The Effects of Novel Histone Deacetylases Inhibitors Against *Trypanosoma cruzi*

Zuma, AA[*1]; Castro, LS[1]; Leite, ACS[1]; Bracher, F[2]; De Souza, W[1];
[1]Laboratório de Ultraestrutura Celular Hertha Meyer, Instituto de Biofísica Carlos Chagas Filho - UFRJ, RJ, Brasil.
[2]Department of Pharmacy, Center for Drug Research, Munique, Alemanha
*zuma@biof.ufrj.br

The protozoan *Trypanosoma cruzi* is the aetiological agent of Chagas disease, an endemic illness in Latin America. There are about 8 million people infected around the world, which encourages the development of new drugs against this parasite. In *T. cruzi* the level of chromatin condensation changes according to parasite's evolutive stage, being more compacted in trypomastigotes than in the epimastigote form. The organization of nuclear DNA is modulated by different enzymes, such as histone deacetylases (HDACs), and the difference of its condensation level is directly related to replication, transcription, repair and gene expression. Based on that, HDACs have been used as chemotherapeutic targets. So, in this work, we evaluated the effects of new HDACs inhibitors (KV46, KV50, KV30 and KV24) in *T. cruzi* epimastigote proliferation, viability and ultrastructure. For this purpose, parasites were treated up to 72 hours with 1, 5, 10 and 50 µM of each compound. After 24 hours, samples were collected for counting on Neubauer's chamber, for cellular viability assays, by MTS/PMS method and propidium iodide incorporation, and for transmission electron microscopy analyses. Our results showed that KV24, KV30 and KV46 were the most effective compounds against *T. cruzi* epimastigote proliferation. After 48 hours of treatment, the IC_{50} values were 7, 14 and 18 µM, respectively. On the other hand, KV50 inhibited 50% of parasite proliferation only with 50 µM. Regarding *T. cruzi* viability, the treatment with 50 µM for 72 hours of KV24, KV30 and KV46 reduced the percentage of viable parasites in approximately 80%. The others concentrations practically did not affect protozoa viability. Transmission electron microscopy analyzes showed that KV46 caused mitochondrial swelling and disorganization of the flagellum. The compound KV50 promoted mainly mitochondrial swelling only when the concentration of 50 µM was used. Interestingly, parasites treated with KV30 did not present the bar shape kinetoplast, which appeared to be less condensed. The inhibitor KV24 caused cytoplasmic vacuolization and cellular degradation. Thus, our data obtained so far suggest that these HDACs inhibitors may act under different mechanisms and can be explored in further analysis about chemotherapeutic studies against *T. cruzi*.

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