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Mini Review

The Biology of Hematophagous Arthropods Addressed by Molecular High-Throughput Approaches

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Abstract

Hematophagous arthropods harbor several pathogens that cause diseases of impact in global public health. In view of that, great efforts have been made to design new strategies for vector and pathogen control. Molecular biology allied to high-throughput approaches has been a powerful tool to understand this taxa´s biology, besides providing platforms for discovery of novel pharmacological compounds and vaccine antigens. Indeed, the field of molecular investigation of bloodsucking arthropods advanced quickly, as "omics" technologies improve in terms of cost, sensitivity, throughput and data integration. Here, we summarize the evolution of high-throughput approaches and discuss its impact on important findings about vector-pathogen-host interactions.

Keywords: Hematophagous arthropods; Genomics; Transcriptomics; Proteomics; Metabolomics

Abbreviations

HA: Hematophagous Arthropod; NGS: Next-Generation Sequencing; SRA: Sequence Read Archive; EST: Expressed Sequence Tag; DNA: Deoxyribonucleic Acid; CDNA: Complementary Deoxyribonucleic Acid; MB: Mega bases; RNA: Ribonucleic Acid; MRNA: Messenger Ribonucleic Acid; MIRNA: Micro RNA; SIRNA: Small Interfering RNA; PIRNA: PIWI-Interacting RNA; NT: Nucleotides; 2DE: Two-Dimensional Gel Electrophoresis; MALDI: Matrix Assisted Laser Desorption/Ionization; TOF: Time Of Flight; MS: Mass Spectrometry; MS/MS: Tandem Mass Spectrometry; LC: Liquid Chromatography; 1DE: One Dimensional Gel Electrophoresis; IEX: Ion Exchange Chromatography; RP: Reverse Phase Chromatography; ^{1}H NMR: Proton Nuclear Magnetic Resonance

Introduction

Blood-feeding habits of arthropods evolved independently over millions of years, leading to several morphological adaptations and a diversity of strategies to overcome barriers imposed by hosts [1]. One common adaptation in Hematophagous Arthropods (HA) includes the development of highly functional salivary glands, which produce pharmacologically active molecules that counteract host homeostasis, inflammation and adaptive immunity, besides playing an important role in the establishment of infections by an infinity of pathogens [2]. Molecular high-throughput approaches applied to the study of these invertebrates are of major interest for understanding vectors´ biology, enabling to explore new control measures and their pharmaceutical potential [3]. In this mini-review, we highlight some important findings achieved by the application of genomics, transcriptomics, proteomics and metabolomics to the study of blood-feeding arthropods and provide insights into the progress and contribution of high-throughput strategies to the molecular investigation of HAs.

Genomics

Genome sequencing is a crucial step to understand the molecular biology of an organism, while in the last few decades, advances in computing and robotics allowed high-throughput sequencing [4]. Some successful decoding of mosquitoes´ genomes employed automated Sanger-sequencing technology [5]. Those include the genomes of *Anopheles gambiae* (vector of *Plasmodium* parasites) [6], *Aedes aegypti* (vector of yellow fever and dengue fever viruses) [7] and *Culex quinquefasciatus* (vector for filarial parasites and West Nile virus) [8]. A sequenced genome facilitates further studies, for example, by providing a basis for approaches aimed to understand molecular mechanisms implicated in odor mediated behavior and host seeking by *An. gambiae* [9]. Furthermore, complete genomes allow the development of tools for genetic modification, a promising strategy for vector control, as observed for *Ae. aegypti* regarding to the development of transgenic insects to assess their vectorial competence, larval competition, adult energy reserve and in approaches aimed at suppression of mosquito population [10,11]. The genome of *Ixodes scapularis* (black-legged tick, vector for Lyme disease), although not fully annotated, was also uncovered by Sanger-sequencing as a result of the *I. scapularis* Genome Project [12]. The black-legged tick genomic data have been useful for the identification of tick immunity-related genes that might be of interest for development of new strategies for tick control [13].

