

Abstract

SAMHD1 Is a Modulator of Nucleos(t)ide Analogues' Efficacy [†]

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Abstract: Nucleos(t)ide analogues are commonly used in the treatment of infectious disease and cancer. SAMHD1 is a deoxyribonucleotide (dNTP) triphosphohydrolase which is involved in the regulation of the intracellular dNTP pool, whose function has been linked to viral restriction, cancer development, and autoimmune disorders. Here, we evaluate SAMHD1 function on the antiviral and antiproliferative efficacy of a wide range of nucleos(t)ide analogues which are currently used to treat infections and cancer. The anti-HIV-1 and cytotoxic activity of compounds was assessed in primary and established cell lines in the presence or absence of SAMHD1. SAMHD1 effectively modified the anti-HIV-1 activity of all the nucleos(t)ide analogues tested, whereas sensitivity to a non-nucleoside inhibitor (nevirapine) or nucleoside phosphonates (cidofovir and tenofovir) was not affected. Interestingly, SAMHD1 could either enhance (gemcitabine, capecitabine, fluorouracil, and floxuridine) or inhibit (Ara-C, fludarabine, cladribine, clofarabine, and nelarabine) the antiviral potency of anticancer analogues, an effect that was not dependent on the specific nucleotide targeted. When cytotoxicity was evaluated, SAMHD1-dependent changes were less evident and were restricted to the increased efficacy of fluorouracil and floxuridine and reduced efficacy of nelarabine and ara-C in the presence of SAMHD1. In summary, our results demonstrate that SAMHD1 modifies the efficacy of a wide variety of nucleoside analogues which are used to treat infections, cancer, and other diseases. In addition, the anti-HIV activity of nucleos(t)ide analogues may represent a more sensitive measure of SAMHD1's impact on drug efficacy. Thus, modulation of SAMHD1's function may constitute a promising target for the improvement of multiple therapies.

Keywords: SAMHD1; dNTPs; nucleoside analogues; HIV



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