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Get rid of pancreatic cancer by inhibiting garbage disposal? Comment on "UAE1 Inhibition mediates the unfolded protein response, DNA damage and caspase-dependent cell death in pancreatic cancer" by Rehemtulla et al

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Pancreatic ductal adenocarcinoma (PDAC) exhibits with a five year survival rate of under 10% one of the worst survival rates of all cancers. In contrast to declining death rates for nearly all other cancer types, PDAC registers rising rates for both new diagnosis and cancer-related death. Since most of the patients already have a progressed tumor at diagnosis, only small numbers of patients are suitable for a potentially "curative" intended resection. Therefore, the majority of the patients only have the option of palliative chemo- and radiotherapeutic approaches with survival rates of approximately six to twelve months.

In addition to the problem of a late and difficult diagnosis, several molecular alterations in PDAC tumor cells and complex interactions with the microenvironment lead to a profound therapy resistance of PDAC. Besides alterations in inflammatory transcription factor pathways and chemokine signalling pathways in PDAC tumor cells mediating apoptosis resistance [1,8], stress pathways including the ER stress, the proteasome and the unfolded protein response (UPR) are increasingly reported to be suitable targets in PDAC [7].

The group of Rehemtulla [13] now elegantly showed that TAK-243, a small molecule inhibitor of Ubiquitin activating enzyme 1 (UAE1, also called UBA1), induced apoptosis in PDAC cells and a subcutaneous mouse model of the disease. UAE1 is the most abundant of two ubiquitin activating enzymes (UAE) regulating the initial step of the ER stress associated protein degradation (ERAD) pathway, which directs ubiquitin tagged misfolded protein for degradation by the proteasome. In this multistep process UAE1 activates ubiquitin and catalyses its transfer to an ubiquitin-conjugating enzyme (E2). In the last step the ubiquitin ligase (E3) in the ER membrane enables the conjugation of ubiquitin to the target substrate, the misfolded protein, which is then degraded by the proteasome.

In other preclinical models of cancer, especially in lymphatic malignancies, this compound showed promising results in directly inducing apoptosis but also in increasing the response to other conventional cytotoxic therapeutic approaches [9,17]. Strikingly, these effects were also reported in cells resistant to drugs that target other protein degradation pathways, like proteasome inhibitors, indicating divergent molecular mechanisms.

Using a cancer therapy evaluation panel Liu et al. [13] showed that TAK-243 was highly efficient to induce apoptosis in several PDAC cell lines. In addition, they showed that TAK-243 induced ER stress, indicated by the upregulation of BiP, XBP1, ATF4 and its target CHOP. Next to the activation of the caspase cascade a G2/M arrest was inducted. Surprisingly and in contrast to other drugs like NGI-1, tunicamycin or PDI inhibitors targeting upstream events of the protein degradation pathway (please refer to the graphical abstract of Liu et al. for an explanation of axact targets of the drugs [13]), TAK-243 led to an increase of the DNA repair protein RAD51.

The safety of the compound was analysed in a mouse model of PDAC in which the specific anti-tumor effect without relevant side effects was confirmed. However, since UAE1 is reported to be crucial for neuronal health [10] and the reduction of the activity of UAE1 is correlated with several neurological diseases like Parkinson disease, it will be very important to carefully monitor especially neurological side effects.

In contrast to other groups which reported additive and syngeneic effects in combining TAK-243 with doxorubicin, melphalan and

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panobinostat in myeloma cells, Liu et al. [13] did not observe synergy with ionizing radiation or gemcitabine in PDAC cells. They suggested that the TAK-243 mediated stabilization of RAD51 was responsible for this lack of additive effect when DNA damaging radiation or gemcitabine was used. Since TAK-243 alone induced relevant DNA damage and other groups observed an increase in the efficacy of doxorubicin, a DNA damaging topoisomerase inhibitor, when combined with TAK-243 in lymphatic neoplasia, it is likely that beyond the stabilization of RAD51 other mechanism contribute. Several reports indicated that UAE1 is crucial for downstream signalling events initiated by DNA single and double strand breaks [14] and cellular responses like autophagy. In addition, for other enzymes involved in ubiquitination processes, like A20, it has already been reported that under some circumstances the ubiquitination is needed for execution of the cell death decision [4].

Therefore, inhibition of UAE1 might have also pro-survival functions under some circumstances.

When trying to translate these very relevant findings into translational clinical research, one important consideration is that monotherapy with gemcitabine or any other drug failed to show relevant effects in the treatment of PDAC patients. Even if TAK-243 is safely used in animal models, the effects on tumor cells only reflect a higher sensitivity of the tumor cells for manipulation of stress response pathways compared to normal cells. Therefore, it will be important to have the observed limitation in combining TAK-243 with the tested established therapeutic options [13] in mind, when starting to test the drug in clinical trials. With regard of the now well established subtypes of PDAC [2] and the results discussed for the lymphoma cell lines it is tempting to suggest that conventional chemotherapeutics and or radiation are not suitable combination partners for TAK-243 for all subtypes of PDAC. Unbiased pharmacological or CRISPR/CAS screening approaches addressing the subtypes in the model might be better ways to find the best combination strategy to increase the efficacy of TAK-243 in a specific PDAC subtype. The importance of these points – subtypes of PDAC and best combination partner - is evident when reflecting the disappointing results for proteasome inhibitors, which showed promising effects in preclinical PDAC models [1] but failed in clinical trials in PDAC patients when combined with gemcitabine. Such a relevance of subtype specific testing was recently shown, when re-addressing this promising treatment strategy with the proteasome inhibitor Carfilzomib in well-defined subtypes of PDAC [6].

In conclusion, the manuscript by the group of Rehemtulla [13] showed promising results for TAK-243 as a treatment option for PDAC but it will be very important to test TAK-243 in combination with drugs currently used in the first line treatment like FOLFIRINOX or gemcitabine plus Nab-Paclitaxel [15] in a subtype specific manner and more complex preclinical and clinical models of the disease. Since the cells of the microenvironment, especially immune cells and fibroblasts, have major impact on the therapeutic response of PDAC in clinical settings, it will be important to use more sophisticated models. These models, for example organoid models combining tumor cells with cells of the microenvironment [11,12,16] or advanced syngeneic animal models [3,5], should be used to address the question for which subtype und with witch combination TAK-243 could be used for are more efficient therapy of PDAC.

Author contribution statement

Dr. Geismann and Dr. Arlt contributed equally in the writing of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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