Thrombin inhibitor and salivary anti-complement protein transmitted by tick spit and the insertion mechanics of the feeding apparatus of Ixodes ricinus ticks

Thrombin-Inhibitor und Speichel Antikomplement Protein im Zecken Speichel und der Stechapparat der Zecken

„Das Ixodes scapularis Speichelprotein (Salp15) ist ein Antigen, das zumindest teilweise eine immunmodulatorische Wirkung von Zeckenspeichel auf erworbene Immunreaktionen des Wirtes vermittelt [http://www.ncbi.nlm.nih.gov/pubmed/12121666]**.**
Die durch Salp15 vermittelte Unterdrückung resultiert aus der Unterdrückung von Calciumströmen, die durch T-Zell-Antigenrezeptor (TCR)-Ligation getriggert werden und von einer anschließenden Verringerung der Interleukin (IL) -2 Produktion. Salp15 bindet an den extrazellulären Domänen (D1-D2) des T-Zell Co-Rezeptors CD4 in Maus-und in menschlichen Zellen [http://www.ncbi.nlm.nih.gov/pubmed/17082567], in einer Region, die sich mit den Bindungsresten von gp120 überlappen könnten".
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2238774/

"Ixodes scapularis salivary protein (Salp15) is an antigen that mediates at least partially the immunomodulatory action of tick saliva on host-acquired immune responses [http://www.ncbi.nlm.nih.gov/pubmed/12121666].
Inhibition mediated by Salp15 results from the repression of calcium fluxes triggered by T cell antigen receptor (TCR) ligation and a subsequent reduction in interleukin (IL)-2 production. Salp15 binds to the most extracellular domains (D1-D2) of the T cell co-receptor CD4 in both mouse and human cells [http://www.ncbi.nlm.nih.gov/pubmed/17082567] in a region that may overlap with the binding residues of gp120".
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2238774/

Hoffmann A, Walsmann P, Riesener G et al. (1991) Isolation and characterization of a **thrombin inhibitor** from the tick ixodes ricinus. Pharmazie 46, 209–212. http://www.ncbi.nlm.nih.gov/pubmed/1881945

De Silva AM, Fikrig E. (1995) **Growth and migration of Borrelia burgdorferi in Ixodes ticks during blood feeding**. Am J Trop Med Hyg. 53(4), 397-404. http://intl.ajtmh.org/content/53/4/397.extract
„We have studied the growth of Borrelia burgdorferi in nymphal ticks (Ixodes scapularis) feeding on mice using confocal fluorescence microscopy to follow the distribution of spirochetes. In starved nymphs, the bacteria were only detected in the midgut and each nymph had a mean of 496 spirochetes. Upon attachment of nymphs to the host, the bacteria grew with a doubling time close to 4 hr and reached a mean of 7,848 spirochetes per nymph 15 hr after attachment. During this initial period (36 hr) of rapid growth, the bacteria appeared to be restricted to the gut, but after 48 hr, the spirochetes had disseminated to the salivary glands in the majority of nymphs examined. Thus, a critical event that allows the spirochetes to disseminate and infect the salivary glands takes place 36-48 hr after attachment. A maximum number of 166,575 spirochetes per nymph was noted 72 hr after attachment. Soon after completion of feeding and detachment from the host (96 hr), the mean number of spirochetes decreased to 95,410 per nymph and the spirochetes appeared to be cleared from organs other than the midgut. Thus, dissemination of spirochetes within the vector appears to be a transient phenomenon. These results provide strong evidence in favor of a salivary route of disease transmission while also demonstrating the utility of confocal microscopy to study vector-pathogen interactions in general."

de Silva AM, Erol Fikrig E (1997) **Arthropod- and Host-specific Gene Expression by Borrelia burgdorferi** The American Society for Clinical Investigation, Inc. 0021-9738/97/02/0377/03 $2.00 Volume 99, Number 3, 377–379 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC507808/

Valenzuela JG, Charlab R, Mather TN, Ribeiro JM (2000) Purification, cloning, and expression of a novel **salivary anticomplement protein** from the tick, Ixodes scapularis. J Biol Chem 275, 18717–18723. http://www.ncbi.nlm.nih.gov/pubmed/10749868

