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Short Commentary Open Acces

Twin-Blade of a novel IMPDH Inhibitor FF-10501

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ABSTRACT

Since chemoresistance hampers a remission and results in a relapse of the patients with cancers, new approaches that do not rely on the existing strategies are needed. FF-10501 is a novel inhibitor for inosine monophosphate hydrogenase (IMPDH), a promising therapeutic target for cancer because IMPDH2 has been reported to be overexpressed in a variety of cancers. We previously reported the mechanism of cell death induced by FF-10501 using hematological malignant cell lines. FF-10501 induces not only apoptosis in a caspase-dependent manner but also induced non-apoptotic cell death. FF-10501 has the potential to be therapeutic drug for cancer and to overcome chemoresistance arise from apoptosis resistance.

Keywords: FF-10501, apoptosis, non-apoptosis, caspase-8, ER stress

Commentary

Treatment of cancer has been substantially improved owing to the development of chemotherapeutic drugs. However, lower responsiveness and resistance to chemotherapy hamper the remission and result in a relapse. Therefore, new approaches that do not rely on the existing strategies are needed.

Inosine monophosphate hydrogenase 2 (IMPDH2) is a promising target for the treatment of cancer. IMPDH consists of two isoforms: IMPDH1 and IMPDH2. Both isoforms are ubiquitously expressed in various tissues but IMPDH2 is increased in a variety of cancers including hematological malignancy. Therefore, many IMPDH inhibitors have been developed as anticancer drugs.

FF-10501 is a novel IMPDH inhibitor developed by FUJIFILM. This agent is promising in cancer treatment because MBR-108, a former code of FF-10501, showed significant antitumor effects for chronic myeloid leukemia and myelodysplastic syndromes with lower toxicity in clinical trials. Recently, new clinical trials for myelodysplastic syndromes and acute myeloid leukemia have been conducted in the United States.

We previously investigated the mechanism of cell death induced by FF-10501 [1]. We treated twelve cell lines derived from different hematological malignancies to see the antitumor spectrum of FF-10501 and found that the clinically relevant dose of FF-10501 significantly inhibited the growth of ten of twelve cell lines. This result suggests that FF-10501 has an anticancer effect on a broad range of hematological malignancies. Among twelve cell lines, a clinically relevant dose of FF-10501 not only arrested growth not only induced cell death in three cell lines; MOLM-13, MOLT3, and OCI-AML3 cells. MOLM- 13 cells are derived from acute myeloid leukemia (AML) classified by M5a in French-American-British (FAB) classification harboring gene mutation such as MLL/AF9 and FLT3-ITD. OCI-AML3 cells are established from the patients with AML FAB M4 harboring mutations on DNMT3A, NRAS, and NPM1. MOLT-3 is an acute T-cell leukemia cell line harboring mutation in NOTCH1, NRAS, and PTEN. Like these, sensitivity to the cytotoxic effect of FF-10501 seems to be independent of gene mutations above.

FF-10501 induced loss of mitochondrial membrane potential, the activation of caspase-8 and caspase-3, and DNA cleavage detected by TUNEL assay in MOLM-13 and MOLT-3 cells. Although pan-caspase inhibitor Z-VAD-FMK suppressed the activation of caspase-8 and caspase-3, this agent unexpectedly did not block FF-10501-induced cell death. However, Z-VAD-FMK reduced apoptotic cells detected as Annexin V+propidium iodide (PI)− population by flow cytometry while increased dead cells at a late phase of cell death (Annexin V+PI+ cells), suggesting caspase-dependent pathway could be associated with FF-10501-induced cell death. At the same time, these results strongly suggested the existence of other mechanisms by which FF-10501 induces cell death. A previous study reported that other IMPDH inhibitor VX-944 induced cell death via apoptosis-inducing factor (AIF) and endonuclease G (Endo G) pathway. Therefore, we assessed the expression of AIF and Endo G in the nucleus of FF-10501-treated cells. However, FF-10501 did not change the intranuclear expression levels of AIF and Endo G. In this instance, the caspase-independent cell death mechanism was unclear.

OCI-AML3 cells annoyed us because FF-10501 did not activate caspase-8, caspase-3, and PARP. Besides, Z-VAD-FMK did not affect the cytotoxic status of FF-10501 in these cells.

Several studies described that Annexin V+PI+ cells represent necrotic cells. Therefore, we next investigated whether FF-10501 induced necrotic cell death. Indeed, FF-10501 increased Annexin

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V+PI+ cells but not Annexin V+PI− cells. Apoptosis has been believed to be the only form of programmed cell death until necroptosis has been discovered. Necroptosis shows morphological features that resemble apoptosis, whereas mechanical features resemble necrosis. Since necroptosis is mainly mediated by a pathway consisting of receptor-interacting protein kinase (RIPK)-1, RIPK3, and mixed lineage domain-like pseudokinase. Therefore, we investigated the effect of necrostatin-1, a specific RIPK1 inhibitor, on FF-10501-induced cell death in OCI-AML3. However, necrostatin-1, unfortunately, did not affect the cell death induced by FF-10501. Stress in the endoplasmic reticulum (ER stress) has been reported as one of the other mechanisms for inducing necroptosis independent of caspase activation. Indeed FF-10501 induced the expression of CCAAT-enhancer-binding protein homologous protein (CHOP), a hallmark of ER stress, in OCI-AML3 cells but not in MOLM-13 and MOLT-3 cells, suggesting that FF-10501 induced ER stress in OCI-AML3 cells. We next investigated the effect of 4-phenyl butyric acid (4-PBA), a chemical chaperon working on suppression of ER stress by stabilization of higher-order structure of proteins, on FF-10501-induced cell death in OC-AML3 cells. 4-PBA significantly inhibited the CHOP induction and cell death in a dose-dependent manner. Interestingly, 4-PBA decreased Annexin V+PI+ cells but not Annexin V+PI− cells. These results suggest that FF-10501 induced necrotic cell death in OCI-AML3 cells. OCI-AML3 cells bear the mutant NPM1, which is observed in 35% of patients with AML. Mutant NPM1 has been demonstrated to suppress caspase-8 through direct interaction with caspase-8, associating with apoptosis resistance. It makes sense that FF-10501 was not able to activate caspase-8 in OCI-AML3 cells. Interestingly, FF-10501 was able to cell death apoptosis resident cells such as OCI-AML3 cells. The evasion from apoptosis is often responsible for tumorigenesis and drug resistance. Therefore, developing approaches to induce non-apoptotic forms of programmed cell death as alternative therapeutics is attractive.

Our previous research addressed the mechanism of FF-10501-induced cell death and demonstrated that FF-10501 induced apoptosis through a caspase-dependent pathway. FF-10501 also induced non-apoptotic cell death via ER stress in case the apoptosis pathway is impaired in the cancer cells. Considering the low toxicity of FF-10501 demonstrated by clinical study, FF-10501 could be a promising therapeutic drug for cancer.

References

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