Perspective

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Vector−borne diseases: Mosquito holobiont and novel methods for vector control

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Female mosquitoes of several species require blood from warm-blooded animals, including humans for the purpose of reproduction. In this process, several microbes residing in the salivary gland and midgut of mosquitoes also get transferred from one human individual to the other – a traditional model by which many vector-borne diseases (VBDs) get transmitted in the population through mosquitoes belonging to *Anopheles*, *Aedes*, *Culex* and other genera. Considering that VBDs are highly dependent on eco-climatic conditions of a particular location, the net holobiont (mosquito and its community of associated microorganisms)[1] of these medically-important mosquitoes possibly forms an "evolutionarily adapted microbial ecosystem". Such an adapted microbial ecosystem in the mosquito's salivary gland and midgut has been shown to be not only essential in their development and survival[2], but also can alter vector competence (ability to transmit pathogens in population) of mosquitoes[3]. This otherwise means that disruption of such a tripartite interaction (mosquito-microflora-pathogens) in an adapted holobiont complex might lead to changes in fitness, vectorial capacity, *etc*. of the mosquitoes, and pathogenic characteristics of different microbes (opportunists can turn pathogenic). In the tropical and subtropical regions of the globe, VBDs like malaria, dengue, chikungunya, Zika, *etc*. constitute one of the primary human health hazards and death. Controlling mosquito population (vector control) is considered as one of the finest ways to control VBDs. While traditional vector control strategies have several limitations, novel vector control approaches, *viz*., (i) reducing vector populations, and (ii) development and usage of mosquitoes refractory to pathogens of VBDs have shown great promises[4]. To this extent, recent advent of techniques for transforming mosquitoes refractory to pathogens (*e.g*. para-transgenesis, gene silencing, gene editing by CRISPR-Cas9, *etc*.) coupled with a gene drive[5] have been widely discussed and in some cases, vividly used for control of *Anopheles* and *Aedes* mosquitoes.

Amongst several approaches, turning mosquitoes that are vectors to different human microbial pathogens into refractory types has gained large momentum. For this, experiments involving two types of symbiotic Gram-negative bacteria that populate mosquito midgut (*Wolbachia* and *Serratia*) have yielded several interesting (and somehow contrasting) results. While *Wolbachia* can help inhibiting malaria parasite, *Plasmodium* infection in both *Anopheles* (*Anopheles gambie* and *Anopheles stephensi*[6,7]) and *Aedes* (*Aedes aegypti*[8]) mosquitoes, evidences have been presented that *Wolbachia* can also enhance *Plasmodium* infection in *Anopheles* (*Anopheles gambie*[9]) and *Aedes* (*Aedes fluviatilis*[10]) in some cases[11]. Similarly, *Serratia odorifera* in one hand inhibits the development of *Plasmodium* but on the other hand enhances susceptibility of *Aedes aegypti* to dengue virus[12]. It seems therefore that in different holobiont complex, two different microbial pathogens (*Wolbachia* and *Serratia*) behave very differently in term of controlling either *Plasmodium* or dengue virus. Very similarly, mosquitoes also differ in transmitting different human microbial pathogens in different eco-climatic settings that possibly influence the composition of the holobiont. For example, the Japanese encephalitis virus is commonly transmitted by *Culex* mosquitoes in almost all the endemic settings but in Malaysia and India, in addition to *Culex*, Japanese encephalitis virus is transmitted by *Aedes butleri*[13] and *Anopheles* subpictus[14], respectively. Furthermore, *Anopheles* has also been shown to transmit an alphavirus, *o'nyong−nyong*[15]. All these results suggest the fact that mosquito holobionts form

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adaptive complexes that differ with mosquito species and eco-climatic conditions prevalent at the habitation of mosquitoes.

In mosquitoes, the CRISPR-Cas9 technique has been initiated relatively recently to disable infection to human pathogens, thereby preventing transmission of vector-borne diseases. For example, by knocking-out of the *FREP1* (fibrinogen-related protein) gene, which is an essential factor of mosquito innate immune system required for maintaining immune-homeostasis (and thereby keeping the adapted mid-gut floral complex in harmony) in the malaria vector *Anopheles gambiae* by CRISPR-Cas9 method could help suppress the growth of *Plasmodium*[16]. Therefore, in a situation where *Anopheles gambiae* mosquitoes are *FREP1*-deleted, due to altered immune homeostasis and disruption of adapted holobiont complex, existing opportunistic microbes in mosquito midgut/salivary gland might turn into pathogenic form for human and pose new threat to human health. It is therefore essential to develop novel vector control strategies for development of refractory mosquitoes to a particular pathogen with due care not to disrupt the adapted holobiont complex. This is necessary for maintaining homeostasis in mosquito midgut and/or salivary gland for better use of the technique in public health. A holistic view including surveillance on the composition of midgut and salivary gland microflora of the mosquito, geographic structure, in-depth analysis of eco-system surrounding mosquito habitation, reservoirs of the disease pathogen and bionomics of the mosquitoes should be taken into consideration before employing refractory mosquito techniques of vector control to improve public health.

Conflict of interest statement

We declare that there is no conflict of interest.

Authors' contributions

USS conceived the idea, retrieved and analysed the data from publications and wrote the first draft of the manuscript. AD made necessary critical revisions for important intellectual content and wrote the final draft of the manuscript.

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