

Saliva-Assisted Transmission

Subjects: Immunology

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Saliva-assisted transmission (SAT) is defined as the property of tick saliva to enhance the transmission and establishment of tick-borne pathogens. Tick saliva contains multiple biomolecules that act to repress host immune responses, hemostasis, inflammation, and itchiness. These molecules can be exploited by tick-borne pathogens by increasing their expression or directly binding. The focus of this entry is in defining the mechanism that tick-borne pathogens use to subvert tick salivary secretions in their advantage.

Keywords: Saliva-assisted transmission ; anaplasma phagocytophilum ; tick-borne encephalitis ; borrelia burgdorferi ; ticks ; tick saliva ; tick-borne diseases

1. Introduction

Ticks transmit a wide variety of pathogens of medical and veterinary importance ^[1]. Ticks produce a feeding pool in the skin of their host by cutting with their chelicerae and inserting their hypostome into the dermis ^[2]. This action produces significant damage, which along with the long period of tick feeding results in the activation of immune and inflammatory responses that try to reject this foreign invader. To survive and finish their bloodmeal, ticks inhibit host immunity and localized hemostasis by injecting a wide array of bioactive molecules. Tick-borne pathogens take advantage of this dysregulation of immune responses to establish an infection niche within their host in a process termed saliva-assisted transmission (SAT) ^{[3][4]}. SAT has also been reported in other vector-pathogen systems, such as dengue ^[5]; as well as plant-insect-pathogen systems ^{[6][7][8][9]}. Thus, this is a conserve mechanism within arthropod-pathogen systems.

Besides facilitating pathogen transmission, tick saliva appears to also enable the acquisition of tick-borne pathogens. Tick feeding results in increased numbers of neutrophils at the bite site, which may promote the acquisition of the intracellular bacterium, *Anaplasma phagocytophilum* ^{[10][11]}. Likewise, tick saliva appears to promote the chemotaxis of the Lyme disease pathogen, *Borrelia burgdorferi* ^[12]. Pathogens take advantage of specific salivary proteins and can influence their expression. This topic entry discusses how specific pathogens, *B. burgdorferi*, *A. phagocytophilum*, and Tick-borne encephalitis virus (TBEV), manipulate tick salivary secretions.

2. Subversion of Tick Salivary Components

As mentioned above, ticks have the capacity to delay wound healing, histamine release, and immune responses of their hosts. The host complement system is a complex of proteins that interact in a sequential cascade that leads to the opsonization or phagocytosis of foreign bodies, B cell activation, T cell regulation, and the upregulation of the inflammatory response ^{[13][14][15]}. *Borrelia burgdorferi* is especially susceptible to the complement pathway ^[16]. Thus, it is not surprising that this pathogen increases the expression of tick salivary proteins involved in the inhibition of the complement pathway ^[17]. Similarly, *B. burgdorferi* subverts tick salivary proteins to escape cellular immune responses by the host. For example, *B. burgdorferi*'s OspC outer membrane protein binds to the tick salivary proteins Salp15, which is known to inhibit T cell and keratinocyte activation ^{[18][19][20]}. For other examples on this topic, please refer to our review ^[21].

3. Global Manipulation of Tick Sialome by Pathogens

Using genomics, transcriptomics, and proteomics, the different components of the tick saliva have been identified and termed the tick sialome. The sialome of ticks comprises a cocktail of proteins, mRNAs, and the most recently discovered miRNAs ^{[22][23]}. Infection with tick-borne pathogens, such as *A. phagocytophilum* and *B. burgdorferi*, can result in the alteration of the expression of particular gene families. For example, *A. phagocytophilum* influences the expression of anti-clotting proteins like *Salp9*, *Salp11*, and *Metis-1* ^{[24][25][26]}. The expression of two of these genes, *Salp11* and *Metis-1*, is also manipulated by *B. burgdorferi* ^[27]. Additionally, both pathogens appear to alter the expression of cement proteins and the proline 4-hydroxylase enzyme ^{[24][27]}. The expression of genes encoding anticlotting, cement, and immune

inhibitors also change during infection with TBEV [28], although the specific genes may not be the same. This indicates the targeting of conserved protein groups among tick-borne pathogens, specifically those involved in enhancing the blood flow and feeding success of ticks to in turn ensure their transmission.

4. Conclusion

Through co-evolution with their vectors, tick-borne pathogens have evolved multiple mechanisms to augment their chances of successful transmission and establishment, including the hijacking of specific tick salivary components and the alteration of tick salivary gene expression. Other mechanisms have been identified more recently. The TBEV complex member Powassan virus, for example, can change the expression of miRNAs in *I. scapularis* salivary glands [23]. Tick-borne viruses can also hijack extracellular vesicles from the vector to invade host tissues [24]. Whether other tick pathogens can manipulate tick salivary miRNAs and extracellular vesicles remains to be determined. Further research should be focused on elucidating how tick-borne pathogens enhance their transmission by manipulating tick salivary secretions.

