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Epi-drug development targeting human G9a H3K9 methyltransferase

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Epigenetic modification of histone is an important mechanism for control of development and maintenance of tissue-specific gene expressions. Anormaly in epigenetic modifications causes an altered pattern of gene expressions and often leads to malignant transformations. Impaired epigenetic control has been considered as one of the key features of cancer and, thus, artificial control of epigenetic modification is an emerging strategy of anticancer therapy. G9a methyl transferase, one of the most prominent histone methylation enzyme, catalyzes transfer of a methyl group from SAM to Lys9 of Histone3 (H3K9), resulting in mono- (me1), di- (me2), and tri-methylated (me3) H3K9. Methylation of H3K9 is one of the repressive histone marks that silence tumor suppressor genes and G9a has been observed to be up-regulated in various cancers, suggesting that G9a is a putative oncogenic protein. Supporting this speculation, G9a knock-down using shRNA resulted in decreases in global H3K9 methylation levels and led to ultimate autophagic or apoptotic cell death. Several G9a inhibitors have been developed as potential cancer therapeutics but with severe cellular toxicity, probably because of off-targeting of other SAM-binding proteins. For the enhanced application to practical cancer therapy, we developed new inhibitors, which are highly selective for H3K9me3 methylation and, thereby, significantly less cytotoxic, via the virtual screening of 18 million compounds and the subsequent biochemical activity assay. Finally, eight candidate compounds with IC50s in a low micromolar range are identified and being optimized for development of new G9a inhibitors with drug potentials.

Biography

Yong-Hwan Lee has completed his PhD majoring in Structural Biology and Protein Chemistry from State University of New York, Stony Brook, and Postdoctoral studies from University of Minnesota School of Medicine. He is an Associate Professor, Department of Biological Sciences, Lousiana State University and has successfuly developed PFKFB3 inhibitors as cancer therapeutics. He has published more than 30 papers in reputed journals and has been serving as an ad-hoc Reviewer of NIH and reputed journals.

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