KINETIC STUDIES ON HUMAN JUMONJI-C HYDROXYLASE JMJD7

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2-Oxoglutarate-dependant (2OG) oxygenases require 2OG, dioxygen (O_2), Fe(II), and, in some cases *L*-ascorbate(1,2), for productive catalysis; they catalyse diverse reactions on a wide range of substrates including RNA, DNA, proteins, and small molecules(3,4). The 2OG oxygenase Jumonji-C domain containing 7 (JMJD7) catalyses the hydroxylation of lysine residues in developmentally regulated GTP-binding proteins 1 and 2 (DRG1/2)(5); however, information on how JMJD7 binds to these substrates and contributes to cancer progression is not yet available.

A high-throughput mass spectrometry (MS)-based assay was developed to enable investigations on how small molecules affect JMJD7 catalysis, including 2OG and synthetic derivatives. Kinetic studies have revealed that the Michaelis constant of JMJD7 for *L*-ascorbate are reminiscent of catalysis by some other human 2OG oxygenases, such as AspH and JMJD5. Investigating a set of small-molecules for JMJD7 cosubstrate activity revealed that JMJD7 can accept cosubstrates other than 2OG, potentially altering product selectivity based on the cosubstrate used.

Investigations on the substrate scope of JMJD7 revealed that JMJD7 can catalyse hydroxylation of residues other than lysine, though the substrate scope still is surprisingly limited, considering that the structurally closely related 2OG oxygenase FIH catalyses hydroxylation of Asp, Asn, His(6) and Leu(7). A screening of reported small-molecule 2OG oxygenase inhibitors for JMJD7 revealed that it is inhibited by typical broad-spectrum inhibitors such as *N*-oxalylglycine (NOG). Crystallographic experiments were performed to obtain further structural information on the development of selective JMJD7 inhibitors. These inhibitors might prove valuable for cellular functional assignment studies, with the overall aim of investigating the role of JMJD7 in normal physiology and disease.

Reference:

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