References

1. Jongejan, F.; Uilenberg, G. The global importance of ticks. *Parasitology* 2004, 129 Suppl, S3-14.
2. Richter, D.; Matuschka, F.-R.; Spielman, A.; Mahadevan, L. How Ticks Get Under your Skin: Insertion Mechanics of the Feeding Apparatus of *Ixodes ricinus* Ticks. *Proc. Biol. Sci.* 2013, 280, 20131758, doi:10.1098/rspb.2013.1758.
3. Brossard, M.; Wikel, S.K. Tick Immunobiology. *Parasitology* 2004, 129, S161-S176, doi:10.1017/s0031182004004834 M4 - Citavi.
4. Šimo, L.; Kazimirova, M.; Richardson, J.; Bonnet, S.I. The Essential Role of Tick Salivary Glands and Saliva in Tick Feeding and Pathogen Transmission. *Front. Cell. Infect. Microbiol.* 2017, 7, doi:10.3389/fcimb.2017.00281.
5. Cox J, Mota J, Sukupolvi-Petty S, Diamond MS, Rico-Hesse R. Mosquito bite delivery of dengue virus enhances immunogenicity and pathogenesis in humanized mice. *J Virol* 2012 86, 7637-49. doi: 10.1128/JVI.00534-12.
6. Arena, G.D.; Ramos-Gonzalez, P.L.; Rogerio, L.A.; Ribeiro-Alves, M.; Casteel, C.L.; Freitas-Astua, J.; Machado, M.A. Making a Better Home: Modulation of Plant Defensive Response by *Brevipalpus* Mites. *Front. Plant Sci.* 2018, 9, 1147, doi:10.3389/fpls.2018.01147.
7. Hogenhout, S.A.; Bos, J.I.B. Effector Proteins that Modulate Plant–insect Interactions. *Curr. Opin. Plant Biol.* 2011, 14, 422-428, doi:https://doi.org/10.1016/j.pbi.2011.05.003.
8. Eigenbrode, S.D.; Bosque-Pérez, N.A.; Davis, T.S. Insect-Borne Plant Pathogens and Their Vectors: Ecology, Evolution, and Complex Interactions. *Annu. Rev. Entomol.* 2018, 63, 169-191, doi:10.1146/annurev-ento-020117-043119.
9. Su, Y.L.; Li, J.M.; Li, M.; Luan, J.B.; Ye, X.D.; Wang, X.W.; Liu, S.S. Transcriptomic Analysis of the Salivary Glands of an Invasive Whitefly. *PLoS One* 2012, 7, e39303, doi:10.1371/journal.pone.0039303.
10. Reppert, E.; Galindo, R.C.; Ayllón, N.; Breshears, M.A.; Kocan, K.M.; Blouin, E.F.; de la Fuente, J. Studies of *Anaplasma phagocytophilum* in Sheep Experimentally Infected with the Human NY-18 Isolate: Characterization of Tick Feeding Sites. *Ticks Tick Borne Dis.* 2014, 5, 744-752, doi:10.1016/j.ttbdis.2014.05.014.
11. Granquist, E.G.; Aleksandersen, M.; Bergström, K.; Dumler, S.J.; Torsteinbø, W.O.; Stuen, S. A Morphological and Molecular Study of *Anaplasma phagocytophilum* Transmission Events at the Time of *Ixodes ricinus* Tick Bite. *Acta Vet. Scand.* 2010, 52, 43, doi:10.1186/1751-0147-52-43.
12. Shih, C.M.; Chao, L.L.; Yu, C.P. Chemotactic Migration of the Lyme Disease Spirochete (*Borrelia burgdorferi*) to Salivary Gland Extracts of Vector Ticks. *Am. J. Trop. Med. Hyg.* 2002, 66, 616-621, doi:10.4269/ajtmh.2002.66.616.
13. Ricklin, D.; Hajishengallis, G.; Yang, K.; Lambris, J.D. Complement: a Key System for Immune Surveillance and Homeostasis. *Nat. Immunol.* 2010, 11, doi:10.1038/ni.1923.
14. Jason, R.D.; Wen-Chao, S. Complement and its Role in Innate and Adaptive Immune Responses. *Cell Res.* 2010, 20, 34-50, doi:10.1038/cr.2009.139.
15. Lubbers, R.; van, E.M.F.; van, K.C.; La, T. Production of Complement Components by Cells of the Immune System. *Clin. Exp. Immunol.* 2017, 188, doi:10.1111/cei.12952
16. Dulipati, V.; Meri, S.; Panelius, J. Complement Evasion Strategies of *Borrelia burgdorferi* sensu lato. *FEBS Lett.* 2020, 594, 2645-2656, doi:10.1002/1873-3468.13894.

