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Mechanism and Inhibition of Histone Modifications

Project Number	Contact PI/Project Leader	Awardee Organization
1R35GM149230-01	ZHENG, Y. GEORGE	UNIVERSITY OF GEORGIA

Description

Abstract Text

Protein methylation on arginine and lysine residues represents a type of versatile posttranslational modifications occurring in all eukaryotic organisms. Protein methyltransferases regulate a plethora of cellular processes ranged from gene transcription, RNA splicing, translation, metabolic pathways, to signal transduction. Many protein methyltransferases are found to be overexpressed or mutated in common human diseases such as cancer, inflammation, diabetes, neurological disorders, and infection. Hence, protein methyltransferases are highly promising novel molecular targets in drug discovery. However, biological functions of the majority of protein methyltransferase enzymes in dictating normal physiology and disease pathways are only poorly defined. Our long-term research goal is to elucidate biological pathways whereby key protein methyltransferases contribute to the pathogenesis of recalcitrant diseases such as cancer and infection, and meanwhile to discover new structural chemotypes for protein methyltransferase-targeted therapy. The present research program is aimed at investigating molecular mechanisms and functions of protein methylation catalyzed by key methyltransferases. Our effort is coupled with and aided by development and application of innovative chemical biology methods and tools. Built upon our recent preliminary results, we will implement experiments to elucidate novel molecular mechanisms and regulation of protein arginine methyltransferase (PRMT) activities. We will extend our efforts to investigate the activity, structure and function of untapped protein methyltransferases, including those in different organisms such as infectious pathogens. Particular efforts will be directed to develop isoform-selective modulators and probes for important PRMT members and apply them to elucidate PRMT- regulated cellular pathways and disease processes. Further efforts will be invested to interrogate potential cross- interactions of protein methylation with lysine acetylation in orchestrating biological regulation. The results of the proposed research together will yield an in-depth understanding of the regulatory mechanism and biological significance of protein methylation in the control of normal physiology and disease pathology, and translate laboratory research leads into therapeutic candidates for the treatment of protein methyltransferase-controlled ailments.

Public Health Relevance Statement

Protein methyltransferases (PMTs) are important enzymes that regulate epigenetics, translation, metabolism, and other fundamental biological pathways that are associated with critical diseased states. Dissecting the mechanism, regulation, and consequence of PMT activities is the key to understanding methylation-mediated disease processes, and meanwhile designing potent and selective drug molecules to target dysregulated PMTs is of immense demand in new therapy development.

Project Terms

Acetylation · Arginine · Biological · Biological Process · Biology · Cell physiology · Chemicals · Coupled · Development · Diabetes Mellitus · Disease · Disease Pathway · Enzymes · Epigenetic Process · Genetic Transcription · Goals · Infection · Inflammation · Investments · Laboratory Research · Lysine · Malignant Neoplasms · Mediating · Metabolic Pathway · Metabolism · Methods · Methylation · Methyltransferase · Molecular · Molecular Target · Mutate · Organism · Pathogenesis · Pathology

Mechanism and Inhibition of Protein Arginine Methylation

Project Number
5R01GM126154-04

Contact PI/Project Leader
ZHENG, Y. GEORGE

Awardee Organization
UNIVERSITY OF GEORGIA

Description

Abstract Text

Protein arginine methylation, which is specifically mediated by protein arginine methyltransferases (PRMTs), represents one of the most important and ubiquitous posttranslational modifications in biological regulation. PRMTs are involved in a variety of cellular processes including epigenetic reprograming, RNA splicing, signal transduction, and DNA repair. Significant amounts of evidence have shown that altered PRMT expression and activity are associated with tumorigenesis, inflammation, diabetes, neurological disorders, and many other recalcitrant disease conditions. PRMTs are highly promising molecular targets in the search for new chemotherapies. However, functions of PRMT enzymes in regulating signaling cascades and disease pathways are poorly understood. Molecular mechanisms of PRMTs in major oncology processes are not yet defined. Importantly, quality chemical leads are scarce for effective targeting of arginine methylation, which significantly hampers current pharmaceutical advance. This research project is aimed at developing novel chemical biology strategies and organic probes as powerful mechanistic means to interrogate PRMT function in key biological pathways and disease processes. We will innovate multiple lines of strategic designs to determine substrate recognition mechanisms of PRMTs and illuminate functional interplays among key histone modifications in epigenetic fate regulation. Great efforts will be engaged in developing potent and subtype-selective small molecule inhibitors with privileged structural scaffolds that can be used to selectively block the enzymatic activity of the major PRMT subtypes. A diversity of library compounds will be screened; chemical analogs will be synthesized; and best leads will be characterized for their pharmacokinetics and pharmacodynamics properties. Detailed biochemical, cellular, and in vivo studies will be conducted in a systematic way to define structure-activity relationship and mechanism of action with the goal of generating a new generation of potent, subtype-selective PRMT inhibitors. Altogether, the projected research will yield in-depth understanding of PRMT-regulated disease mechanisms and translate laboratory leads into clinical candidates for the treatment of PRMT-related ailments.

Public Health Relevance Statement

Protein arginine methyltransferases (PRMTs) play critical roles in various disease conditions and are highly promising drug targets in developing new therapies. The proposed research will provide rich information and significant mechanistic insights into PRMT-mediated disease processes and create subtype-selective PRMT chemical leads for therapeutic discovery.

NIH Spending Category

Cancer Genetics

Project Terms

Acute Myelocytic Leukemia Affinity Amidines Animal Cancer Model Arginine Binding Biochemical Biochemistry Biological Biology Cell physiology Cells Chemicals Clinical Complex Computer Assisted DNA Repair Diabetes Mellitus Disease Disease Pathway Diversity Library Drug Targeting Enzymes