how PDAC escape PI3K-AKT-MTOR inhibition is needed.

Methods:
By the use of a dual-recombinase system, which is based on the flippase-FRT (Flp-FRT) and Cre-loxP recombination technologies, we generated a murine PDAC model allowing the genetic analysis of MTOR functions in tumor maintenance and adaption of PDAC cells to the loss of MTOR expression. RNA-seq data were analyzed to find pathways relevant to cope with MTOR deletion. Cross-species validation and pharmacological intervention studies were used to recapitulate genetic data and to develop novel combination therapies. Viability and clonogenic assays were used to validate novel combination therapies.

Results:
Blocking MTOR genetically as well as pharmacologically results in adaptive rewiring of oncogenic signaling with activation of ERK- and AKT- pathways. In addition, analysis of RNA-seq data demonstrated activation of the pro-survival NFκB signaling pathway. In contrast to ERK- and AKT-activation, which occur with latency, activation of NFκB target genes was already detected six hours after MTOR inhibition, an effect blocked by BET inhibitors (e.g. JQ1
or OTX-015). Consequently, MTOR inhibitors (e.g. INK-128) and BET inhibitors synergize in human and murine PDAC models.

**Conclusions:**

Our data demonstrate that MTOR inhibitor induced adaptive expression of NFκB target genes can be blocked by BET inhibitors. MTOR- and BET-inhibitor combination therapies should be further developed in PDAC.