Vampires are alive and among us – known as Hematophagous arthropod vectors

The bacteria malaria, and filariasis and dengue, and other mosquito-borne viruses influence the vector in favor of the pathogens. New insights into insect sciences open new frontiers for fighting the "vampires".

Among the blood-sucking insects are mosquitos transmitting viruses causing a wide variation of diseases, and as far as bacteria are concerned, malaria and filariasis (1). Anopheles spp. transmit malaria, and in Africa filariasis, Culex spp. is involved in spreading filariasis in the Americans and Aedes spp. as well as Mansonia spp. in Asia and the Pacific. Aedes aegypti and Aedes albopictus are causing dengue diseases in many countries. Mosquito-related virus infections of major interest for Southeast Asia are diseases caused by the dengue- and Zika viruses. Besides hemorrhagic fever, arboviruses cause arthritis, encephalitis, and meningitis in numerous world areas.

"Smart" mosquitos and pathogens

The next time a mosquito bite and you swat it, just hold in. You are interfering with a most astonishing development of evolution. Evolution not just worked in favor of us but also cared for other living things to survive, multiply, and produce themselves. About 14.000 species of insects need blood for survival, a "nutrient" that is not easy to come by. Several hundred blood-sucking insect species attack humans who fight back, determined to eradicate the nuisance. Sucking blood, the female mosquito is not only at risk of being killed, but it is a life-or-death question for the vector to be successful. It also must find a suitable hoist maneuvering through a forceful, even hostile environment.

Evolution created a big unpleasant problem and one that is life-threatening for us. Insects harbor microorganisms and parasites, and evolution took care of it in that the insect-human connection is efficiently used to spread the infective go-betweens (2). One of the most astonishing achievements of evolution is the sophisticated life cycle of malaria parasites. Within the mosquito, the parasites develop from gametocytes into sporozoites, which are injected into the host and develop into the host's liver into merozoites, infecting red blood cells. Finally, gametocytes are taken up from specified mosquito vectors. Similarly, evolution equipped "the mosquito-borne virus life cycle" which innovative tools to instrumentalize the mosquito vector to multiply (3).

Viruses are not only a nuisance but even could be life-threatening. To balance that, evolution works for us as well. Viruses are hypothesized to come first and trigger life on earth and are thought to be essential for animal protein adaptation, such as immune- and non-immune functions (4-6).

No "silver bullet" yet against vector-borne diseases

Still, vector-borne diseases are one of the most overwhelming and challenging problems for public health. To a certain extent, malaria could be weakened through various means in many countries but remains a serious problem affecting especially children in sub-Saharan Africa. The parasite is resistant to the "most widely used treatments and increasingly resistant to insecticides". Recently a malaria vaccine was introduced after trying desperately to develop one since the 1980th. The vaccine was tested in a trial phase in three African countries "despite limited and nagging safety concerns" and recommended by WHO for widespread use in sub-Saharan Africa and other regions with a high P. falciparum malaria transmission (7, 8).

Vaccination against dengue fever and Zika virus is a tricky issue because of the danger of Antibody-Dependent-Enhancement (ADH), as mentioned in a foregoing entry into this blog. ADH could be triggered in dengue patients formerly infected by the zika virus and the other way round (9). Presently a Dengue vaccine is only recommended for those living in an endemic area and supposed to have had contact with one of the dengue viruses before. A paper from Pakistan, published this year, illustrates the increasing problems caused by mosquito-borne viral diseases, especially felt in urban areas (10). So far, it seems the mosquitos are always a step in front of the human host, and the hope for the "silver bullet" to solve all the problems once and for all is in vain (11). Vectors, unfortunately, are pretty "smart". They developed cognitive abilities and memorized with thermos sensors and "olfactory behavior", how to find and bite us (12). Not only do those vectors become resistant to insecticides, but they also develop behavior to avoid the time insecticides are spread to fight them (13).

Already in use, or in the trial phase, are several sophisticated vector control measures such as interfering with the host-seeking senses of the insect, luring the female mosquito to oviposition attractants with larvicidal formulations, or treating peri domestic animals, such as goats, smelling for the mosquito similar as humans (11).

Temperature sensing vector and virus-initiated smell sensing

Nowadays, omics sciences increased the understanding of the biology of the vectors, and how the parasites are transmitted are investigated in depth (2). For instance, a gene, the inotropic receptor IR21a in the sensory cells of female mosquitos Anopheles gambiae, an important malaria vector in Africa, enables the insect to react to the change in the temperature by locating the host (14). Temperature sensitivity, facilitated by thermoreceptors, is well developed in insects, and the advantage probably is to avoid resting on too hot grounds but also serves to detect differences in temperature (15). For long-range orientation, after carbon dioxide activation, besides heat also, water vapor and vision could guide the insect to its host (16).

