Leveraging proteomics, bioinformatics, and ecotoxicology models to select new targets overcoming *L infantum* drug resistance

Lorenzo Tagliazucchi[a,b], Giulia Malpezzi[a,b], Bryan W. Brooks[c], Eli S. J. Thoré[d,e], Michael G. Bertram[d], Francisco Gamarro[f], Maria Paola Costi[a]

a. Department of Life Sciences, University of Modena and Reggio Emilia, Via Campi 103, 41125 Modena Italy.
b. Clinical and Experimental Medicine (CEM) PhD Program, University of Modena and Reggio Emilia, Via Campi 287, 41125 Modena, Italy.
c. Environmental Health Science Program, Department of Environmental Science, Baylor University,Texas, USA.
d. Department of Wildlife, Fish, and Environmental Studies, Swedish University of Agricultural Sciences, Skogsmarksgränd 17, 907 36 Umeå, Sweden.
e. TRANSfarm - Science, Engineering, & Technology Group, KU Leuven, Bijzondereweg 12, 3360 Lovenjoel, Belgium.
f. Institute of Parasitology and Biomedicine López-Neyra, Avda. del Conocimiento 17, 18016, Granada, Spain.

All Authors are COST Action CA21111 participants (www.onehealthdrugs.com

The excessive use of the few available antileishmanial agents has led to the emergence of highly-resistant *Leishmania infantum* strains, resulting in untreatable infections, therapeutic failure, and exacerbating the chronic burden of the disease. This topic has a significant impact on human and animal health in endemic regions worldwide, and in areas where dogs and other sylvatic animals serve as reservoirs for infection. There is an urgent need to design and develop new drugs to fight and overcome drug resistance, as the commonly used antimonials, paromomycin, and miltefosine show lower efficacy. Recent advancements in Vector-Borne Parasitic Diseases research have also highlighted and increased the consideration of environmental drug safety and their ecotoxicological impact, while simultaneously focusing on understanding and preventing resistance issues from the outset of the drug discovery projects[1]. To address this challenge, the exploitation of brand-new technologies like high resolution Mass Spectrometry and bioinformatic/ecotoxicology predictive models, can help identify the proteins and metabolic pathways modulated in the parasite during the infection phase, and suggest new drug targets and innovative drug combination strategies. Herein, we have investigated the biochemical mechanisms of resistance to sodium stibogluconate, paromomycin, and miltefosine[2] in three distinct parasitic strains derived from human clinical isolates. Human immortalized THP-1 cultures were infected with the resistant *Leishmania* parasites to mimic the acute phase of the infection, and were submitted to bottom up, whole-cell LC-MS/MS proteomics pipeline. Among the identified proteins of differentially expressed proteins (DEPs), the 14 DEPs identified, only peroxiredoxin emerged in all resistant strains. DEPs profile was compared with their mRNA expression profile, and finally functional association networks tools allowed the comparison of parasitic to human proteomes. Guest-host cross talking proteins and pathways were well defined to discard those proteins/pathways involved in both the human and parasitic networks. To assess the environmental impact of the remaining proteins, a SeqAPASS analysis was employed to predict cross species homology and drug target susceptibility, based on the evolutionary conservation of protein. The MATH domain-containing protein, ATP-binding cassette B2, histone H4, calpain-like cysteine peptidase, and trypanothione reductase emerged as top candidates. In an optic of a drug discovery program driven by One Health approach, by exploiting bioinformatic tools and predictive ecotoxicological platforms, we propose the above-mentioned target to undergo further molecular investigation to be considered to overcome parasitic drug resistance.

References

1. COST ACTION CA21111 www.onehealthdrugs.com
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