Despite of the major accomplishments, automated Sanger-sequencing is highly time-consuming and expensive in a cost effective point of view. In the last years, innovative technologies for sequencing (454, IonTorrent, Illumina, SOLiD and Helicos), collectively called Next-Generation Sequencing technologies (NGS) came up to obtain cheaper, faster and increased throughput of high quality data [14]. Development of NGS technologies were basically driven by interest involving human genomes [14]. Currently is widespread for several organisms. Indeed they have been successfully employed in studies focused into genomic analysis of blood-feeding arthropods. Combined approaches of both Sanger and NGS technologies yielded the complete genome of *Rhodnius prolixus*, a triatomine vector of the Chagas disease parasite, *Trypanosoma cruzi* [15]. Moreover,

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Table 1: Data collection at NCBI resources of hematophagous arthropods with sequenced genome.

Species	Vector of	Genome ID	Size (MB)	Transcriptome or Gene Expression Bioprojects			SRA[a]		dbEST[b]
				Sequencing	Array	Total	DNA	RNA	
Aedes aegypti	Dengue virus and Lymphatic filariasis	44	1,376.42	14	32	46	64	348	301,596
Aedes notoscriptus	Dengue virus	34525	15,851 bp[c]	-	-	-	-	-	-
Anopheles gambiae	*Plasmodium*	46	265.01	66	25	91	8,183	59	153,332
Anopheles sp[d]	*Plasmodium* and Lymphatic filariais		98 to 288	20	0	20	2,029	64	27,915
Culex quinquefasciatus	Saint Louis encephalatis and West Nile Virus	393	579.04	5	2	7	1	39	207,116
Cimex lectularius	Unknown	11279	650.48	6	-	6	3	13	7,129
Rhodnius prolixus	*Trypanosoma cruzi*	447	702.65	2	-	2	8	9	16,281
Glossina sp[e]	*Trypanosoma*		315 to 370	1	-	1	37	32	1,127[f]
Lutzomyia longipalpis	*Leishmania*	758	154.23	1	-	1	2	16	35,801
Phlebotomus papatasi	*Leishmania*	10999	363.77	1	-	1	4	-	44,123
Pediculus humanus corporis	*Borrelia, Bartonella, Rickettsia*	522	110.78	1	-	1	1	-	4,508
Ixodes scapularis	*Borrelia, Anaplasma,*	523	502.56	24	1	25	4	35	193,773
Rhipicephalus microplus	*Babesia, Anaplasma*	2797	144.77	7	7	14	2	3	52,901
Lepeophtheirus salmonis	*Salmon anemia virus*	11279	650.48	6	-	6	3	13	7,129

Table 2: Gene expression data collection at NCBI resources of hematophagous arthropods with no reference genome described.

Family/Sub-family	Common name	Number of species (a)	SRA[b]		dbEST[c]	GEO[d]
			DNA	RNA		Microarray
Ixodidae	Hard ticks	24 (6)	193[e]	63	59,471	10
Argasidae	Soft ticks	7 (4)	1	-	14,766	-
Triatominae	Kissing bugs	8 (4)	-	11[f]	12,525	-
Phlebotominae	Sand flies	7 (2)	-	1	12,750	-
Corethrellidae	Frog-biting midges	1	-	1	-	-
Culicidae	Mosquitoes	16 (5)	13	118[g]	3,640	58
Ceratopogonidae	Biting midges	1	-	14	3,028	-
Simuliidae	Black flies	3 (1)	-	-	5,683	-
Tabanidae	Horse flies	1	1	-	-	-
Glossinidae	Tsetse flies	3 (1)	12	8	81,028[h]	-
Ceratophyllidae	Fleas	2 (2)	-	2	-	-
Pulicidae	Fleas	2 (2)	-	2	7,018	-

*DNA and cDNA sequence data deposited until December 5, 2014. a. number of genera in parenthesis; b. SRA (Sequence Read Archive) is the NCBI database that stores raw sequence data from NGS technologies; c. db EST is the Expressed Sequence Tags database from NCBI that stores short single transcript sequences obtained by Sanger technology; d. GEO (Gene Expression Omnibus) is a functional genomics data repository for Array- and sequence-based studies; e. 186 from *Amblyomma americanum* and 6 from *Ixodes ricinus*; f. 10 from *Triatoma infestans*; g. 80 from *Aedes albopictus*; h. 79,292 from *Glossina morsitans*

application of both technologies also resulted in the genome sequencing of the Tsetse fly (*Glossina morsitans*): vector of the African trypanosomiasis, and led to the discovery of chromosomal integrations of bacterial (*Wolbachia*) genome sequences, a family of lactation-specific proteins, reduced complement of host pathogen recognition proteins and reduced olfaction/chemosensory associated genes [16]. The ability of NGS to sequence the whole genome of many related organisms has also allowed large-scale comparative studies to be performed [14]. Aimed to investigate the genetic basis of vectorial capacity of 16 *Anopheles* mosquito species, a recent NGS-based study found faster rates of gene gain and loss, elevated gene shuffling on the X chromosome, and more intron losses, when compared to *Drosophila*. The dynamics of anopheline genomes was implicated in their capacity to adapt to new ecological niches, including humans as primary hosts [17].

