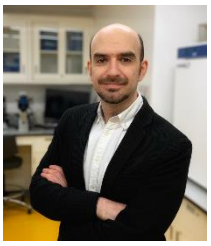
MICROBIOLOGIE, INFECTIOLOGIE ET IMMUNOLOGIE

Université de Montréal

CONFÉRENCE



Jeudi 7 décembre 2023 à 11h30

Université de Montréal, Pavillon Roger-Gaudry (B)
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Uncovering the Odds of Finding a Message in a tiny Bottle: EVs and Drug resistance

Extracellular vesicles (EVs) are nano-sized vesicles secreted by all eukaryotic cells whose contents (proteins, DNA/RNAs, lipids) vary as a function of their cellular origins. EVs have been the focus of numerous studies due to their involvement in intercellular communication. However, the potential roles of EVs in the survival and spread of drug-resistant parasites remain unexplored. Considering that the molecular content of eukaryotic EVs is a fingerprint of the origin cell, reflecting its physiological/functional status, our team recently explored the composition of leishmanial EVs in the context of drug resistance. In this way, we were able to identify *L. infantum* EVs' core proteome, as well as the proteins specifically enriched in EVs released by antimony-, miltefosine- and amphotericin-resistant parasites. We demonstrated for the first time that drug-resistance mechanisms can induce changes in the morphology, size, and distribution of EVs in *Leishmania*, with drug-resistant parasites releasing larger vesicles in comparison to their wild-type counterparts. Of note, several virulence factors, transcription factors, as well as proteins encoded by drug-resistance genes were identified among the drug-specific enriched proteins. Based on these exciting findings, we then explored the potential transfer of different traits of drug resistance from drug-resistant to naïve parasites. However, horizontal gene transfer (HGT) events had never before been demonstrated in eukaryotic parasites. Herein, we explore the DNA content of EVs derived from drug-resistant parasites, as well as their role in both intra- and interspecies HGT events. Next-generation sequencing and PCR assays confirmed the enrichment of circular amplicons carrying drug-resistance genes associated with EVs. Transfer assays of drug-resistant EVs showed an import shift in the drug-sensitivity profile of recipient parasites; this phenomenon was confirmed to be induced by the expression of genes transferred by EVs. Moreover, recipient parasites displayed enhanced growth and better control of reactive oxygen species. Overall, our work provides the first evidence that *Leishmania* EVs constitute an efficient platform for HGT, facilitating the rapid transmission of drug-resistance genes while increasing the global fitness of recipient parasites.

References: 1) Douanne et al. International Journal for Parasitology: Drugs and Drug Resistance (2020) 13, 28-37. 2) Douanne et al. PLoS neglected tropical diseases (2020) 14, e0008439. 3) Douanne et al. Cell Reports (2022) 40, 111121. 4)M Olivier, A Minguez-Menendez, C Fernandez-Prada. Trends in parasitology (2019) 35, 1018-1019.

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