17. Schuijt, T.J.; Coumou, J.; Narasimhan, S.; Dai, J.; Deponte, K.; Wouters, D.; Brouwer, M.; Oei, A.; Roelofs, J.J.; van, D.A.P., et al. A Tick Mannose-binding Lectin Inhibitor Interferes with the Vertebrate Complement Cascade to Enhance Transmission of the Lyme Disease Agent. *Cell Host Microbe* 2011, 10, doi:10.1016/j.chom.2011.06.010.
18. Hovius, J.W.; Schuijt, T.J.; Groot, K.A.; Roelofs, J.J.T.H.; Oei, G.A.; Marquart, J.A.; Beer, R.; van 't Veer, C.; van der Poll, T.; Ramamoorthi, N., et al. Preferential Protection of *Borrelia burgdorferi* Sensu Stricto by a Salp15 Homologue in *Ixodes ricinus* Saliva. *J. Infect. Dis.* 2008, 198, 1189-1197, doi:10.1086/591917 M4 - Citavi.
19. Marchal, C.; Schramm, F.; Kern, A.; Luft, B.J.; Yang, X.; Schuijt, T.; Hovius, J.; Jaulhac, B.; Boulanger, N. Antialarmin Effect of Tick Saliva during the Transmission of Lyme Disease. *Infect. Immunit.* 2010, 79, 774-785, doi:10.1128/iai.00482-10 M4 - Citavi.
20. Sukumaran, B.; Narasimhan, S.; Anderson, J.F.; DePonte, K.; Marcantonio, N.; Krishnan, M.N.; Fish, D.; Telford, S.R.; Kantor, F.S.; Fikrig, E. An *Ixodes scapularis* Protein Required for Survival of *Anaplasma phagocytophilum* in Tick Salivary Glands. *J. Exp. Med.* 2006, 203, 1507-1517, doi:10.1084/jem.20060208
21. Pham, M.; Underwood, J.; Oliva Chávez, A.S. Changing the Recipe: Pathogen Directed Changes in Tick Saliva Components. *Int. J. Environ. Res. Public Health* 2021, 18, 1806. <https://doi.org/10.3390/ijerph18041806>
22. Valenzuela, J.G.; Francischetti, I.M.; Pham, V.M.; Garfield, M.K.; Mather, T.N.; Ribeiro, J.M. Exploring the Sialome of the Tick *Ixodes scapularis*. *J. Exp. Biol.* 2002, 205, 2843-2864.
23. Hermance, M.E.; Widen, S.G.; Wood, T.G.; Thangamani, S. *Ixodes scapularis* Salivary Gland microRNAs are Differentially Expressed During Powassan Virus Transmission. *Sci. Rep.* 2019, 9, 13110, doi:10.1038/s41598-019-49572-5.
24. Ayllón, N.; Villar, M.; Galindo, R.C.; Kocan, K.M.; Šíma, R.; López, J.A.; Vázquez, J.; Alberdi, P.; Cabezas-Cruz, A.; Kopáček, P., et al. Systems Biology of Tissue-specific Response to *Anaplasma phagocytophilum* Reveals Differentiated Apoptosis in the Tick Vector *Ixodes scapularis*. *PLoS genet.* 2015, 11, e1005120, doi:10.1371/journal.pgen.1005120.
25. Narasimhan, S.; Koski, R.A.; Beaulieu, B.; Anderson, J.F.; Ramamoorthi, N.; Kantor, F.; Cappello, M.; Fikrig, E. A Novel Family of Anticoagulants from the Saliva of *Ixodes scapularis*. *Insect Mol. Biol.* 2002, 11, doi:10.1046/j.1365-2583.2002.00375.x.
26. Ribeiro, J.M.C.; Alarcon-Chaidez, F.; B. Francischetti, I.M.; Mans, B.J.; Mather, T.N.; Valenzuela, J.G.; Wikel, S.K. An Annotated Catalog of Salivary Gland Transcripts from *Ixodes scapularis* ticks. *Insect Biochem. Mol. Biol.* 2006, 36, 111-129, doi:10.1016/j.ibmb.2005.11.005 M4 - Citavi.
27. Cotté, V.; Sabatier, L.; Schnell, G.; Carmi-Leroy, A.; Rousselle, J.-C.; Arsène-Ploetze, F.; Malandrin, L.; Sertour, N.; Namane, A.; Ferquel, E., et al. Differential Expression of *Ixodes ricinus* Salivary Gland Proteins in the Presence of the *Borrelia burgdorferi* sensu lato Complex. *J. Proteom.* 2014, 96, 29-43, doi:10.1016/j.jprot.2013.10.033.
28. Hart, C.E.; Ribeiro, J.M.; Kazimirova, M.; Thangamani, S. Tick-Borne Encephalitis Virus Infection Alters the Sialome of *Ixodes ricinus* Ticks During the Earliest Stages of Feeding. *Front. Cell. Infect. Microbiol.* 2020, 10, doi:10.3389/fcimb.2020.00041.