

Abstract

Many eukaryotic microbes possess RNA virus-like elements, the role and significance of which are usually unknown. We have studied the trypanosomatid protozoan parasite *Leishmania* in South America, which often bear the dsRNA *Leishmaniavirus* (LRV1), as a new paradigm of protozoal viral virulence. Like most Totiviruses, LRV1 is neither shed nor infectious, and thus may be viewed as a persistent endobiont. Perspectives on the importance of protozoal viruses changed upon discovery that *L. guyanensis* LRV1 is associated with hypervirulence and increased metastasis in animal models, the latter being a hallmark of the more severe forms of leishmaniasis (Ives *et al. Science* 2011). For *Leishmania* we developed RNA interference tools for reproducibly generating isogenic lines lacking LRV1s (Brettmann *et al PNAS* 2016). This has allowed extension of findings with *L. guyanensis* to *L. braziliensis*, the predominant agent of mucocutaneous leishmaniasis (MCL). An important question is the contribution of LRV1 with *Leishmania* pathogenicity in human infections, where disease manifestations differ greatly from those seen in murine models. Recently we showed that the presence of LRV1 was associated with increased relapse and/or treatment failures in human *L. braziliensis*-infected patients treated with pentavalent antimonials in Peru and Bolivia, as well as in *L. guyanensis* infections treated with pentamidine (Adauai *et al & Bourreau et al. J. Inf. Dis* 2016). The association of LRV1 with clinical drug treatment failure could serve to guide more effective treatment of tegumentary disease caused by *Leishmania* sp., possibly through the use of LRV1 inhibitors (Kuhlmann *et al PNAS* 2017), the first against any totivirus.

We have embarked on a systematic survey of known and new viruses in *Leishmania* as well as their monoxenous insect trypanosomatid relatives and other parasites, using a wide range of methods including next-gen RNA sequencing (Grybchuk *et al PNAS* 2018). This has greatly expanded our knowledge of the parasitic protozoal virome with the discovery of multiple new viruses. The properties, evolution and potential contributions of these to virulence and biology will be discussed.