Systems Biology Approach to Investigate Epigenetic Regulation of Macrophages Exposed to HIV Infection and Methamphetamine

Shulei Lei[1], Katarzyna Pawlak[1], Jayme Wiederin[1], Spencer Jaquet[1], Brenda Morsey[1], Fang Yu[1], Hang-Gyeong Chin[2], Sriharsa Pradhan[2], Adam Karpf[1], Howard Fox[1] and Pawel Ciborowski[1]

University of Nebraska Medical Center, Omaha, NE
New England Biolabs Inc., Ipswich, MA

HIV infection and substance abuse both lead to untoward effects of multiple physiological systems including the immune and central nervous systems. Amongst abused drugs methamphetamine (Meth) affects macrophages in multiple ways leading to increased susceptibility to HIV infection, increased viral replication in infected cells, and potentially increased production of neurotoxic molecules. Our work includes:

1. Epigenetic studies:
    a. We profiled post-translational modifications (PTMs), including acetylation, methylation, phosphorylation, and ubiquitination on histones isolated from macrophages exposed to Meth (or control unexposed). We have found several changes, i.e. H3K9Ac, H4 K9me3, H4K8me1, H4K12me3 which are being now quantified using label-free targeted mass spectrometry.
    b. We are performing high resolution open chromatin profiling using the NicE-seq (nicking enzyme assisted sequencing) technique to assess open chromatin sites (OCSs) and transcription factor occupancy at single nucleotide resolution in Meth-treated (and control) macrophages.
2. Omic-phenotype studies:
    a. We performed semi-targeted profiling of Meth-treated macrophage exometabolome. Now we proceed to identification of their promoter regions and their interactions with histones' PTMs to unravel epigenetic regulatory mechanisms.
    b. RNA-seq has been performed on Meth-treated and control macrophages, revealing a set of genes whose expression is differentially regulated by Meth.
3. Performed experiments are intended to establish a baseline of Meth effect on macrophage. Currently we are adding effect of HIV-1 infection which, while another layer of complexity will model the appropriate condition in HIV-infected drug users. Preliminary results in all areas described above will be presented.

This work is supported by NIH grant R01DA043258