Systems biology approach reveals novel insights into altered functions of HIV-1-infected or methamphetamine exposed macrophages.

Ariel Burns[1,2], Nicole A. Haverland[1,3], Pawel Olszowy[1,4] and Pawel Ciborowski[1]

[1]University of Nebraska Medical Center, Omaha, NE, USA
[2]Current: Quest Diagnostics, Kansas City, MO, USA
[3]Current: Northwestern University, Evanston, IL, USA
[4]Current: Polpharma, Starogard Gdanski, Poland

HIV-1 infection of macrophages results in cell survival and viral persistence. Although it has been shown that infecting virus deregulates macrophage function, the mechanism for cell survival remains unknown. Moreover, HIV infection is often complicated by concurrent use of illicit drugs and may potentiate already adverse effect of viral infection. Taken together, it is very difficult to manage these two devastating factors. Therefore, understanding molecular mechanisms is of the utmost importance at this stage of our fight against HIV.

In our previous studies, we used a systems biology approach to investigate transcription factors and regulators in HIV-1 infected monocyte derived macrophages (MDM). We showed that HIV infection affects several regulatory pathways associated with transcription activity of MDM. In subsequent analyses, we profiled the nuclear proteome to investigate how MDM reacts to exposure to an illicit drug – methamphetamine (Meth). Based on this experience, we began to characterize post-translational modifications of histones as a part of epigenetic regulatory mechanisms.

Post-translational modifications (PTM) of histones are extremely complex and give rise to a universal system for epigenetic regulation of cellular functions. The major source of complexity originates from multiple combinations of homogenous and heterogeneous PTMs. During cellular exposure to various stimuli, PTMs of histones, which are also referred to as the “histone code”, undergoes changes resulting in phenotypic and functional changes of the cells. Using O^{16}/O^{18} technique to quantify relative changes in histone PTMs in MDM, we have determined that after 48 hours exposure to 100 µm Meth several histone PTMs were altered. For example, acetylation of lysine-19 on Histone 3 (H3K19Ac) was downregulated, whereas monomethylation of lysine-34 on Histone 2 type B (H2BK34Me) was upregulated. Further, global screening studies led to the discovery that the cytokines CXCL16 and CXCL1 were up-regulated following exposure to Meth. We also showed CCL7 as an extensively down-regulated chemokine after Meth exposure, which led us to hypothesize that Meth dysregulates the MyD88-dependent Toll-like receptor 9 (TLR9) signaling pathway.

The exact mechanism of downregulation is not known. However in preliminary studies we did not observe changes in DNA methylation in CCL7 promoter region, however the specific histone PTMs that regulate the CCL7 promoter has not yet been identified. Nevertheless, our preliminary data provide evidence that the components of transcription regulation complexes can be identified using the ChIP assay in MDM.

Summarizing, we postulate that a systems biology approach to investigate regulatory mechanisms will provide unique information that will lead to the identification of new paradigms on how the macrophage responds to the complex environment of HIV infection and/or Meth insult.