Form 2

Dissertation Abstract

Report no.	(Course-based) No.1 0 2 5	Name	ASAD ALI SHAH
Dissertation title	Epigenetic regulation by synthetic and endogenous small molecules (内因性および合成小分子化合物によるエピジェネティック制御に関する研究)		

Abstract

※ The abstract should be in keeping with the structure of the dissertation (objective, statement of problem, investigation, conclusion) and should convey the substance of the dissertation.

Sirtuins are a family of nicotinamide adenine dinucleotide (NAD)-dependent lysine deacetylases shown to play biological and physiological roles in diverse cellular processes such as metabolism, transcription, and DNA repair. Mammals have seven sirtuins that display different subcellular localizations and functions. SIRT2 is a predominantly cytosolic protein and has been involved in various cellular processes including gene transcription, genome constancy, and the cell cycle. In addition, SIRT2 is deeply implicated in diverse diseases including cancer. In this study, we identified a small molecule inhibitor of SIRT2 with a structure different from known SIRT2 inhibitors by screening from a chemical library. The hit compound showed a high selectivity toward SIRT2 as it only inhibited SIRT2, and not other sirtuins including SIRT1 and SIRT3 or zinc-dependent histone deacetylases (HDACs) including HDAC1 and HDAC6, *in vitro*. The compound increased the acetylation level of eukaryotic translation initiation factor 5A (eIF5A), a physiological substrate of SIRT2, and reduced cell viability of human breast cancer cells accompanied with a decrease in c-Myc expression. In addition, the compound inhibited cancer cell migration by possibly increasing acetylation of cortactin, an actin-binding protein important for cancer cell invasion and metastasis. These results suggest that the compound is cellular effective and has potential for development as a therapeutic agent against breast cancers by specific inhibition of SIRT2.

2-Hydroxyglutarate (2-HG) produced by mutant isocitrate dehydrogenases (IDH) observed in some types of cancer has been recently emerged as an oncometabolite, which contributes to tumorigenesis by inhibiting ferrous iron (Fe^{2+}) and α-ketoglutarate (α-KG)-dependent dioxygenases such as jumonji C domain-containing histone demethylases (JHDMs) and ten-eleven translocations (TETs) DNA demethylases, and

by stabilizing hypoxia-inducible transcriptional factor, HIF-1α. Our lab previously identified *N*-acyldopamines, known as ligands against vanilloid receptors, as activators of transcriptional activity of HIF-1α through screening of a lipid-related metabolite library. *N*-acyldopamines stabilized HIF-1α under the normoxic conditions by inhibiting prolyl hydroxylase 2 (PHD2)-mediated proline hydroxylation of HIF-1α. Because *N*-acyldopamines directly inhibited enzymatic activity of PHD2 that is a Fe^{2+} and α-KG-dependent dioxygenases, we hypothesized that *N*-acyldopamines can inhibit other Fe^{2+} and α-KG-dependent dioxygenases such as JHDMs and TET families of dioxygenases. We identified *N*-acyldopamines as inhibitors of JHDMs and TET1 DNA demethylases, which are involved in histone and DNA demethylation, respectively. *N*-acyldopamines increased both histone and DNA methylation in cells. Our results indicate that *N*-acyldopamines possess 2-HG-like properties. Thus, *N*-acyldopamines may act as novel oncometabolites that promote tumorigenesis by inhibiting histone and DNA demethylation.