Omics technologies as a new tool in ecotoxicology

26-3-2024

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 [c,d,] Michael G. Bertram[d,], Francisco Gamarro[e,], 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. Institute of Parasitology and Biomedicine López-Neyra, Avda. del Conocimiento 17, 18016, Granada, Spain.

Lorenzo.tagliazucchi@unimore.it

There is an urgent need to develop new drugs to overcome drug resistance issue in Leishmaniases, as the commonly used antimonials, paromomycin, and miltefosine show low efficacy due to the emergence of hyper-resistant strains. Recent advancements in Vector-Borne Parasitic Diseases research have also highlighted the consideration of environmental drug safety, while simultaneously focusing on preventing resistance phenomena from the outset of the drug discovery projects. To address this challenge, the exploitation of Omics technologies like high resolution Mass Spectrometry proteomics/ PRC transcriptomics and bioinformatic/ecotoxicology predictive models, can help suggesting new biological mechanism, new drug targets and innovative drug combination strategies. Herein, we have investigated the biochemical mechanisms of resistance to sodium stibogluconate, paromomycin, and miltefosine in three distinct parasitic strains derived from human clinical isolates [1,2]. THP-1 cultures were infected with the clinical isolates of resistant *Leishmania* parasites to mimic the acute phase of the infection and were submitted to MS proteomics pipeline. Among all the cellular proteins, 14 emerged as differentially expressed (DEP), and only peroxiredoxin emerged as a DEP in all resistant strains. Human protein modulation was studied by MS, too, to evaluate the parasite impact on the monocytes' proteome. 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. The MATH domain-containing protein, ATP-binding cassette B2, histone H4, calpain-like cysteine peptidase, and trypanothione reductase emerged as top candidates. In parallel, human proteins from THP-1 were studied, and two main enzymes (Transferrin Receptor C and Nucleoside Diphosphate Kinase) emerged as DEP both in proteomics, and

transcriptomics studies. This suggests that their overexpression is caused by specific patterns proper of the drug resistant parasitic phenotype, and their inhibition or modulation should increase the parasite drug sensitivity. In an optic of a drug discovery program driven by One Health approach, we propose the above-mentioned targets to undergo further molecular investigation to be considered to overcome parasitic drug resistance, and to study the efficacy a of a dual guest-host antileishmanial therapy.

References

1. Tagliazucchi L, et al. ACS Infect Dis. 2023 Mar 10;9(3):470-485. doi: 10.1021/acsinfecdis.2c00457.
2. García-Hernández R, et al. OMICS. 2022 Mar;26(3):165-177. doi: 10.1089/omi.2021.0185.

Acknowledgment

This work was supported in part by the COST Action CA211 and, by the Grant RTI2018-097210-B-100 funded by MCIN/AEI/10.13039/501100011033.

WG3 WG4 Workshop "Omics technologies as a new tool in ecotoxicology "

26/03/2024 h15

online

Workshop of the COST Action CA21111
One Health drugs against parasitic vector borne diseases in Europe and beyond
OneHealthdrugs

The event is open to PhD, young innovators and senior scientists from both academia and pharma

Description

In the development of new active substances, consideration of possible effects on non-target organisms is becoming increasingly important. Assessment of environmental effects is still in its infancy in drug development. Here, the One Health approach often still falls short, as environmental health is an integral part of this concept, in addition to animal and human health. Efficient, innovative but also standardizable test methods and assays are needed to assess the behavior and effects of active ingredients released into the natural environment. This joint workshop of WG3 and WG4 will provide a platform to present and discuss the application of the “omics” approach in ecotoxicological testing.

Programme

15:00 to 15:45 Sebastian Eilebrecht "OMICs fingerprints in model organisms for environmental hazard prediction of substances" Head of Department Ecotoxicogenomics

Fraunhofer Institute for Molecular Biology and Applied Ecology IME

15:45 to 16:15 Xiaojing Li "Precision Environmental Health - Identifying Hazardous chemicals within Environmental Mixtures"

16:00 to 16:25 L. Tagliazucchi . University of Modena and Reggio Emilia "Leveraging proteomics, bioinformatics, and ecotoxicology models to select new targets overcoming L infantum drug resistance".

16:30 to 17:00 General discussion and closure of the workshop

- The event registration requires two steps : 1) create an e-COST account in the www.cost.eu and 2) register here: Concerning the non-Action-participants registration to the event, they can register here: https://docs.google.com/forms/d/e/1FAIpQLSdaE4hIq8W1HRoKC837LN9utTvoFJmuTek2NHSZ-AnwXDTu2A/viewform?usp=sharing