Dysregulation of cell death pathways is a hallmark of cancer progression. Hence pharmacological intervention to restore the apoptotic balance in tumors is considered to be a major objective for current cancer treatment strategies. At the molecular level, apoptosis is orchestrated by pro-apoptotic Bcl-2 family proteins and relies on the dual performance of Bax and Bak proteins, upon activation by BH3-only proteins Bim, Bid or Puma, leading to cell death via mitochondrial outer membrane permeabilization. As a safeguard mechanism, cancer cells rely on Bcl-2 pro-survival proteins (Bcl-2, Bcl-xL, Mcl-1, Bcl-W, Bcl-2A1/Bfl-1 and Nrh/Bcl2L10) to directly bind to the BH3 domain of Bax and Bak, as well as that of BH3-only proteins, via the hydrophobic groove formed by their BH3, BH2 and BH1 domains [5]. From this valuable knowledge gathered during the last three decades, the “BH3-mimetic” class of small-molecules was designed to mimic BH3 binding to the hydrophobic groove of pro-survival Bcl-2 proteins (see Figure 1 below). Currently, these molecules represent the main strategy to restore apoptosis either in combination therapy applications by only inhibiting pro-survival Bcl-2 proteins, or as single therapy agents able to displace Bcl-2-bound Bid, Bim or Puma to re-activate Bax and Bak.

However, growing evidence suggests that limiting the role of pro-survival Bcl-2 proteins to their sole capacity to inhibit Bax, Bak and BH3-only proteins might be incorrect. Indeed, Bcl-2 and Bcl-xL have also been shown to regulate calcium handling at the Endoplasmic Reticulum (ER), mostly by interacting with the Inositol 1,4,5-triphosphate Receptors (IP3Rs). Recently, our group demonstrated that another pro-survival Bcl-2 homolog from the Bcl-2 family, namely Nrh/Bcl2L10 or Bcl-B, could also interact with IP3Rs via its N-terminal BH4 domain. In contrast to Bcl-2 and Bcl-xL, Nrh is mainly found at the membrane of the ER where it was shown to negatively regulate apoptosis induced by thapsigargin or chemotherapeutic drugs by suppressing IP3Rs-mediated calcium signaling (Nougarede et al., 2018). Our study provided a much needed mechanistic insight into the newly uncovered role of Nrh in multiple myeloma [2]. Indeed, Hamouda and colleagues unveiled that the expression of Nrh alone was sufficient to drive tumorigenesis of B-cells in a mouse model, an unprecedented characteristic for a pro-survival Bcl-2 protein, the expression of which is generally considered to be insufficient to elicit a fully transformed phenotype. Further strengthening the relevance of Nrh as a therapeutic target in cancer, its expression was detected in more than 45% of breast cancer patients in a large cohort and was associated with a higher rate of metastatic relapse (Nougarede et al., 2018). Based on the action of Nrh at the ER, we then proposed to use a peptide comprising the sequence of the Nrh BH4 domain (dTAT-NDP), as a decoy to release full-length Nrh from IP3Rs and restore apoptosis in cancer cells. This strategy, involving for the first time a true Bcl-2 protein “BH4-mimetic” molecule, provided promising results by potentiating the action of chemotherapeutic drugs both in vitro and in vivo [4]. Interestingly, the use of the sequence of the BH4 domain as a targeted therapy discriminates Nrh from other Bcl-2 proteins, since it was sufficient, when used alone, to prevent full-length Nrh binding without blocking IP3Rs. It should also be noted that a peptide derived from the Bcl-2 binding site of IP3R was developed to restore apoptosis and IP3R signaling impaired by Bcl-2. This peptide, referred to as BIRD2, acting in fact as a “BH4-antagonist”, was used successfully to trigger...
apoptosis of human primary CLL cells [3]. Moreover, the selectivity of Bcl-2 family proteins towards specific IP3R isoforms, namely Bcl-2 for IP3R2 and Nrh for both IP3R1 and IP3R3, provides an additional level of specificity for therapies targeting the BH4 domains of the Bcl-2 family of cell death inhibitors [1].

One of the challenges facing current BH3-mimetic therapies is the de novo or acquired resistance to selective inhibitors, which is due to the high level of redundancy of the hydrophobic pocket of Bcl-2 family proteins. Using BH4-mimetics or -antagonists could be a means of alleviating resistance to therapy and sensitizing cancer cells to apoptosis. This concept was recently illustrated by using the BIRD-2 peptide to sensitize diffuse large B-cell lymphoma cell lines that were resistant to the FDA-approved Bcl-2 specific inhibitor ABT-199, or Venetoclax [6].

Nevertheless, several ongoing issues have to be addressed to facilitate the transfer of BH4 modulators into clinical applications, including (i) gaining a better understanding of their pharmacodynamic and pharmacokinetic properties, and (ii) investigating the possibility of using BIRD-2 and TAT-NDP peptides directly or replacing them by other kinds of small molecules.

Finally, it is worth noting that BH4-mimetics or -antagonists are not an attempt to replace BH3-mimetic therapies in the future, but rather offer a highly specific complementary tool to improve the success of current anti-cancer strategies.

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