

Dual function of histone H3K76 methylation in cell cycle regulation and development differentiation in *Trypanosoma brucei*

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Trypanosoma brucei is a unicellular eukaryotic parasite that causes Sleeping Sickness in humans and "Nagana" in life stock in sub-Saharan Africa. Trypanosomes developed a complex life cycle that includes different parasite forms: the procyclic form, which lives in the intestinal tract of an insect vector (the tsetse fly) and the bloodstream form, which is adapted to the vascular system of a mammalian host. Many cellular processes, including cell cycle control, changes in protein expression profiles and morphology have to be carefully coordinated and adapted in order to survive in these different environments. There is increasing evidence that changes in chromatin structure are associated with developmental differentiation of trypanosomes during the life cycle. In our projects, we aim to unravel the function of these changes in chromatin structure with an emphasis on posttranslational histone modifications (PTMs) and the enzymes that are responsible for them. After dissecting the repertoire of PTMs in two life cycle stages in trypanosomes, we focused on methylation of histone H3 on lysine 76 in the histone core, which is mediated by methyltransferases of the DOT1 family. In *Saccharomyces cerevisiae*, Dot1-mediated H3K79 methylation is associated with telomere silencing, meiotic checkpoint control, and DNA damage response. In higher eukaryotes, DOT1 enzymes also play important roles in heterochromatin formation and in embryonic development.

Interestingly, trypanosomes have two different DOT1 enzymes, which we called DOT1A and DOT1B. To our surprise, these two enzymes do not only exhibit different enzymatic activities but they seemed to have developed two completely different functions during evolution of trypanosomes: DOT1A is responsible for regulation of replication and cell cycle progression and DOT1B is involved in transcriptional control and is also essential for distinct steps of the differentiation process. In our current projects we want to explore how these enzymes are regulated, how they acquired different functions and if there might be a mechanistic overlap between the mode of action of DOT1A and DOT1B.