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The Icoaraci Virus (ICOV) Non-Structural Protein N (NSs) modulates the Infection of Macrophages by *Leishmania amazonensis*

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Abstract

Leishmania (L.) amazonensis is a causative species of Cutaneous Leishmaniasis and the main species found in cases of Anergic Diffuse Cutaneous Leishmaniasis, a more severe form of the disease. This species is accidentally transmitted to humans by *L. flaviscutellata*. Recently, we demonstrated that *L.amazonensis*/Amazonian Phlebovirus Icoaraci(ICOV) coinfection enhanced the parasite load in vivo and in vitro, along with the modulation of the expression of IFN1beta. Phleboviruses are RNA viruses organized into three segments. The S segment encodes the NSs protein, the main virulence factor of phleboviruses, which affects the expression of some antiviral-responsive genes and downregulates key factors of the host transcriptional machinery. Phlebotominae sand flies transmit Phleboviruses to vertebrates, including humans, and the cocirculation of Leishmania and Phlebovirus species has been widely reported. Given the importance of Leishmaniasis for public health and the known importance of viral coinfections, it becomes relevant to analyze the role of the ICOV Nss, considering that previous studies have observed the ability of ICOV infection to improve parasite load in a coinfection model. Due to the lack of information on the role of phlebovirus NSs in America's Phleboviruses, we decided to study the role of ICOV NSs. To this end, we obtained, through lentivirus-mediated transduction, macrophage cell lines stably expressing the ICOV/ NSs. Infection index assays with the NSS/ expressing macrophages showed a favorable effect on infection by *L. amazonensis*. In qPCR assays, a relative increase in INF beta and IL-10 mRNA was observed in cells expressing NSs and in the expression of genes related to the antioxidative response: NRF2, HO-1, and SOD-1. Western blot assays corroborated the augment of NRF2 in macrophages expressing NSs. Our data suggests that ICOV/NSs induce the antioxidative response, favoring the parasite infection.

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