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Commentary

Targeting the translational machinery to overcome apoptosis resistance in pancreatic cancer

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A commentary on: Therapeutic effects of an innovative BS-HH-002 drug on pancreatic cancer cells via induction of complete MCL-1 degradation.

The pancreatic ductal adenocarcinoma (PDAC) is predicted to be the second leading cause of cancer-related deaths over the next decade, and it is usually detected at an advanced stage, precluding curative resection [1]. Current therapies for PDAC patients are predominantly based on radiotherapy and chemotherapy using combinations of different cytostatic drugs (e.g. FOLFIRINOX, nab-Paclitaxel + Gemcitabine) [2]. Integration of genomic data has shown that targeted therapies, e.g., targeting the DDR pathway, may be promising and are evolving as tailored therapeutic options [2]. However, many PDAC patients do not benefit from even harsh chemotherapy due to rapid development of drug resistance [3]. Pancreatic cancer is characterized by malfunctions in the execution of apoptosis programs, which contribues significantly to low therapeutic efficacy and resistance.

Cell death occurs in many facets; one variant of programmed cell death is apoptosis, which can be induced intrinsically via the mitochondrial pathway and extrinsically via the death receptor pathway [4]. The intrinsic apoptosis pathway can be triggered in the absence of growth factors, cellular stress, or cell death stimuli like cytotoxic agents and is predominantly controlled by the BCL2 protein family [4]. The family is divided into pro-apoptotic BH3-only proteins, pro-apoptotic pore-forming proteins and anti-apoptotic protector proteins [5]. The anti-apoptotic protector proteins possess all four BCL2 homology domains (BH1, BH2, BH3, and BH4), and include BCL2, BCL-x_L, BCL-w, BCL-B, MCL1, and A1. By directly interacting with the proapoptotic multidomain pore-forming proteins (BAX, BAK and BOK), the protector proteins inhibit the pore-forming proteins and thus apoptosis initiation. In addition to the multidomain pro-apoptotic proteins, the BCL2 protein family consists of the proapoptotic BH3-only proteins such as BIM, BID, BIK, BMF, BAD, HRK, PUMA, and NOXA. By BH3-only protein mediated neutralization of the protector proteins and BH3-only protein binding to the BH3 grove of pore-forming proteins BAX/BAK oligomerize on the outer mitochondrial membrane, resulting in pore formation and cytochrome c release. When APAF1 oligomerizes with cytochrome c, it attracts caspase 9 and forms an apoptosome, which activates caspases 3, 6, and 7 and, in turn, induces substrate cleavage and apoptosis [4,5].

Especially in solid tumors such as pancreatic cancer, the anti-apoptotic protein MCL1 is highly expressed, resulting in an apoptotic imbalance, which leads to a reduced apoptotic activity and ensures pancreatic cancer cell survival [4]. MCL1 is a key factor in resistance to both cytotoxic drugs and targeted therapies. Therefore, combination therapies with MCL1 inhibitors could overcome this resistance.

In the study of Wang and colleagues, the cytotoxic alkaloid homoharringtonine (HHT) derived from the evergreen tree (*Cephalotaxus spec.*) was modified by replacing a hydroxyl group with a carboxylate group, thus changing the secondary structure and improving bioavailability [6]. The therapeutic effect of the resulting compound BS-HH-002 was subsequently investigated in pancreatic cancer cell culture models and xenografts.

By treatment with BS-HH-002, the authors observed a significant apoptosis induction in cell culture models as well as in xenograft models, which was accompanied by a decreased MCL1 expression. The treatment with BS-HH-002 did not affect BCL2 or BCL-x_L expression, but

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significantly reduced MCL1 expression was consistently observed [6].

BS-HH-002 is a derivative of the parent compound HHT (Synribo / Omacetaxine), which was approved in 2012 by the FDA for the treatment of chronic myeloid leukemia [7]. This inhibitor competes with the amino acid side chains of entering aminoacyl-tRNAs that bind in the acceptor or A-site of the ribosome. By blocking the A-site of the large ribosomal subunit, the access of aminoacyl-tRNAs is blocked and thus the translation elongation process is stopped [8]. In contrast to BCL2 with a protein half-life of 10 h [9] and BCL-x_L with a half-life of 18 h [10], MCL1 has only a very short half-life of about 30 min [11], which may explain why MCL1 in particular is affected by global translation inhibition.

In addition to a reduction in MCL1 protein levels, Wang and colleagues showed in several PDAC cell lines that the transcription factor MYC, whose half-life is approximately 20–30 min [12], was also affected by treatment with BS-HH-002[6].

In gastric cancer cells, MCL1 but not BCL-x_L was shown to be transcriptionally controlled directly by MYC [13]. MYC, in turn, orchestrates many biological processes at the transcriptional level and thereby regulates metabolism, apoptosis, proliferation, growth, as well as the cell's most energy-consuming process of protein synthesis, among others through transcriptional regulation of eukaryotic initiation factors (eIFs) [13–15]. Due to the also low *MCL1* mRNA half-life of approximately 3 h [16], treatment with BS-HH-002 likely causes a dual targeting of MCL1 expression by interference of both transcription and translation, explaining the strong suppression of MCL1 expression [6].

In PDAC, the translational machinery is highly regulated and produces a very high protein abundance, which is reflected, among other things, in an increased unfolded protein response [17]. There are many ways to influence translation with pharmacological inhibitors, and individual components of the translational machinery can be specifically inhibited. The drug mechanism and its effect on the target protein and also the pharmacodynamic activity are important factors for clinical success [18]. Further development of natural compounds as shown here for the HHT derivative BS-HH-002 and deciphering the exact molecular mode of action are important components to enable targeting of dysregulated translation in PDAC. Wang and colleagues showed that the inhibition of the translational process by BS-HH-002 showed no serious side effects and higher plasma concentrations than with HHT administration were also achieved, making this compound an attractive candidate for potential combination therapies. A combination of components of standard therapy with substances that inhibit the translational machinery, e.g. by compounds such as BS-HH-002 could reduce resistance and lead immediately to an improved response in PDAC patients.

CRediT authorship contribution statement

Matthias Wirth: Conceptualization, Writing – original draft.

Declaration of Competing Interests

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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