Tick Spit Dampens Immunity (2001) http://news.sciencemag.org/sciencenow/2001/03/27-01.html

Narasimhan S, Koski RA, Beaulieu B, Anderson JF, Ramamoorthi N, et al. (2002) A novel family of **anticoagulants from the saliva** of Ixodes scapularis. Insect Mol Biol 11, 641–650. http://www.ncbi.nlm.nih.gov/pubmed/12421422

Zeidner NS, Schneider BS, Nuncio MS, Gern L, Piesman J. (2002) Coinoculation of Borrelia spp. with tick salivary gland lysate enhances spirochete load in mice and is tick species-specific. J Parasitol. 88(6), 1276-8. http://www.ncbi.nlm.nih.gov/pubmed/12537131

Anguita J, Ramamoorthi N, Hovius JW, Das S, Thomas V, et al. (2002) **Salp15,** an ixodes scapularis salivary protein, inhibits CD4(+) T cell activation. Immunity 16, 849–859. http://www.ncbi.nlm.nih.gov/pubmed/12121666

Hannier S, Liversidge J, Sternberg JM, Bowman AS (2004) Characterization of the **B-cell inhibitory protein factor** in Ixodes ricinus tick saliva: a potential role in enhanced Borrelia burgdorferi transmission. Immunology 113, 401–408. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1782588/

Kovár L. (2004) **Tick saliva** in anti-tick immunity and pathogen transmission. Folia Microbiol (Praha). 49(3), 327-36. http://www.ncbi.nlm.nih.gov/pubmed/15259776

Ramanoorthi N, Narasimhan S, Pal U et al. (2005) The Lyme disease agent exploits a tick protein to infect the mammalian host. Nature. 436, 573-577 http://www.ncbi.nlm.nih.gov/pubmed/16049492

Francischetti IMB, Mather TN, Ribeiro JMC (2005) Tick saliva is a **potent inhibitor of endothelial cell proliferation and angiogenesis**. Thrombosis and Haematosis. 94(1), 167-174

Prevot PP, Adam B, Boudjeltia KZ, Brossard M, Lins L, et al. (2006) Anti-hemostatic effects of a serpin from the **saliva of the tick** Ixodes ricinus. J Biol Chem 281, 26361–26369. http://www.ncbi.nlm.nih.gov/pubmed/16672226

Garg R, Juncadella IJ, Ramamoorthi N, Ashish, Ananthanarayanan SK, Thomas V, Rincon M, Krueger JK, Fikrig E, Yengo CM, Anguita J. (2006) Cutting edge: CD4 is the receptor for the tick saliva immunosuppressor, Salp15. J Immunol. 177, 6579–6583. http://www.ncbi.nlm.nih.gov/pubmed/17082567

Schroeder H, Daix V, Gillet L, Renauld JC, Vanderplasschen A (2007) The paralogous salivary anti-complement proteins IRAC I and IRAC II encoded by Ixodes ricinus ticks have **broad and complementary inhibitory activities against the complement** of different host species. Microbes Infect 9, 247–250. http://www.ncbi.nlm.nih.gov/pubmed/17223370

Tyson K, Elkins C, Patterson H, Fikrig E, de Silva A (2007) Biochemical and functional characterization of **Salp20**, an Ixodes scapularis tick salivary protein that inhibits the complement pathway. Insect Mol Biol 16, 469–479. http://www.ncbi.nlm.nih.gov/pubmed/17651236

Hovius JW, Ramamoorthi N, Van't Veer C, de Groot KA, Nijhof AM, et al. (2007) Identification of **Salp15** homologues in Ixodes ricinus ticks. Vector Borne Zoonotic Dis 7, 296–303. http://www.ncbi.nlm.nih.gov/pubmed/17896872

Schuijt TJ, Hovius JW, van Burgel ND, Ramamoorthi N, Fikrig E, et al. (2008) The tick salivary protein **Salp15** inhibits the killing of serum-sensitive Borrelia burgdorferi sensu lato isolates. Infect Immun 76, 2888–2894. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2446733/

Hovius JW, de Jong MA, den Dunnen J, Litjens M, Fikrig E, et al. (2008) **Salp15** binding to DC-SIGN inhibits cytokine expression by impairing both nucleosome remodeling and mRNA stabilization. PLoS Pathog 4, e31. http://www.ncbi.nlm.nih.gov/pubmed/18282094

