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Emerging Paradigms for Small Molecules-Based Therapies Targeting P53 in multiple myeloma

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Multiple Myeloma (MM) is a plasma cell malignancy characterized by the accumulation of malignant plasma cells in the bone marrow [1]. Despite recent advances in the introduction of the new drugs MM is still an incurable disease for its resistance to current therapies [1, 2]. Understanding the mechanisms of programmed cell death or apoptosis is essential for the development of novel interventions to improve the survival of cancer patients. p53, a tumor suppressor protein with its ability to induce apoptosis and being central to pro-apoptotic signalling in cancer therapy, has been used as a target for cancer therapy for the past two decades. p53 senses various stress signals and upon activation p53 coordinates a diverse cellular stress response. These responses prevent the accumulation of cancer cells and are important for the function of p53 as well as for cellular responses to cancer therapy. The tumor suppressive function of p53 is frequently lost in human cancers which can be mediated either by mutations or deletions within the p53 gene itself, or by over-expression of its negative regulators such as MDM2. Thus, modulation of p53 pathway activity may target any of the above factors [2, 3]. This general strategy is being extensively explored through a variety of approaches. In view of this, novel small-molecule activators of p53 have been discovered through biochemical and cell-based screens. Several of these identified small molecule compounds demonstrated antitumor activity in preclinical models, and a few of those have entered clinical trials [2, 3].

Due to the fact that newly diagnosed cases of MM are mostly presented with wild type p53, attempts have been made to identify and evaluate small molecule compounds that are able to activate wild type p53 through inhibition of the interaction between p53 and MDM2. Of the low molecular weight antagonists that inhibit MDM2-p53 interactions, the most investigated so far are the nutlins [4]. RG7112, a derivative of nutlin, has been in clinical trials in patients with leukemias and sarcomas [3]. Preclinical studies on nutlin indicated that anti-myeloma activity of nutlin has been limited to wild type p53 [5-8]. Mechanistically, nutlin-induced apoptosis in MM cells was shown to be mediated by both p53-transcription dependent and independent pathways suggesting that transcriptional and mitochondrial functions of p53 are equally important for Nutlin-triggered apoptosis [6]. Another small molecule inhibitor of the p53-MDM2 interaction named as RITA, identified by cell based screen, was initially described as a wild type p53 activating compound [9, 10]. However, two independent studies reported p53-independent anti-myeloma activity of RITA [8, 11]. Studies by Jones et al. showed that RITA potently induced cell cycle arrest and apoptosis in resistant cells which were found to harbor p53 mutations after prolonged exposure to both nutlin-3 and MI-63 [11]. A most recent study by Surget et al. described anti-myeloma activities of RITA in a large number of MM cell

lines and patients samples bearing wild type, mutant or null p53 [8]. These studies explained the previous observations for activation of JNK signaling pathway by RITA in addition to p53 signaling in MM cells suggesting multiple target sites for RITA [8, 12]. Although p53 mutations are common in cancer, they are not universal. For example, mutation of p53 gene is a rare occurrence at diagnosis of MM; however, the incidence increases as the stage of disease advances [1-3]. Importantly, mutations/deletions of p53 have been associated with poor prognosis and survival. Furthermore, these subgroup of patients often show resistant to current therapies [1-3]. These findings, together with the evidence that mutant p53 is usually expressed at high levels, render mutant p53 as an important study target for cancer therapy. In view of this, p53 mutant reactivating agents have been developed.

Of these, the most widely investigated are PRIMA-1 (also known as APR-017) and PRIMA-1^{Met} (now named as APR-246). PRIMA-1 was originally discovered by screening a library of low molecular weight molecules for their ability to restore the tumor suppressive properties of mutant p53 [13]. Although initial reports with PRIMA-1 or PRIMA-1 ^{Met} indicated that their anti-tumor activity was dependent on the presence of mutant p53 in different solid tumor types [3,13] recent finding in MM suggest that PRIMA-1 ^{Met} can induce apoptosis of MM cells independent of p53 expression and p53 status [14,15]. Mechanistic evidence suggested that PRIMA-1 ^{Met} induced apoptosis and inhibited cell growth via induction of p73 and Noxa [14, 15] or by induction of ROS [15]. Currently, PRIMA- 1^{Met} is undergoing a proof of concept phase Ib/II clinical trial in patients with prostate or ovarian cancer and different types of hematologic malignancies [16]. While PRIMA-1^{Met} has been mostly investigated drug among the small molecule p53 activators, several other molecules including CP31398, MIRA-1, MIRA-3, STIMA-1, RETRA-1 have also been reported to restore active function of mutant p53. MIRA-1, structurally distinct from PRIMA-1, is a small molecule compound that targets mutant p53 with higher potency than PRIMA-1 [17]. First investigation of MIRA-1 in MM showed its anti-myeloma activity independently of p53 status similar to PRIMA-1 ^{Met} [18]. In contrast to both PRIMA-1 ^{Met} and MIRA-1 which appear to work on MM cells irrespective of p53 status, some of these compounds bind preferentially to specific mutant forms of p53. The effect of such molecules in MM cells has yet to be studied.

Furthermore, additive or synergistic responses have been found between the anticancer activity of the described small molecules and both clinically-approved and investigational agents in MM cells of different p53 status. For instance, nutlin displayed wide synergy with various conventional chemotherapeutic drugs, e.g., melphalan, etoposide, lexatumumab, and velcade [5, 7, 19]. Synergistic response of RITA was found with nutlin, dexamethasone or MI-63 [10, 11]. In the case of the mutant p53-targeting compound PRIMA-1^{Met} or MIRA-1, synergy has been observed with chemotherapeutic drugs including dexamethasone, doxorubicin, or velcade [14, 18]. Synergistic response of PRIMA-1^{Met} or MIRA-1 with dexamethasone and PRIMA-1^{Met} with L-Buthionine SulphOximine (BSO), an irreversible inhibitor of γ-Glutamyl Cysteine-Synthase (g-GCS) was demonstrated in both in vitro and in vivo model [14, 15, 18]. Such combination therapy will be helpful to prevent the emergence of resistant clones as well as reduce the toxicity of the drugs.

These latest agents might lead to a paradigm shift in the treatment of patients with MM. Understanding the precise mechanism of action of these drugs along with their targets would aid in the future design of a novel and improved compound for the treatment of MM. Further investigations in this aspect are strongly required to clarify the many questions regarding the optimal use and sequence of these agents as well as to understand the versatility of the drugs while maximizing its killing capacity.

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