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Immunomodulating properties of *Amblyomma variegatum* saliva and role on tick-borne disease transmission

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The tropical bont tick, *Amblyomma variegatum*, is a major pest of ruminants, causing direct skin lesions, vectoring the obligate intracellular rickettsial *Ehrlichia ruminantium*, the causative agent of heartwater, and being able to reactivate dermatophilosis. In general, tick salivary proteins are the result of host blood feeding adaptation and are known to contain inhibitors of blood clotting, platelet aggregation and angiogenesis, as well as vasodilators and immunomodulators. The general objective of this study was to better understand the role of the saliva in the tick interaction with the host but also in pathogen transmission or diseases activation. We therefore first analysed the immunomodulating properties of semi-fed *A. variegatum* female saliva on bovine peripheral blood mononuclear cells (PBMCs) *in vitro*. Flow cytometry and cytokine ELISAs have been used to evaluate the saliva impact on PBMCs. We focused on immunosuppressive properties by analysing both lymphocytes proliferation and monocyte-derived macrophages phenotype characterised by inhibition or induction of stimulatory and co-stimulatory molecules such as MHC-II, CD40, CD80 or CD86, and production of pro- or anti-inflammatory cytokines such as interleukin (IL)-2, IL-4, IL-6, IL-10, IL-12p40, and tumor necrosis factor (TNF)- α . Moreover, a proteomics exhaustive molecular characterisation of *A. variegatum* saliva was performed to cluster data set according to the evidenced immunomodulatory properties, and allowed refined characterisation of *Amblyomma* sialome. Bioinformatics functional analysis of tick saliva highlighted molecular determinants that could, at least in part, explain the biological effects observed on bovine PBMCs. Our results bring new insights for a better understanding of tick-ruminant interactions, and open new perspectives to develop integrative strategies to interfere with the infectious pathoimmunological process of such tick-borne infections.

Keywords: *Amblyomma variegatum*, tick saliva, immunomodulation, proteomics