Kaufman WR (2010) **Ticks: physiological aspects with implications for pathogen transmission *Ticks and Tick-Borne Diseases*.** Ticks and Tick-borne Diseases 1, 11–22. http://www.ncbi.nlm.nih.gov/pubmed/21771507
„I then turn attention to the salivary glands of female ixodid ticks, which serve the on-host osmoregulatory function in this family of ticks, (iv) and I discuss the pharmacological control of salivary

fluid secretion. (v) Finally, I link the latter to the mechanism of pathogen transmission by the salivary glands, using the tick-borne Thogoto virus as a specific example ».

Schuijt TJ, Narasimhan S, Daffre S, DePonte K, Hovius JWR, et al. (2011) Identification and Characterization of Ixodes scapularis Antigens That Elicit Tick Immunity Using Yeast Surface Display. PLoS ONE 6(1), e15926. doi:10.1371/journal.pone.0015926 http://www.ncbi.nlm.nih.gov/pubmed/21246036

Mason LMK, Veerman CC, Grijtenbeek TBH (2013) Ménage à trois: Borrelia, dendritic cells, and tick salvia interactions. Cell Press [in press] Trends in parasitology

Leitner W, Wali T, Coetero-Saint-Denis A (2013) **Is arthropod saliva the Achilles´ heel of vector-borne diseases?** Frontiers in Immunology. 4(255), 1-3 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3757298/

Ibelli AMG , Kim TK, Hill CC et al. (2014) A blood meal-induced Ixodes scapularis **tick saliva serpin** inhibits trypsin and thrombin, and interferes with platelet aggregation and blood clotting. International Journal for Parasitology http://www.sciencedirect.com/science/article/pii/S0020751914000526

Qiu Y, Nakao R, Ohnuma A, Kawamori F, Sugimoto C (2014) **Microbial population analysis of the salivary glands of ticks; a possible strategy for the surveillance of bacterial pathogens.** PLoS One. 9(8), e103961. doi: 10.1371/journal.pone.0103961. eCollection 2014.

Mudenda L, Pierle SA, Turse JE (2014) Proteomics informed by transcriptomics identifies novel secreted proteins in Dermacentor andersoni saliva. International Journal for Parasitology xxx (2014) xxx–xxx

Sultana H, Patel U, Toliver M et al. (2015) **Molecular identification and bioinformatics analysis of a potential anti-vector vaccine candidate, 15-kDa salivary gland protein (Salp15), from Ixodes affinis ticks.** Ticks and Tick-borne Diseases. Available online 8 August 2015 http://www.sciencedirect.com/science/article/pii/S1877959X1500151X

Bernard Q, Gallo RL, Jaulhac B (2015) **Ixodes tick saliva suppresses the keratinocyte cytokine response to TLR2/TLR3 ligands during early exposure to Lyme borreliosis.** Exp Dermatol. doi: 10.1111/exd.12853. http://www.ncbi.nlm.nih.gov/pubmed/26307945

Wagemakers A, Coumou J, Schuijt TJ et al. (2016) **An Ixodes ricinus Tick Salivary Lectin Pathway Inhibitor Protects Borrelia burgdorferi sensu lato from Human Complement.** Vector Borne Zoonotic Dis. 2016 [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/26901751
«We have identified a TSLPI ortholog, which protects B. burgdorferi s.l. from complement-mediated killing in I. ricinus, the major vector for tick-borne diseases in Europe. «

➔ **(2016) 1st Annual Lyme Disease in the Era of Precision Medicine Conference - 3**
https://www.youtube.com/watch?v=ogQniFqSQ9o

Der Stechapparat der Zecken. The feeding apparatus of Ixodes ricinus ticks.

Dania Richter D, Matuschka1 F-R, Andrew Spielman A, Mahadevan L (2013) How ticks get under your skin: insertion mechanics of the feeding apparatus of Ixodes ricinus ticks. Proc. R. Soc. B *22* vol. 280 no. 1773 20131758 doi: 10.1098/rspb.2013.1758
http://rspb.royalsocietypublishing.org/content/280/1773/20131758.full
http://rspb.royalsocietypublishing.org/content/280/1773/20131758/suppl/DC1