A search at NCBI database resources such as Genome, Sequence Read Archive (SRA) and Expressed Sequence Tag (EST), provided a rapid overview about sequence deposition (DNA and cDNA sequences obtained either by Sanger technology or NGS) from HAs with sequenced genome (Table 1), as well for those with no reference genome (Table 2). From 135 Arthropoda genomes at Genome database, 34 are from hematophagous species. Numerical data displayed in (Tables 1, 2) revealed which species and/or group

of species are the most studied. The Vector Base database is also an important resource for blood-feeding arthropod genomes and pre-released genome projects [18], at this resource, *I. scapularis* and *A. aegypti* genomes present the largest sizes, over 1,300 Mega Bases (Mb). Indeed, several NGS-based studies of vector´s whole genome are expected to emerge with cost constrain and improvements in NSG, such as longer sequence reads [5].

Transcriptomics

Transcriptomics emerged as a field to understand the whole set of RNAs transcribed by a genome in a tissue or cell type under several conditions [19].It is employed to discern the dynamics of gene expression, helping to interpret the blood-feeding arthropods/hosts interaction and uncovering novel pharmacologically active compounds. Up to date, about 75 species of HA without reference genome present data from gene expression studies (Table 2).

Expressed sequence tags

Most of the molecular high-throughput studies evaluated gene expression of HAs´ tissues with automated Sanger-sequencing of reversely transcribed mRNA into cDNA libraries, generally, yielding hundreds to thousands of ESTs, per study. Due the potential for discovery of novel compounds or even vaccine subunits [20], numerous transcriptomes from sand flies, ticks, fleas and mosquitoes have been produced by traditional sequencing methods; we emphasize the large amount of studies focused on their salivary glands [21–36]. Those studies resulted in great advance into the understanding of gene expression in HAs, allowing the discovery of a large number of genes coding for several protein families, such as, housekeeping genes involved in metabolic processes, structure, signal transduction, protein synthesis among other constitutive functions. Important tissues for hematophagy, such as midgut (blood digestion) and salivary glands (saliva production), present a wide range of transcripts coding for proteolytic enzymes [37] and anti-hemostatic/immunomulatory proteins, respectively [1]. Of note, disintegrins, which have been described in the salivary glands of ticks, have been fundamental on the understanding of integrin function and for the development of anti-thrombotic drugs [38]. Hard ticks and Tsetse flies without reference genome present the largest collections of EST data (Table 2).

Microarrays

Limitations on throughput and cost of Sanger-sequencing also raised the development of methods based on nucleic acid hybridization (microarrays) to analyze gene expression. Due to the lack of genome information of HAs, data generated by EST sequencing have been the basis of studies that addressed gene transcription of HAs by microarray technology [9,39–44]. A microarray approach allowed the evaluation of gene expression profiles from salivary glands of *A. americanum* tick, where the transcriptional patterns change dramatically during blood-feeding. Genes associated with tick survival are increased in early feeding stages, while in contrast, transcripts associated with survival were down-regulated at the end of tick infestation [39]. Interestingly, a microarray-based study demonstrated that, infection with *P. falciparum*, induced at least 43 genes to be differentially expressed in the salivary glands of *An. gambiae.* One of those genes codes for Agaphelin, whereby the characterization of its ability to inhibit neutrophil elastase promoted the description of a novel anti-hemostatic mechanism in hematophagy [44].

