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Proteomics Loans in Kinetoplastids during the Last Decade

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Editorial

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Editorial

Kinetoplastida are flagellated protists characterized by the presence of an organelle called kinetoplast. This characteristic feature is an unusual large DNA- containing granule located within the single mitochondrion, associated with the basal body of the cell's flagellum. It contains many copies of the mitochondrial genome. These organisms are commonly referred to as "kinetoplastids". This group comprises parasites responsible for serious diseases in humans as well as other animals. Among kinetoplastids, the family of Trypanosomatids, is notable as it includes some organisms which are exclusively parasitic such as *Trypanosoma* and *Leishmania*.

Regarding the tropical neglected diseases produced in humans by these parasites, Trypanosomiasis Americana or Chagas disease is caused by *Trypanosoma cruzi*. The common transmission of the parasite in endemic areas is through infected *Triatoma* infestans vector. Also, it can be transmitted through laboratory accidents, blood transfusions, organ transplants or congenitally from mother to baby. The disease can be classified in acute or chronic phases, being cardiomyopathy the most relevant and severe consequence that leads to ventricular systolic dysfunction, heart failure, and sudden cardiac death.

African Trypanosomiasis, also known as sleeping sickness, is an insect- borne parasitic infection too. In this case, *Trypanosoma brucei* is usually transmitted by the bite of an infected tsetse fly, common in rural areas. Sleeping sickness disrupts the sleep-wake cycle, leading to coma and death if left untreated. On the other hand, *Leishmania*sis, also neglected vector-borne parasitic diseases, comprise a varied collection of clinical manifestations caused by protozoa belonging to the *Leishmania* genus. It is usually spread through the bite of phlebotomine sandflies, Phlebotomus, and occurs most frequently in the tropical and sub-tropical areas of the Americas. The disease can present in three main ways: cutaneous, mucocutaneous, or visceral.

Taking into account that genomic and transcriptional studies alone seemed not to be any more skillful for solving complex biological whodunits, proteomics emerged as responsible for the identifications into the field of both parasite biology and its interactions with the host. It is worth mentioning that proteomics, in combination with genomics and bioinformatics, could support to eradicate several diseases.

Proteomics and nanotechnology strategies have shown to be valuable tools for sensing pathogens and host alteration signatures within microfluidic detection platforms providing novel solutions to fight against parasitic diseases. The most recent methodological and technological advances with great potential for bio- sensing parasites in their hosts, have shown the opportunities offered by modern "- omics" and platforms for parasite detection and control and this has been properly reviewed [1].

Early, insights into the biology of the nuclear envelope and flagellar pocket of trypanosomes were analyzed by proteomics [2]. Regarding the work performed among Trypanosomatids, some reports contribute to the understanding of the mechanisms of metabolic adaptation in *Leishmania* showing that the integration of proteomics and metabolomics approaches can produce complementary data to better understand the parasite metabolism [3].

Leishmania spp have made available an outlook on the developments in *Leishmania* proteomics and their clinical implications, proposing proteome profiles that could provide target molecules for vaccine development and therapeutic involvement as well as potential future novel discoveries [4].

Considering that intracellular pathogens invade their host cells and replicate within specialized compartments such as phagosomes, while these cell initiate a defensive response trying to kill the invasive agent, the intracellular lifestyle implies morphological and physiological changes in both pathogen and host cell. Therefore, *Leishmania* spp. is internalized by professional phagocytes such as macrophages, and resides within the parasitophorous vacuole inhibiting their microbicidal activity. Although the components of *Leishmania*'s intracellular niche, an endolysosomal compartment, have not been fully decoded, protocols of purification of both the intracellular parasites and also of the phagosomes that dock them followed by gel free proteomics were performed [5].

Also, the characterization by proteomics strategies has exposed the starring role of the post-translational modifications of the proteins involved in these host-pathogen interactions. The relevance of these motifs in the biology and biological cycle of kinetoplastid parasites is emphasized with key examples showing the potential to act as targets against protozoan diseases in addition to potential promise for vaccines developments, immunotherapies and personalized medicine [6].

In particular, a genome-wide quantitative proteomics approach and phosphoproteomics analysis of *Leishmania* spp. was carried out during differentiation by mapping the protein expression profiles of various developmental stages of of *Leishmania* donovani parasites using high-resolution mass spectrometry [7].

On the other hand, metabolomics, lipidomics and proteomics profiling of myoblasts infected with T. cruzi after treatment with different drugs against Chagas disease, allowed to a researcher group to validate the metabolic fingerprinting strategy for a complex host-cell parasite system to be hypothetically applied in the early stage of drug discovery helping to prioritize early leads or reconfirmed hits for further development [8].

To get deeper into studies related with genome-wide proteomics and phosphoproteomics analysis of *Trypanosoma cruzi* and taking into account that metacyclogenesis has been exploited by scientists in different ways, it is interesting to know both how metacyclogenesis is triggered and controlled by cell signaling and which are the differentially expressed proteins and post-translational modifications involved in this differentiation process. In this sense, an important cell signaling pathway is the protein phosphorylation, and it is reinforced in T. cruzi in which the gene expression control occurs almost exclusively post- transcriptionally. Additionally, the number of protein kinases in T. cruzi is relatively high compared to other organisms. Thus, phosphoproteomics and proteomics evaluation has described the steps from the cell protein extraction, digestion and fractionation, phosphopeptide enrichment, to LC-MS/MS analysis as well as a brief overview on peptide identification [9].

The proteomics studies were carried out on African trypanosomes and on the interactions with their vector and mammalian hosts. Interestingly, early progresses in proteomics proposed new tools to better understand host-vector- parasite cross-talks happening during the complex parasitic developmental cycle, allowing determining the outcome of both transmission and infection [10].

T. brucei motility, transmission, and virulence depend on its flagellum that consists of several different specialized subdomains T. brucei flagellum holds an essential and multifunctional role. Then, approaches that enable proteomic analysis of their individual subdomains were indeed required. Having validated the use of APEX2 protein in T. brucei, it was attempted to distinguish flagella subdomains by fusing APEX2 to a flagella membrane protein that is restricted to the flagellum tip (AC1), and another one that is excluded from the tip (FS179). Fluorescence microscopy demonstrated subdomain-specific biotinylation, and principal-component analysis showed distinct profiles between AC1-APEX2 and FS179-APEX2. The comparison of the two profiles allowed identifying an AC1 proximity proteome, which is enriched for tip proteins, including those involved in signaling. These findings have demonstrated that APEX2-based proximity proteomics is effective in T. brucei, thus solving the proteome composition of flagellum subdomains, which cannot themselves be easily purified [11].

Therefore, this capacity opened the possibility to study the composition and function of other compartments. This approach might be extended to other eukaryotic pathogens and was proposed to enhance the utility of T. brucei as a model organism to study ciliopathies (those related with flagella), transmissible human diseases in which cilium function is compromised [3].

In conclusion, progresses in proteomics as well as in novel sensitive and affordable procedures could greatly impact on sustainable control programs against parasitic diseases, which have a pronounced influence in human health especially in low income situations.

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