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Dinaciclib effectively inhibits AKR1C3, a promising therapeutic target for cancer treatment

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Dinaciclib (MK-7965, SCH727965) is a cyclin-dependent kinase inhibitor. Dinaciclib recently enters Phase III clinical trial for the treatment of leukaemia. The results of the study shows its promising anti-leukemia activity and a tolerability. Dinaciclib causes apoptosis to several cancer cell lines, including those that are resistant to anthracyclines. The reductive metabolism of anthracyclines to their secondary C13-hydroxy metabolites is one of the main mechanisms leading to cancer resistance. To date, this kind of metabolism has been associated with members of the short-chain dehydrogenase/reductase (SDR) and of aldo-keto reductase superfamilies (AKR). In our study, dinaciclib was identified as an effective inhibitor of aldo-keto reductase 1C3 (AKR1C3), the enzyme that is overexpressed in many cancer types and its increased metabolism contributes to the pharmacokinetic resistance to antracyclines in tumor tissues. In our study, dinaciclib inhibited AKR1C3 in the experiments with purified recombinant enzyme (IC_{50}=220 nM, Ki=170 nM) and was equally active at the cellular level (IC_{50}=235 nM). Molecular docking studies predicted that dinaciclib occupies a part of the cofactor binding site, which is consistent with the noncompetitive mechanism of inhibition determined in our in vitro experiments. Furthermore, we demonstrated that pretreatment with dinaciclib significantly sensitized AKR1C3-overexpressing anthracycline-resistant cancer cells to daunorubicin. Our results indicate that dinaciclib may potentially increase the therapeutic efficacy of anthracyclines, prevent anthracycline resistance and minimize their adverse effects.

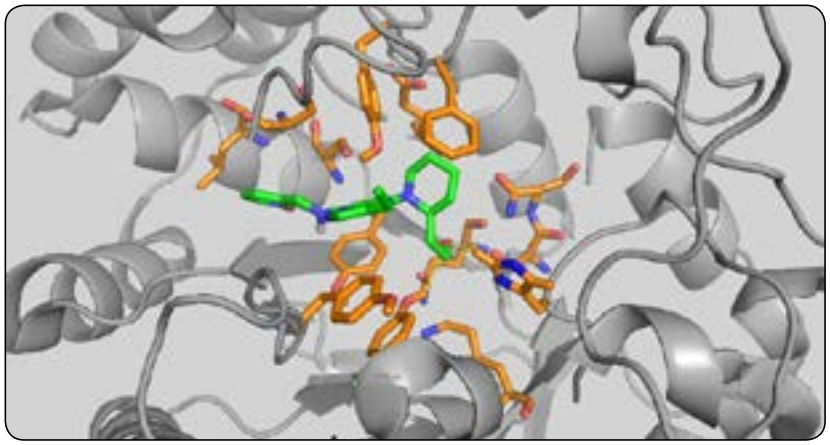

Figure 1: Dinaciclib occupies a part of the cofactor-binding site. Flexible molecular docking of dinaciclib into AKR1C3. Dinaciclib is depicted in green, protein residues surrounding the ligand within 4 A are shown in orange.

Recent Publications

1. Bains O S, Grigliatti T A, Reid R E and Riggs K W (2010) Naturally occurring variants of human aldo-keto reductases with reduced in vitro metabolism of daunorubicin and doxorubicin. J. Pharmacol. Exp. Ther. 335(3):533-545
2. Fu W et al. (2011) The cyclin-dependent kinase inhibitor SCH 727965 (Dinaciclib) induces the apoptosis of osteosarcoma cells. Mol. Cancer Ther. 10(6):1018-1027
3. Ghia P et al. (2015) A phase 3 study to evaluate the efficacy and safety of dinaciclib compared to ofatumumab in patients with refractory chronic lymphocytic leukemia. Blood. 12:4171

4. Heibein A D et al. (2012) Role of aldo keto reductases and other doxorubicin pharmacokinetic genes in doxorubicin resistence, DNA binding, and subcelllular localization. BMC Cancer. 12:381
5. Minotti G et al. (2004) Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxiticy. Pharmacol. Rev. 56(2):185-229.

Biography

Eva Novotna has her expertise in the preparation and purification of recombinant enzymes. She studies interactions of potential inhibitors with carbonyl reducing enzymes using human recombinant enzymes and cancer cell lines. Her research interest include: carbonyl reducing enzymes, inhibitors and cancer drug resistance.

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