



Editorial overview: Recent advance in chemical genetics and chemical epigenetics

Xiaoguang Lei and Xiang David Li



Current Opinion in Chemical Biology 2019, 51:A1–A3

For a complete overview see the [Issue](#)

Available online 31st July 2019

<https://doi.org/10.1016/j.cbpa.2019.07.002>

1367-5931/© 2019 Elsevier Ltd. All rights reserved.

Xiaoguang Lei

Beijing National Laboratory for Molecular Sciences, Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Department of Chemical Biology, College of Chemistry and Molecular Engineering, Synthetic and Functional Biomolecules Center, and Peking-Tsinghua Center for Life Sciences, Peking University, Beijing 100871, China
e-mail: xglei@pku.edu.cn

Prof. Dr. Xiaoguang Lei obtained BSc degree in chemistry from Peking University in 2001. He then moved to Boston and conducted his PhD research on natural product synthesis and chemical biology under the supervision of Prof. John. A. Porco at Boston University. He received Ph.D. in 2006, and then conducted his postdoctoral training in bioorganic chemistry with Prof. Samuel J. Danishefsky at Columbia University. In early 2009, Dr Lei returned back to China, and started his independent research career as a Principal Investigator and Director of Chemistry Center at the National Institute of Biological Sciences (NIBS) in Beijing. In early 2014, he received a tenured full professorship from Peking University, and moved his research group to the College of Chemistry at Peking University. He also joined the Peking-Tsinghua Center for Life Sciences as a senior PI. The major research areas of Prof. Lei's laboratory are: natural product synthesis, chemical biology, synthetic biology and drug discovery.

Xiang David Li

Department of Chemistry, The University of Hong Kong, Hong Kong, China
e-mail: xiangli@hku.hk

Prof. Dr. Xiang David Li obtained his B.Sc. degree in chemistry from Fudan University in 2003. He then moved to Hong Kong and conducted his Ph.D. research on developing

Chemical genetics is one of the most well-established research areas in chemical biology and is defined as the study of biological systems using small molecule tools. Traditional genetic tools are powerful but are less effective for studying essential genes or transient processes and in most part, not feasible in the system most relevant to human health. Chemical genetic approach using small molecules is complementary to the classic genetic methods, because these small molecules act conditionally and rapidly, can directly target the gene's protein product. They can also hit on several proteins simultaneously, and can be used in a combination for multiple pathways in cultured human cells.

Chemical epigenetics is an emerging research direction that focuses on the study of epigenetic mechanisms at the molecular level by developing and using chemical tools and approaches. In human cells, genomic DNA is packaged into chromatin, a compacted structure formed by DNA wrapped around proteins 'spools' called histones. As a genome-organizing platform, chromatin is known to be decorated by the addition of diverse covalent modifications, such as methylation, acetylation and phosphorylation, onto histones. Moreover, a methyl group can be directly installed onto a cytosine base to form 5-methylcytosine (5mC) in DNA, which can be subsequently converted into other related modifications such as 5-hydroxymethylcytosine (5hmC). Besides DNA and histones, RNA has also been found to carry various modifications, such as a methylation at adenosine N6 position (m6A) in mRNA. These modifications on histones, DNA and RNA provide a complex indexing system for our packaged genome and play key roles in the epigenetic regulation of almost all the chromatin-templated biological processes including gene transcription, DNA replication, and DNA damage repair. In addition to these modifications, recent evidences also suggest that expression of noncoding RNA (e.g. microRNA), ATP-dependent chromatin remodelling and even cellular metabolism are also involved in epigenetic regulation. The development of chemical tools and approaches has provided innovative and complementary strategies with traditional biological methods to investigate how these regulatory mechanisms define the epigenetic landscape.

In this special issue, we will discuss the recent exciting advance in these two research fields. The topics cover: (1) using small molecules to modulate actin cytoskeleton, to dissect natural polypharmacology, and to control the cell fate reprogramming and the acquisition of plasticity in somatic cells; (2) developing and applying novel tools to explore the influences of histone modifications on chromatin dynamics, to identify and characterize regulating enzymes and protein effectors of histone modifications, to examine the

synthetic ion channels under the supervision of Prof. Dan Yang at The University of Hong Kong. After receiving his Ph.D. in organic and bioorganic chemistry in 2008, he moved to New York to conduct his postdoctoral training in chemical biology with Prof. Tarun M. Kapoor at The Rockefeller University. In 2011, Dr Li returned back to The University of Hong Kong and started his independent career as an Assistant Professor at the Department of Chemistry. In 2016, Dr Li was promoted to Associate Professor (with tenure). Dr Li's research focuses on developing chemical tools and approaches to decipher the biological significance and regulatory mechanisms of histone posttranslational modifications.

impact of metabolism on epigenetic regulation, and to understand the crosstalk between microRNA and epigenetics.

