Editorial: Combined inhibition of SHP2 and mutated RTKs prevent adaptive resistance in leukemia

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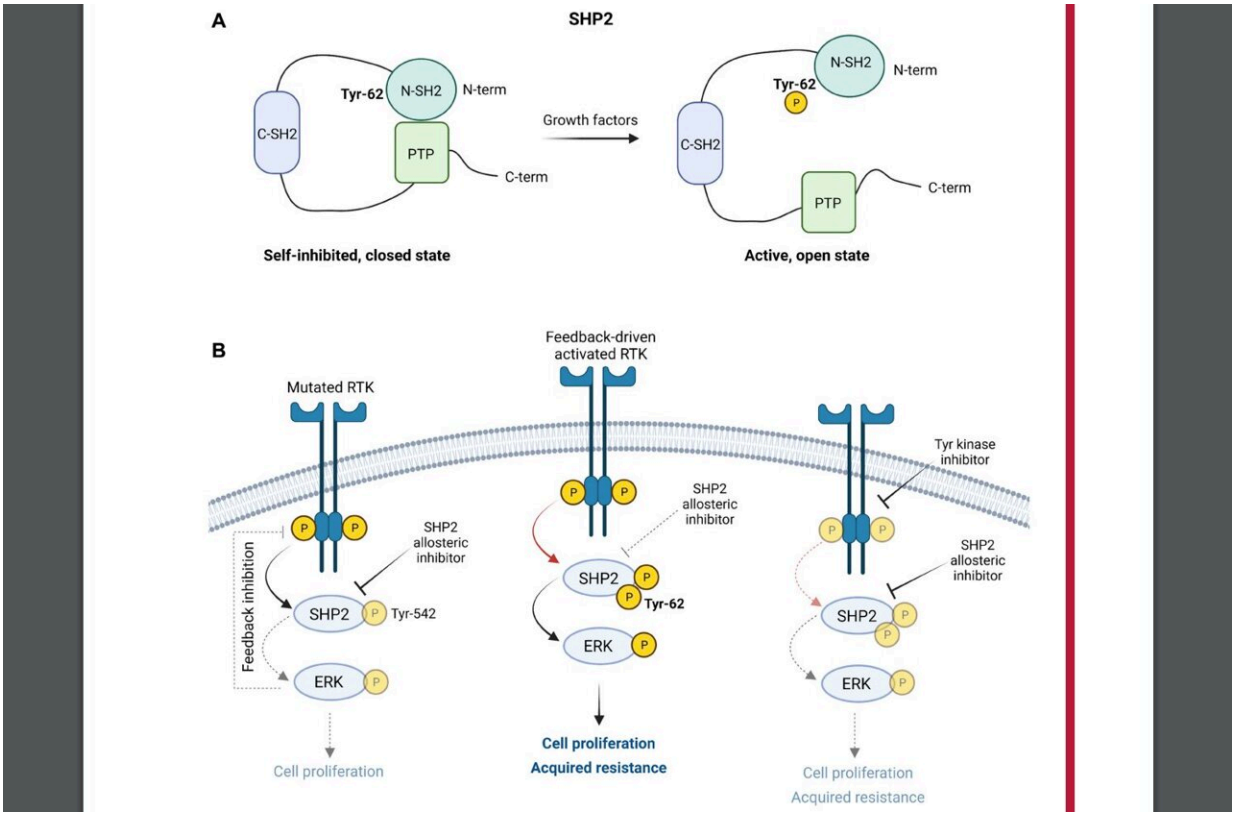

Graphical illustration of the main findings from Pfeiffer et al., Cancer Research, 2022. Credit: *Oncotarget* (2023). DOI: 10.18632/oncotarget.28392

A new editorial paper was published in *Oncotarget*, titled "Impact of

SHP2 tyrosine phosphorylation on the development of acquired resistance to allosteric SHP2 inhibitors."

The SH2 domain-containing tyrosine phosphatase 2 (SHP2) is a ubiquitously expressed non-receptor protein tyrosine phosphatase, encoded by the PTPN11 gene. It is positively regulated by upstream receptor tyrosine kinases (RTKs) to activate downstream the RAS-ERK pathway.

In this new editorial, researchers Giulia Franciosa and Jesper V. Olsen from the University of Copenhagen discuss potential leukemia therapies that effectively prevent adaptive resistance. Acute myeloid leukemia (AML) is a bone marrow malignancy characterized by a blockage of differentiation and an uncontrolled proliferation of myeloid hematopoietic progenitor cells.

The internal tandem duplication (ITD) in the juxtamembrane domain of the RTK FLT3 is an oncogenic driver mutation that leads to constitutive activation of its tyrosine kinase activity. Consequently, FLT3 inhibitors that block its tyrosine kinase activity represent the targeted treatment option for patients with FLT3-ITD AML, often administrated in combination with induction chemotherapy.

"Nevertheless, the short duration of remission urges the development of novel combinatorial therapies for FLT3-ITD AML," the researchers write.

Since 2016, several potent and selective allosteric, noncovalent SHP2 inhibitors have been developed and tested in clinical trials for solid tumors. A recent study reported the effectiveness of short-term treatment with the allosteric SHP2 inhibitor SHP099 as a single agent in clinically relevant mouse models of Flt3-ITD AML. This observation was in contrast with published data showing that allosteric SHP2

inhibition is only effective as combination treatment with inhibitors of other nodes of the RAS-ERK pathway.

In a research article published by Pfeiffer et al., the Olsen's lab at University of Copenhagen showed that two commercial FLT3-ITDpositive AML cell lines (MV-4-11 and MOLM-13) developed adaptive resistance after prolonged treatment in vitro with the allosteric SHP2 inhibitor SHP099.

"All in all, the findings by Pfeiffer et al. suggest that combined inhibition of SHP2 and mutated RTKs are effective in preventing adaptive resistance, but also highlight the need for development of more potent and effective SHP2 inhibitors and combination therapies for clinical applications," the researchers conclude.

More information: Giulia Franciosa et al, Impact of SHP2 tyrosine phosphorylation on the development of acquired resistance to allosteric SHP2 inhibitors, *Oncotarget* (2023). DOI: 10.18632/oncotarget.28392

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