Not only temperature but how the host might smell attracts the mosquito. From malaria, it is known that individuals harboring the gametocytes of P. falciparum draw the A. gambiae vector (17). That is a nasty trick of evolution at the cost of humans, serving the parasite to continue its life cycle. What the malaria parasite can achieve, the dengue and zika viruses can do as well (18, 19). Mice infected with the zika or the dengue virus were especially approached by the mosquitos. The odorant emitted by the mice was acetophenone. Patients infected with dengue also emitted acetophenone more than the healthy controls. The mechanism involves the bacteria on the skin being the primary source of acetophenone. Usually, the skin's microbiota inhibits, to a certain extent, the smell by excreting a protein labeled RELMα. Mice infected with one of the two flaviviruses reduced RELMα enabling the bacteria to proliferate and increase the smell. Feeding the mice a derivative of Vitamin A, isotretinoin, increased the RELMα and by this mosquito were less attracted. Future findings like this might help diagnose the infection by special sensors and reduce the allure of people to the vectors.

Salvia of the mosquito bite affects the acquisition and transmission stage

The attraction of mosquitos to find and bite the human also indirectly favors the virus. There are direct favorable effects for the virus during the acquisition- and transmitting stage, which influences the virulence of the virus while passing through the insect (3, 20). While the mosquito bites, the saliva of the mosquito, containing hundreds of active proteins and RNAs, already helps to facilitate the infection. Blood coagulation is decreased. The mosquito bite promotes an inflammatory response and inhibits the host's innate immunity, starting to infect the keratinocytes of the epidermis. The mosquito saliva is of particular interest for further research not only because it facilitates the virus infection during transmission but because different mosquito species use other mechanisms for transmission due to their salvia components (21).

The virus, on its way through the vector

The female mosquito sucks more blood over its weight. Together with the blood meal, the virus passes through the mosquito, infecting the epithelial cell of the mosquito gut and spreads into the hemocoel. The hemocoel is the cavity of the insect which has no blood vessels, and within the hemolymph, the organs of the mosquito are located. The complex events surrounding the digestion of the blood meal and metabolic and immunological procedures partly inhibit but partly increase the proliferation of the virus. Procedures seem to differ between vector species and infective agents involved and are subject to numerous investigations. Proteases and other digestive enzymes reduce the blood meal volume in a relatively short time. What happens in the midgut also partly inhibits the infective agent but partly supports virus proliferation. So, for instance, heme is toxic and causes oxidative stress affecting the virus, and as far malaria is concerned, the plasmodium. On the other hand, iron facilitates egg production, a favorable issue for the mosquito but also seems vital for viral proliferation.

The midgut of the mosquito harbors bacteria, fungi, etc., the so-called microbiota. Its role still is under investigation since it affects the immune response of the vector toward the pathogen. In some vector-virus systems, microbiota reduces infection, but other systems can probably assist the virus in attaching better to the vector. Also, the immune response of the vector towards pathogenic attacks probably differs between vector and pathogen systems. Generally, an immune response of the vector to the virus weakens the vector's ability to reproduce. Favorable for the virus is the reduction of the innate immunity, but the virus has more difficulties overcoming the cellular- and humeral immunity.

The process of making its way to the vector takes some time for the pathogen, as found through laboratory investigation with A. aegypti and dengue viruses (22). After acquiring the virus, midgut infection occurs in 3 to 5 days, and the passage through the various parts of the vector up to reaching the salivary glands seven to 10 days, and the virus is transmitted to the next host in 10 to 14 days.

Outlook

The vector not only acquires the pathogen and serves as a vehicle to transmit it to the host, but the biology of the vector influences the virulence and progression of the pathogen. An important factor, but still not very well understood, is the role of the microbiome of the mosquitos in terms of immunological reactions (20). Intensive research is needed to investigate specific and different mechanisms between mosquito species while transmitting arboviruses and the role of the salivary proteins of the mosquito (3).

The importance of the environment in determining the breeding behavior of the mosquito has been recognized for decades and helped to understand where and why there are specific endemic areas for arthropod vectors creating a high risk for malaria, filariasis, and serious viral diseases (23, 24). So, for instance, the danger of getting malaria in the border area of Thailand is due to malaria vectors preferring oviposition forest areas with clean water streams. In Indonesia, malaria vectors are common in beach areas because for breeding brackish water, a mix of fresh and seawater is preferred.

Nowadays, with the help of sophisticated research tools, understanding the mosquito-borne virus life cycle will help develop new tools to fight the diseases. For instance, the first trial with a vaccine against mosquito salvia was inaugurated. There might be a dream for a universal arborvirus vaccine based on the immunity against mosquito salvia (25, 26).

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