Gunning et al. (<https://www.sciencedirect.com/science/article/pii/S1367593118301789>) report opportunities and challenges associated with targeting the actin cytoskeleton through its structural regulators. In particular, they highlight emerging data acquisition and analysis trends driving phenotypic, imaging-based compound screening. They also discuss how the confluence of these trends is now bringing functionally integral machineries such as the actin cytoskeleton, and associated structural regulatory proteins, into an expanded repertoire of druggable targets with previously unexploited clinical potential.

Aye et al. (<https://www.sciencedirect.com/science/article/pii/S1367593118301765>) report the recent progress in studying the native electrophile signalling and developing new technology to profile and interrogate these non-enzyme-assisted signalling subsystems. These breakthroughs have led to the rational design and discovery of more effective polypharmacologic covalent inhibitors, which could also facilitate the better evaluation of target engagement and the development of a function-guided understanding of polypharmacology.

Using small molecules to control cell fate and reprogram stem cells has become a very exciting new research direction over the past decade. The use of chemical cocktails to directly alter cell fate could provide tremendous opportunities to develop new effective regenerative medicine. Zhao (<https://www.sciencedirect.com/science/article/pii/S1367593118302084>) reviews and discusses the recent advance in this field by highlighting the new developments, inspirations, as well as the challenges encountered when modulating cell fate reprogramming with chemicals.

Post-translational modifications (PTMs, or marks) of histones and other chromatin-associated proteins underlie one key mechanism for the epigenetic regulation. The histone PTMs can directly change the physicochemical properties of the environment around the modification sites, and thereby alter the chromatin dynamics to regulate the chromatin-templated processes. Fierz and Boichenko (<https://www.sciencedirect.com/science/article/pii/S1367593118301959>) review the chemical biological and biophysical methods that facilitate the analysis of how histone PTMs affect the chromatin dynamics, with an emphasis on the processes of chromatin silencing.

Other than changing the chromatin dynamics, histone PTMs also serve as the docking platforms for the recruitment of effector proteins ('readers') to translate the messages of the modifications to the downstream cellular events. Li et al. (<https://www.sciencedirect.com/science/article/pii/S1367593118301777>) describe the development of chemical tools for the identification and characterization of 'readers' for histone PTMs. The newly reported 'readers' and histone modifications are also reviewed.

Most of the epigenetic marks on histone and non-histone proteins are tightly regulated by corresponding modifying enzymes that catalyze the addition ('writers') and removal ('erasers') processes. To fully understand the biological significance and regulatory mechanisms of the marks, it requires the identification and characterization of their regulating enzymes. Sirtuins are a class of NAD-dependent deacylases. Lin et al. (<https://www.sciencedirect.com/science/article/pii/S1367593118301972>) summarize the

recent advances on the understanding of the roles played by sirtuins in epigenetic regulation. The molecular mechanisms of how the sirtuins realize their functions by hydrolyzing the acylation marks have also been discussed.

The regulatory enzymes of epigenetic marks usually require cellular metabolites as cofactors to carry out their enzymatic reactions. Some of the highly reactive metabolites have also been found to modify proteins in an enzyme-independent manner. In recent years, more and more evidences support that the cellular metabolism offers another level of regulation for epigenetics. Meier *et al.* (<https://www.sciencedirect.com/science/article/pii/S136759311930002X>) describe the development and applications of chemical proteomics approaches to examine how endogenous metabolites participate in the epigenetic regulation.

While histone and DNA modifications are two major focuses of epigenetic studies, recent investigations on microRNA (miRNA) reveal that miRNAs can influence the global transcriptional landscape by affecting the epigenetic machinery. In return, the expression of miRNAs can also be regulated by epigenetic modifications. Zhou *et al.* (<https://www.sciencedirect.com/science/article/pii/S1367593118301868>) describe the advances on the understanding of crosstalk between miRNA and epigenetics. The therapeutic potential of targeting aberrant miRNA-epigenetics feedback loop is also discussed.

We hope that you will find this special issue in *Current Opinion in Chemical Biology* informative and inspiring for your research study. We also expect the exciting chemical genetics and epigenetics research fields will generate many new impacts on biomedical research and drug discovery in the near future.