SETting OP449 into the PP2A-Activating Drug Family

Paolo Neviani1 and Danilo Perrotti2

The protein phosphatase 2A (PP2A) tumor suppressor is inactivated in different leukemias through the activity of its endogenous inhibitors (e.g., SET), which are aberrantly regulated by oncogenic tyrosine kinases. Like other effective and nontoxic PP2A-activating drugs (PAD), OP449 inhibits SET and impairs leukemogenesis. This further supports the immediate use of PADs in patients with leukemia. Clin Cancer Res; 20(8): 2026–8. ©2014 AACR.

In this issue of Clinical Cancer Research, Agarwal and colleagues (1) identified OP449 as a new PAD (PP2A-activating drug) with antileukemic activity toward tyrosine kinase inhibitor (TKI)–resistant chronic myelogenous leukemia (CML) and acute myelogenous leukemia (AML) cell lines and primary patient samples. OP449 is a novel, cell-penetrating peptide able to interact with the SET oncoprotein.

SET is a potent endogenous inhibitor of the tumor suppressor protein phosphatase 2A (PP2A; Fig. 1; ref. 2). This phosphatase is known to be a negative regulator of several survival and proliferation pathways that are frequently activated in malignancies as a result of aberrant activation of oncogenic kinases (2). In light of several recent reports showing that PP2A is frequently functionally inhibited in numerous solid tumors and leukemias (2), there is a considerable interest in the development of compounds that can induce the activity of PP2A and counteract oncogenic signals. Because of the complexity of the network of PP2A regulatory subunits and binding partners (reviewed in ref. 2), inhibition of the activity of PP2A can be achieved at multiple levels: for example, through loss of its structural A subunit, mutations of one or more of its several interchangeable regulatory B subunits, or alterations of its endogenous inhibitors and binding partners (e.g., SET, CIP2A, and SETBP1; ref. 2).

In CML, AML, JAK2V617F+ myeloproliferative neoplasms (MPN), and Philadelphia-positive B-cell acute lymphoblastic leukemia (ALL), inhibition of PP2A is essential for leukemogenesis (Fig. 1; ref. 2). PP2A is functionally inhibited as a consequence of the overexpression and/or posttranslational modifications (e.g., phosphorylation) of SET, which results in an overall inhibition of PP2A phosphatase activity in both leukemic progenitors (3–7) and stem cells (8). Genetic (SET short hairpin RNA–mediated downregulation) or pharmacologic (i.e., PADs) restoration of PP2A activity halts malignant cell survival and proliferation both in vitro and in different animal models of leukemia (1, 3, 4, 6, 8, 9).

PADs that, like the synthetic peptide OP449, directly bind SET and/or interfere with its PP2A-inhibiting function, not only have strong prosapoptotic activities toward leukemic stem/progenitor cells but also have a desirable nontoxic profile in ex vivo primary cells and long-term animal studies (1, 2, 9). In this regard, it is noteworthy that the orally available sphingosine analogue FTY720 (fingolimod, Gilena; Novartis) is a PAD with strong antileukemogenic activity and that its adverse effects in relapsing patients with multiple sclerosis (i.e., bradycardia and atrioventricular conduction block) are not only clinically manageable and observed at the time of FTY720 therapy initiation but they can also be avoided with the use of FTY720 nonimmunosuppressive derivatives (e.g., OSU-2S and S-FTY720-regiosomer), which, like FTY720, are also active against CML stem cells and CD34+ progenitors from CML patients refractory to TKIs (2, 4, 7, 8).

Although CML that is diagnosed early in the chronic phase is currently very well managed with TKIs (e.g., imatinib, nilotinib, dasatinib, and ponatinib), a small but significant percentage of these patients still develop resistance or intolerance to one or more TKIs and are likely to progress to the still fatal blastic phase of the disease (10). Conversely, the prognosis of AML is still very dismal and the current therapeutic options are greatly limited due to the vast heterogeneity of the disease and, mostly, rely on standard chemotherapy and, ultimately, bone marrow transplantation (11). Thus, PADs, which antagonize both oncogenic kinase–dependent and kinase–independent signals while sparing normal hematopoiesis (2), represent a very promising class of anticancer drugs that can be used alone or in association with either kinase inhibitors or traditional chemotherapy.

References


Note: P. Neviani and D. Perrotti contributed equally to this work.

Corresponding Author: Danilo Perrotti, University of Maryland, The Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, Maryland E-mail: dperrotti@som.umaryland.edu

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PADs are very effective and selective drugs in several types of tumors demonstrated to have low PP2A activity (2). The small peptide OP449 (also known as COG449) has also been previously reported to exert antineoplastic potential in chronic lymphocytic leukemia and non-Hodgkin lymphoma cells, likely through direct binding to SET and mouse cell lines and induction of apoptosis in TKI-sensitive and TKI-resistant cells (T315I and E255V/T315I BCR–ABL1). Interestingly, when used in combination with first-generation TKIs, OP449 and other PADs exert their antileukemic activity upon interaction with SET and inhibition of its ability to interact with PP2A catalytic subunit (PP2Ak) and inhibit PP2A phosphatase activity.

OP449 impairs myeloid leukemogenesis (1) totally supersedes its antileukemic activity correlated with inhibition of major signal transducers (e.g., STAT5, AKT, and ERK) found activated in AML cells (1) and also described as direct and/or indirect targets of PP2A phosphatase activity (Fig. 1; ref. 2).

Finally, the authors assessed the effect of combinations of OP449 with known FLT3 and JAK (Janus-activated kinase) kinase inhibitors in MOLM-14 and CMK cells, harboring FLT3–ITD and JAK3A572V mutations, respectively, and found that the drug combination (TKI + PAD) had a synergistic cytotoxic effect on these leukemic cells (1), further indicating that the combination of kinase inhibitors and PADs may be a valid therapeutic option for these acute leukemias (Fig. 1). Consistent with this observation, it has been reported that the combination of imatinib and FTY720 exerts a more powerful proapoptotic effect toward primary CD34+ progenitors from CML chronic phase and blast crisis patients (8). The ability of PADs to potentiate the proapoptotic effect of TKIs, and vice versa, is not surprising. In fact, PAD-induced PP2A reactivation not only results in silencing and/or degradation of oncogenic tyrosine kinases (e.g., BCR–ABL1, Jak2, and KIT; refs. 2, 7), but it can also permanently switch off signaling pathways found aberrantly activated in all AMLs and ALLs (2, 11).

Thus, the data presented in this issue of Clinical Cancer Research by Agarwal and colleagues (1) reinforce the central role played by PP2A as a central regulator of cell homeostasis capable of restraining aberrant proliferating and survival signals generated by the activity of different oncogenic kinases. Moreover, their observation that the SET antagonist OP449 impairs myeloid leukemogenesis (1) totally supports both the immediate recognition of this and other
PADs as clinically relevant anticancer drugs that need to be introduced into therapeutic protocols for patients with hematopoietic and nonhematopoietic malignancies characterized by functional loss of the PP2A tumor suppressor.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References

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Writing, review, and/or revision of the manuscript: P. Neviani, D. Perrotti

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