CYSTEINE PROTEASE INHIBITORS IN THE SALIVA OF THE TICK *IXODES SCAPULARIS* CONTRIBUTE TO FEEDING SUCCESS THROUGH THEIR IMMUNOMODULATORY ACTION TO THE VERTEBRATE HOST

Michalis Kotsyfakis[1], Anderson Sá-Nunes[1], Shahid Karim[2], Ivo M.B. Francischetti[1], Thomas N. Mather[2], John F. Andersen[1] and José M.C.Ribeiro[1]

[1]Vector Biology Section, Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, Maryland 20852, USA and [2]Center for Vector-Borne Disease, University of Rhode Island, Kingston, Rhode Island 02881, USA

Here we report the ability of the tick *Ixodes scapularis*, the main vector of Lyme disease in the U.S., to actively and specifically affect the host proteolytic activity in the sites of infestation, through the release of cystatin constituents of its saliva. Cystatins are cysteine protease inhibitors and their presence in tick saliva was verified both biochemically and immunologically. We named the two proteins sialostatin L and sialostatin L2 because of their inhibitory action against human cathepsin L. Sialostatin L2 transcripts are greatly increased in the salivary glands as tick feeding progresses and not surprisingly sialostatin L2 RNAi ticks are incapable of feeding. We also show that the proteases that both cystatins target, although limited in number, have a prominent role in the proteolytic cascades that take place in the extracellular and intracellular environment, resulting an anti-inflammatory action and a reduction in the proliferation of T-lymphocytes. Beyond unravelling new components accounting for the properties of tick saliva and contributing to feeding success and pathogen transmission, we describe a novel tool for studying the role of papain-like proteases in diverse biologic phenomena and a protein with numerous potential pharmaceutical applications against diseases such as malaria, leismaniasis, cancer and multiple sclerosis.