RNA sequencing

By overcoming issues raised by traditional methods as cost, high throughput, time, sensitivity, low sample input and low background, NGS also impacted the investigation of global gene expression. Recently, NGS-based transcriptomes were reported for two triatomines, *Rhodnius prolixus* [45] and *Triatoma brasiliensis* [46], from four *Amblyoma* ticks [47,48] and *Ixodes ricinus* [49] , some mosquitos [50–55] and for *Cimex lectularius*, the bed bug [56]. It should be denoted that one advantage of NGS technology over conventional methods is the significant increase in the amount of data that is produced. As an example, we have demonstrated that, in comparison with two Sanger-based sequencing of cDNA libraries prepared from salivary glands of *Amblyomma cajennense* ticks, NGS-based sialotranscriptome yielded approximately 180-fold more sequences (70% of novel sequences), besides the larger number of full-length sequences. While conventional methods yielded less than one Mb of data, the NGS-based dataset produced over 69 Mb [48]. Furthermore, we were able to demonstrate that the salivary gland gene expression is affected not only by tick species, but also developmental stage and host species [48]. Indeed, combination of biochemical and molecular biology with NGS-based technology have the potential to define gene structure, gather understanding into RNA metabolism, provide insights into post-translational modifications and characterize small non-coding RNAs as miRNA, siRNA, and piRNA, with lengths shorter than 35 nt [19]. Ixodid ticks and mosquitoes are the HAs with the largest RNA sequencing data deposited at NCBI resources (Tables 1 and 2).

Proteomics

One of the significant contributors in the post-genomics era is the field of proteomics, which is defined by the systematic identification and characterization of protein sequence, abundance, post-translational modifications, interactions, activity, sub-cellular localization and structure in a given sample, e.g. salivary glands from HAs [57]. Three major proteomic strategies have been used: (i) 2DE-based separation, spot excision and protein identification by MALDI-TOF MS peptide mass fingerprint, MALDI-TOF MS/MS, or LC-MS/MS; (ii) 1DE-based separation, slice excision and protein identification by LC-MS/MS; (iii) shotgun approaches based on preparation of a total protein extract, multidimensional peptide fractionation (i.e. IEX/RP) and identification by MS/MS [58]. Several studies have addressed the protein dynamics of a diversity of tissues and conditions from mosquitoes of genus *Anopheles* [59–69], *Aedes* [70–78] and *Culex* [79,80]; from several tick species [81–92], triatomines [93–96], sand flies [97–102], fleas [103,104], biting midges [105,106] and black fly [107]. These studies contributed to validate findings achieved by evaluation of HAs´ patterns of gene expression and, they have been useful to understand the dynamics of protein networks and biological processes. Of interest, proteomic investigation of soluble olfactory proteins in *An. gambiae* demonstrated that females express a larger number and higher quantities of odorant-binding proteins in their antennae than males [68], which corroborate with transcriptional profiles of molecular mechanisms implicated in odor mediated behavior and host seeking by *An. gambiae* [9]. Moreover, proteomic analysis of *Dermacentor reticulatus* tick unfed larvae demonstrated that metabolic and cellular processes involved in protein synthesis as the most active, suggesting that ticks are very active during this life

stage [91]. Furthermore, proteomic approaches have been useful to the identification of several flea and phlebotomine sand flies [98,104].

Metabolomics

Metabolomics covers qualitative and quantitative analysis of metabolites found in biological fluids, cells and tissues upon different conditions that may influence metabolite profiles. The most commonly used methods of probing the metabolome are: mass spectrometry and proton nuclear magnetic resonance (^{1}H NMR) [108]. While large-scale studies of HAs-derived metabolites are still in their infancy, we highlight a recent report aimed to evaluate the chemical composition of feces from three triatomine species (*Triatoma infestans, Rhodnius prolixus* and *Panstrongylus megistus*). This work identified several putative metabolites with constant frequency among all species, whereas of prenol lipids, amino acids, glycerolipids, steroids, phenols, fatty acids and derivatives, benzoic acid and derivatives, flavonoids, glycerophospholipids, benzopyrans, and quinolines were differentially identified among the triatomines [109]. These results are in line with other findings, which showed that ingested blood lipids are degraded into free fatty acids in the triatomine intestinal tract and are implicated on the differentiation of *Trypanosoma cruzi* [110]. The metabolic profile of vectors and their influence over pathogens and hosts merits further investigation in order to understand the role of individual metabolites on vector-parasite-host interactions.

Conclusion

In summary, high-throughput approaches accelerated the study of several molecular features of disease vectors. Functions, genes, proteins families and metabolites previously unreported for blood-feeding arthropods are now described. Therefore, advances and improvements of current technology provide new perspectives over: (i) HAs´ biology through combined generation of complete genomes and transcriptomes; (ii) design of innovative strategies for control of vector-borne diseases; (iii) identification and characterization of new drugs and their mechanisms of action.

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