Western University of Health Sciences

College of Osteopathic Medicine of the Pacific

COMP Seminar Series

Slowing the Spread of Sleeping Sickness: Chromatin readers regulate lifecycle transitions in the African trypanosome.

Presented by

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Friday, August 18, 2017

12:00pm - 1:00pm

HSC, Compatriot's Hall, Pomona

Eastmoreland, Lebanon

Lunch will be served with RSVP to
kking@westernu.edu by noon, August 15.

Slowing the Spread of Sleeping Sickness: Chromatin readers regulate lifecycle transitions in the African trypanosome.

Trypanosoma brucei, the causative agent of African sleeping sickness, is transmitted to its mammalian host by the tsetse. In the fly, the parasite's surface is covered with invariant procyclin, while in the mammal it resides extracellularly in its bloodstream form (BF) and is densely covered with highly immunogenic Variant Surface Glycoprotein (VSG). In the BF, the parasite varies this surface VSG, using a repertoire of ~2500 distinct VSG genes. Recent reports in mammalian systems point to a role for histone acetyl-lysine recognizing bromodomain proteins in the maintenance of stem cell fate, leading us to hypothesize that bromodomain proteins may maintain the BF cell fate in trypanosomes. Using small-molecule inhibitors and genetic mutants for individual bromodomain proteins, we performed RNA-seq experiments that revealed changes in the transcriptome similar to those seen in cells differentiating from the BF to the insect stage. This was recapitulated at the protein level by the appearance of insect-stage proteins on the cell surface. Furthermore, bromodomain inhibition disrupts two major BF-specific immune evasion mechanisms. First, monoallelic expression of the antigenically varied VSG is perturbed. Second, rapid internalization of antibodies bound to VSG on the surface of the trypanosome is blocked. Thus, our studies reveal a role for trypanosome bromodomain proteins in maintaining lifecycle stage identity and immune evasion. Importantly, bromodomain inhibition leads to a decrease in virulence in a mouse model of infection, establishing these proteins as therapeutic drug targets for trypanosomiasis. Our 1.25Å resolution crystal structure of a trypanosome bromodomain in complex with a known acetyl-lysine mimetic reveals a novel binding mode of the inhibitor, which serves as a promising starting point for rational drug design.

Bromodomain inhibition attenuates infection in vivo