Editorial: Hematophagous arthropod saliva: a multifunctional tool

Regis Gomes1*, Iva Kolářová2, Anderson Sá-Nunes3,4 and Matheus Carneiro5

1Biotechnology, Oswaldo Cruz Foundation, Eusébio, Brazil, 2Laboratory for Biology of Insect Vectors, Department of Parasitology, Faculty of Science, Charles University, Prague, Czechia, 3Laboratory of Experimental Immunology, Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil, 4National Institute of Science and Technology in Molecular Entomology, National Council of Scientific and Technological Development, Rio de Janeiro, Brazil, 5Snyder Institute for Chronic Diseases, University of Calgary, Calgary, Canada

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Introduction

In recent years, an increasing body of evidence shed light on the importance of salivary proteins from hematophagous arthropods. Although the first studies on the cutaneous reactions to mosquito bites in humans date back about a century (Gordon, 1922; Boycott, 1928), it took many decades for hematophagous arthropod saliva to be recognized as a source of bioactive molecules on host hemostasis and immunity (Ribeiro, 1995). Several groups demonstrated that the salivary secretion of blood feeding vectors could enhance pathogen transmission and/or establishment. This phenomenon, named saliva-assisted transmission (Nuttall, 2018), was initially proposed for ticks and later expanded to other hematophagous arthropods. These findings created several lines of investigation now involving the hematophagous vector-pathogen-vertebrate host triangle (Gomes and Oliveira, 2012). In addition, several groups have been also working with the concept of saliva-based vaccines, showing promising results in different models of vector-borne diseases (Manning et al., 2018; Sá-Nunes & Oliveira, 2021).

Due to the limitation of dissecting the whole salivary glands or direct collecting of pure saliva, the “omics” approaches represented a revolution to the research field on saliva from blood-feeding arthropods. Thus, proteomes, transcriptomes and genomes of hematophagous arthropods provided a huge catalog of potential new molecules to be explored. This led to the discovery and development of saliva-derived biotherapeutic molecules useful in different clinical settings. The 4 articles published on this special topic bring some of the new discoveries, putting important pieces of puzzle into the
picture helping us to understand the complex interaction between saliva-parasite-host and its further use in human/patients benefit.

In a minireview by Aoki et al. the readers can learn how sand fly saliva can act as multifunctional bioactive molecules. Many studies reveal the potential use of sand fly salivary proteins for the control of Leishmaniasis, either as anti-Leishmania vaccines or as biomarkers of vector exposure (Valenzuela et al., 2001; Gomes et al., 2012; Grespan et al., 2012; Lestinova et al., 2017). Nevertheless, Aoki et al. also stressed out that some sand fly salivary proteins were identified as triggering autoimmunity in humans. The development of anti-sand fly saliva antibodies that cross-react with the ectodomain of human desmoglein 1 (Dsg1), is associated with skin autoimmune diseases, such as Pemphigus. Previous work from this group demonstrated a possible cross-reactivity between IgG4 and IgE antibodies against the sand fly Lutzomyia longipalpis LJM17 and LJM11 proteins with human Dsg1. Moreover, some sand fly salivary proteins (e.g., Phlebotomus papatasi PsSP32) can induce immunocomplexes with desmogleins, triggering Pemphigus in genetically predisposed individuals. Therefore, we should bear in mind that salivary proteins might elicit autoimmune response and thus every vaccine candidate should be carefully tested for such side effects.

One of such vaccine candidates was introduced in an interesting approach by Lajevardi et al. They showed a multivalent live vaccine against cutaneous leishmaniasis using Leishmania tarentolae as a vector co-expressing PsSP15 and PsSP9 salivary proteins plus CpG as an adjuvant. BALB/c mice were immunized and challenged with two different parasites, Leishmania major and Leishmania tropica, resulting in a protective Th1 immunity. Importantly, this is the first study testing a live vaccine based on the combination of two different salivary proteins that protect against two different species of Leishmania, opening a new pathway for development of a safe saliva-based vaccine combining different salivary antigens.

Carvalho-Costa et al. further explore the salivary glands and intestine omics from the triatome Rhodnius neglectus, a potential vector of Trypanosoma cruzi, giving an important contribution in this area. The authors analysed the global transcriptional genes of intestine omics from the triatome during fasting, in blood fed and in blood fed plus T. cruzi. In summary, blood plus parasite inhibited the expression of blood processing genes involved in insect metabolism (e.g., Antigen-5 precursor, Pr13a, and Obp), detoxification (Sult1) in the intestine and acid phosphatases in the saliva. They also demonstrated a decrease of lipocalins and nitrophorins expression in salivary glands and the presence of two new proteins in the intestine, named as pacifastin and dipterin. Importantly, several transcripts of unknown proteins with potentially interesting function were found in the saliva and intestine. The results suggest that the parasite can change the transcriptomic profile, thereby contributing to our understanding of parasite-vector interactions and opening new directions to investigate the network between feeding physiology and post-meal/infection in triatomines.

In an elegant study, Praca et al. used high-throughput transcriptomics and proteomics to report the first salome study on the synanthropic triatome Triatoma sordida. The authors sequenced 57,645,372 reads that were assembled into 26,670 coding sequences. From these, a total of 16,683 were successfully annotated. Interestingly, sialotranscriptomic profile shows lipocalin as the most abundant protein family within putative secreted transcripts, also demonstrated in the aforementioned study by Carvalho-Costa et al. Trypsins and Kazal-type protease inhibitors were highlighted followed by ubiquitous protein families and several enzyme classes. The proteomics further identified 132 proteins in T. sordida salivary gland soluble extract, including lipocalins, Hemiptera-specific families of proteins, CRISP/Antigen-5 and Kazal-type inhibitors. Having the salome of T. sordida in hand, the next step could be to explore the immunopharmacological activities of these molecules.

There is a great interest in the development of new immunomodulators, vaccines, anti-inflammatory, and anti-hemostatic drugs, in addition to markers of exposure for hematophagous vectors based on their salivary proteins. The articles published in this Research Topic highlight several important aspects that can effectively select promising candidates, help understanding vector’s physiology and vector-host interactions, as well as the evolutionary mechanisms leading to the insect’s adaptation to the blood-feeding behavior. The articles clearly show the advantage of the “omics” approach that represent state-of-the-art technique in the research of saliva from blood-feeding arthropods, providing catalogues of potential new molecules to be explored in silico and in biological platforms. We hope that more research groups will further invest their effort in this topic, exploring also other hematophagous arthropods trying to understand the natural interaction of vector-host-pathogen in its whole complexity.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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