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Viruses of parasites as actors in the parasite-host relationship: A "ménage à trois"

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ABSTRACT

The complex parasite-host relationship involves multiple mechanisms. Moreover, parasites infected by viruses modify this relationship adding more complexity to the system that now comprises three partners. Viruses infecting parasites were described several decades ago. However, until recently little was known about the viruses involved and their impact on the resulting disease caused to the hosts. To clarify this situation, we have concentrated on parasitic diseases caused to humans and on how virus-infected parasites could alter the symptoms inflicted on the human host. It is clear that the effect caused to the human host depends on the virus and on the parasite it has infected. Consequently, the review is divided as follows:

Viruses with a possible effect on the virulence of the parasite. This section reviews pertinent articles showing that infection of parasites by viruses might increase the detrimental effect of the tandem virus-parasite on the human host (hypervirulence) or decrease virulence of the parasite (hypovirulence).

Parasites as vectors affecting the transmission of viruses. In some cases, the virus-infected parasite might facilitate the transfer of the virus to the human host.

Parasites harboring viruses with unidentified effects on their host. In spite of recently renewed interest in parasites in connection with their viruses, there still remains a number of cases in which the effect of the virus of a given parasite on the human host remains ambiguous.

The triangular relationship between the virus, the parasite and the host, and the modulation of the pathogenicity and virulence of the parasites by viruses should be taken into account in the rationale of fighting against parasites.

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1. Introduction

As defined from an ecological view-point, a parasite is an organism that lives in association with another organism generally considered the host, and as a consequence of this association, the parasite receives an advantage at the expense of the host. The parasite-host relationship produces detrimental effects on the host and then gains a fitness cost for the parasite over the host. Following this simple definition, parasitism can be seen as a non-mutual symbiotic relationship and many organisms, from viruses to bacteria to vertebrates are parasites. However, traditionally and for historical reasons, the term parasite has been directed toward parasitic organisms with medical or veterinary importance, that depending on their location with respect to the body of the host, are grouped as endoparasites or ectoparasites. Endoparasites consist in parasitic protozoa (unicellular eukaryotes) and helminths (parasitic worms), whereas ectoparasites are generally arthropods. Moreover, parasites are known to be "parasitized" by viruses although a detrimental effect on the parasite is not always clearly visible. The aim of this review is precisely to analyze the relationships between classical protozoan parasites and their viruses, and their effects on the parasite-host relationship.

The first reports of viruses in parasites were based on electron microscopy studies. They revealed the presence of virus-like particles (VLPs) in several parasitic protozoa such as *Entamoeba histolytica* (Diamond et al., 1972) and *Leishmania hertigi* (Molyneux, 1974). Later, having detected viral-like molecules such as nucleic acids in the parasite host, understanding viral infection in parasites began to be accepted (reviewed in Miles 1988; Wang and Wang, 1991; Hartley et al., 2012; Banik et al., 2014). Several viruses of a broad group of parasites have since been characterized at the molecular level. A virus infecting *Trichomonas vaginalis*, the agent of trichomoniasis, was the first virus described in protozoa; this *Trichomonasvirus* was characterized biochemically and identified as a double-stranded RNA (dsRNA)-containing virus (Wang and Wang, 1985). As in *T. vaginalis*, many parasitic protozoa analyzed from diverse groups also contain viruses with dsRNA genomes (Table 1). Such is the case of the *Giardia lamblia* (Wang and Wang, 1986), the causative agent of giardiasis, and of *Leishmania* spp. (Tarr et al., 1988; Widmer et al., 1989), the agent of leishmaniasis. Several of these viruses, *Trichomonasvirus* (*Trichomonas RNA Virus,* TRV), *Giardiavirus* (*Giardia RNA Virus*, GRV) and *Leishmaniavirus* (*Leishmania RNA Virus*, LRV) harbor closely-related monopartite dsRNA genomes and are classified in the *Totiviridae* family; their genomes are packaged in isometric particles with no lipid or carbohydrate content (reviewed in Fauquet et al., 2005; Hartley et al., 2012). These genomes possess two overlapping open reading frames encoding the coat protein and an RNA-dependent RNA polymerase. Members of this virus family and of other families with a dsRNA genome are well represented among fungal viruses. Other parasite viruses such as that of *E. histolytica,* possibly have a (−) sense single-stranded RNA (ssRNA) genome and are of the *Rhabdoviridae* family (Bird and McCaul, 1976). Mattern et al. (1979) also reported that *Entamoeba* probably contains a DNA virus. Moreover, the occasional free-living *Acanthamoeba* spp. pathogen can harbor adenoviruses that are dsDNA-containing viruses (Scheid and Schwarzenberger, 2012).

An interesting aspect of the presence of viruses in parasites is related to hypotheses on the effect that this situation can have on the parasite-host relationship. Certain viruses when residing in parasites might modulate the interaction of the parasites with their host and might have consequences on the infection and pathogenesis of the parasite. In this setting, different conceivable scenarios have been proposed (Fig. 1).

Certain viruses might function as an additional weapon of the parasite, and in cases in which increased infectivity or persistence of the parasite in its own host is observed, this effect could be triggered by the virus of the parasite and result in a possible hypervirulence (Fig. 1A).

In other cases, the presence of the virus in the parasite might attenuate the disease caused by the infected parasite on its host, leading to hypovirulence (Fig. 1B). This capacity presents the virus as ally of the parasite's host (i.e., symbiont viruses of fungi).

Another possibility is when the virus uses the parasite as vector or Trojan horse to enter into the host of the parasite (Fig. 1C). This kind of parasite can accommodate several microorganisms including viruses, and act as reservoir for viruses, protecting them from unfavorable environmental conditions; in this case they might affect the dissemination or transmission of the virus.

These possibilities are discussed below. For the sake of clarity, only parasitic protozoa infecting humans are considered here. The study of the presence of viruses in parasites is acquiring more importance. The idea that viral infections could modify certain aspects of the interaction of the parasite with its host (the macrohost, in this tripartite relation) is interesting and increasing number of evidence supports this idea. In the future, the role of the virus in the parasite-host relationship should be taken into account as an important component when strategies against parasites are being designed.

2. Viruses in parasites

2.1. Viruses with a possible contribution to virulence of the parasite

The relationship of some bacteria with a virus seems to increases the virulence of the bacteria. Such is the case of the bacteria *Corynebacterium diphtheria*, *Salmonella enteric* and *Vibrio cholera* that are causative agents of important diseases in humans (Freeman, 1951; Figueroa-Bossi and Bossi, 1999; Waldor and Mekalanos, 1996). In the parasitic protozoa of the genera *Leishmania*, *Trichomonas* and *Cryptosporidum*, viral infection might also exacerbate virulence of the protozoa (hypervirulence). These cases would represent an example, at least for the parasite, of a virus as mutual symbiont or "good virus" (Roossinck, 2011). In some cases, a deleterious effect of the virus on the parasite could suggest a decrease in virulence (hypovirulence) such as in the case *Giardia.*

2.1.1. Leishmania *viruses*

For the *Leishmania* parasites an interesting hypothesis has been proposed that associates a dsRNA virus to members of the *Totiviridae* family as partially responsible for complications of the disease that this parasite produces (Ives et al., 2011). *Leishmania* parasites transmitted by an insect vector to the vertebrate host, are the causative agents of leishmaniasis that presents a wide variety of clinical manifestations including visceral and cutaneous manifestations, and destructive metastatic mucocutaneous forms of the disease; this latter manifestation canbe refractory to treatment.