Journal of Rashid Latif Medical College 1 (2022) 7-9

Journal of Rashid Latif Medical College

journal homepage: www.jrlmc.org

Expert Opinion

Agents Targeting Apoptosis Take Center Stage in the Battle against Cancer

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Effective therapy of cancer requires elimination of tumor cells through programmed cell death or apoptosis, which is a highly regulated process that avoids the unwanted inflammatory response when cells die. Morphologically, the manifestation of apoptosis is similar across various cell types and species, and is observed as a series of cellular changes that begin with chromatin condensation, followed by nuclear fragmentation, cell shrinkage, blebbing and finally phagocytosis[1,2]. When tumor cells are exposed to therapeutic agents, the damage to cellular organelles or macromolecules creates substantial intracellular stress, which triggers the onset of the apoptotic cell death program. DNA is a well-known target of several classes of antitumor agents, such as anthracyclines, alkylating agents, platinum-based drugs and ionizing radiation, and the stress induced by DNA damage results in a cascade of signaling events, which result in modulation of a large number of proteins, including enzymes and transcription factors that coordinate the cell death program. One such protein is the tumor suppressor p53, which has a central role in apoptosis, but its mutation in about 50% of all cancers inhibits transcriptional activation of downstream genes and suppresses the apoptotoic stimuli[3]. This impairment in p53 function essentially renders tumor cells resistant to therapeutic antitumor agents, including the kinase targeted inhibitors, such as imatinib (Gleevec) and gefitinib (Iressa)[4,5].

It is important to note that mutation of p53 is not a prerequisite for rendering it ineffective as an inducer of apoptosis. Indeed, several cancers, such as mesothelioma, renal cell carcinoma and non-small cell lung cancer, predominantly express wild-type p53, but are generally resistant to a variety of therapeutic strategies[6]. Moreover, such refractory cancers may express the phenomenon of a gain-of-resistance phenotype, which is directly attributable to wild-type p53[6]. This is contrary to expectations, and reveals an unexpected novel function of wild-type p53 that correlates with greater resistance of the tumor cell as compared to cells harboring mutant p53.

Apart from functional loss of p53 and other pro-apoptotic proteins, a host of other mechanisms can also attenuate the apoptotic stimuli, and these can generally be grouped into failure of the surveillance system to detect DNA dmage, downregulation of pro-apoptotic regulatory pathways and upregulation of survival pathways[6,7]. Such negative alterations upstream in the tumor cell can impact both the extrinsic (involving caspase-8) and intrinsic (involving caspase-9) pathways of apoptosis, and this can create an unfavorable balance between pro-survival and pro-death signals toward surival. This understanding has spurred the rational development of therapeutic options that are designed to directly activate the cell death program, and some of these are shown in Figure 1 and discussed below.

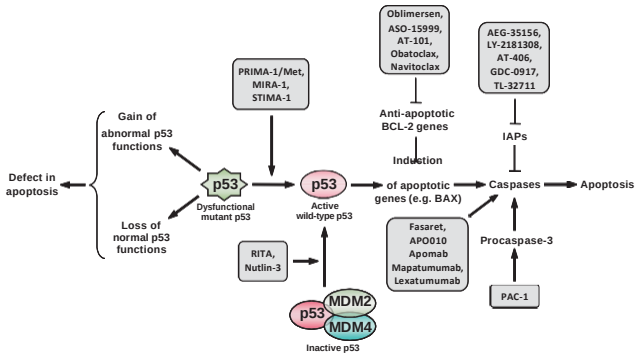

Figure 1: Stimulating the apoptotic pathway with novel agents in development

An obvious downstream target is procaspase-3 to generate the active caspase-3, which not only is the terminal executioner protein, but also is common to both the extrinsic and intrinsic pathways of apoptosis. Moreover, procaspase-3 is overexpressed in a variety

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of tumor types[8], and agents such as PAC-1 have been identified for their potential to take advantage of this overexpression and generate active caspase-3 intracellularly in effective quantities[9]. However, overexpression of inhibitors of apoptosis (IAPs), particular the more potent XIAP and survivin, may downregulate caspase activities. In this case antisense targeting of IAPs with AEG-35156 and LY-2181308 can be effective at both preclinical and clinical levels[10,11]. The IAPs are usually negatively regulated endogenously by SMAC/DIABLO, and consequently SMAC/DIABLO mimetics (e.g., AT-406, GDC-0917 and TL-32711) have entered clinical trials to take advantage of their capacity to inactivate the IAPs and restore caspase activity[11,12].

A major apoptotic target upstream of caspases is p53. In its wild-type state, p53 can be inactivated by overexpression of the p53-binding MDM2 protein. To inhibit this binding and reactivate p53, RITA and Nutlin-3 have been developed as prototype drugs, which are presently undergoing preclinical and clinical development, respectively[13,14]. Mutant p53, particularly the more problematic gain-of-function mutants, has also received attention, with several agents in development to enforce conformational change and rescue wild-type p53 function. Clinical trials of the small molecule PRIMA-1/Met have been intitiated, and others, such as MIRA-1 and STIMA-1 are in preclinical development to affect the rescue[15-17].

Between p53 and caspases along the intrinsic apoptotic pathway are a number of proteins related to the BCL-2 family, members of which have important roles in apoptotis, having either pro-apoptotic or anti-apoptotic effects. Some members are in fact targets of wild-type p53 to promote the apoptotic process, with the proapoptotic targets BAX, NOXA, PUMA nad BID upregulated and antiapoptotic target BCL-2 downregulated[18,19]. However, in absence of p53 function, antiapoptotic members of the BCL-2 family can be targeted to tip the balance in favor of apoptosis. Antisense (oblimersen and ASO-15999) and small molecule inhibitors and antagonists (AT-101, obatoclax and navitoclax), for instance, attenuate the effects of BCL-2 and related family members to prime tumor cells for apoptosis[20-23]. In a similar manner, the extrinsic pathway has also been targeted to activate apoptosis by stimulating the extracellular TNF-R1, DR4/5 or Fas receptor with cognitive ligands TNF-á, TRAIL or FasL ligands, respectively, using adenoviral vectors to mediate overexpression. The vector Fasaret encoding FasL is such an example, although the synthetic hexameric FasL ligand APO010 has also been effective in activating the Fas receptor[24]. Agonistic antibodies, such as apomab, mapatumumab and lexatumumab, on the other hand, have been developed to directly activate the DR4 and DR5 death receptors[25].

It is clear that apoptosis is finally receiving due attention as a means to advance cancer chemotherapy in a more rational manner. Many of the strategies discussed here are still in investigational phase, either preclinically or clinically, but the overall approach holds much promise and is likely to lead to more effective therapeutic options for care of the cancer patient in the near future.

Acknowledgement

The author is grateful for research support from the U.S. Public Health Service grants CA127263 and CA160687, Support Grant CA16672 to MD Anderson Cancer Center from the National Cancer Institute, and in part from the Megan McBride Franz Endowed Research Fund.

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