[Frontiers in Bioscience 13, 6938-6946, May 1, 2008]

Overview: Ticks as vectors of pathogens that cause disease in humans and animals

Jose de la Fuente[1,2], Agustin Estrada-Pena[3], Jose M. Venzal[3], Katherine M. Kocan[1], Daniel E. Sonenshine[4]

[1]Department of Veterinary Pathobiology, Center for Veterinary Health Sciences, Oklahoma State University, Stillwater, OK 74078, USA, [2]Instituto de Investigación en Recursos Cinegeticos IREC (CSIC-UCLM-JCCM), Ronda de Toledo s/n, 13005 Ciudad Real, Spain. [3]Department of Parasitology, Veterinary Faculty, University of Zaragoza, Miguel Servet 177, 50013-Zaragoza, Spain, [4]Department of Biological Sciences, Old Dominion University, Norfolk, Virginia USA

TABLE OF CONTENTS

1. ABSTRACT

Ticks (Acari: Ixodidae) transmit a wide variety of pathogens to vertebrates including viruses, bacteria, protozoa and helminthes. Tick-borne pathogens are believed to be responsible for more than 100,000 cases of illness in humans throughout the world. Ticks are considered to be second worldwide to mosquitoes as vectors of human diseases, but they are the most important vectors of disease-causing pathogens in domestic and wild animals. Infection and development of pathogens in both tick and vertebrate hosts are mediated by molecular mechanisms at the tick-pathogen interface. These mechanisms, involving traits of both ticks and pathogens, include the evolution of common and species-specific characteristics. The molecular characterization of the tick-pathogen interface is rapidly advancing and providing new avenues for the development of novel control strategies for both tick infestations and their associated pathogens.

2. INTRODUCTION: TICKS AND THE PATHOGENS THEY TRANSMIT

Molecular biology has made it possible to determine many of the genes that control the biological functions of numerous modern organisms, including blood feeding arthropods and the disease-causing pathogens that they transmit to humans and animals. Consequently, a substantial literature on these subjects has accumulated, including molecular studies of ticks and the disease agents that they transmit. This book compiles in a single comprehensive review the rapidly accumulating new knowledge of tick genomics and the molecular basis for many of the tick's biological processes, e.g., reproduction, salivation and innate immunity. In addition, it also reviews the latest findings on the molecular basis of the interactions between the tick vectors and their pathogens, e.g., tick-borne viruses, piroplasms, rickettsiae and borreliae. Finally, it brings together the new and often novel strategies for exploiting these findings to control ticks and tick-borne pathogens.

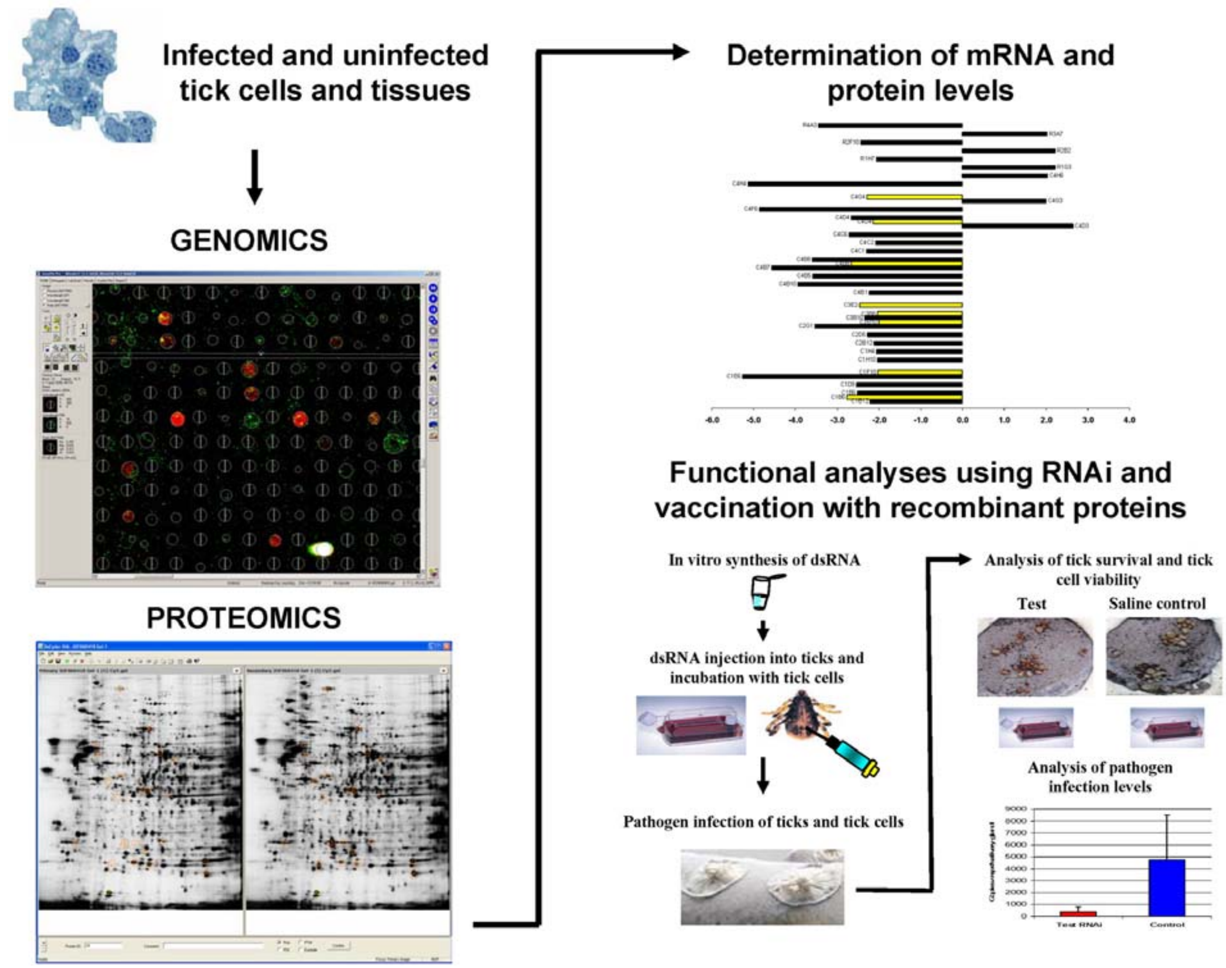

Figure 1. Systems biology approaches for the study tick-pathogen interface and development of vaccines for the control of tick infestations and the transmission of tick-borne pathogens.

A current and comprehensive listing of pathogens, their respective tick hosts and geographical distributions is presented in Table 1. This compilation is based on current literature, but readers are encouraged to consult the rapidly expanding literature which has been greatly impacted by molecular biology, especially concerning molecular methods for the identification of these pathogens and the definition of their relationship with ticks. The general name of the disease, which is often variable, has been included in the table when the name has been widely accepted. For viruses, only those with a demonstrated incidence in human and/or animal health have been included; disease names are rarely listed, except in limited cases where adequate clinical information was available. Proven vector species are included and complementary data, based on experimental evidence, is provided on the vector status of other tick species. Several *Rickettsia,* described recently in ticks or tick feeding lesions, are not included in the table, but rather are proposed as "*candidatus*" pending further information. In addition, changes in the taxonomic status of some pathogens are included that have been proposed or used in the scientific literature in recent years. For tick species, we have incorporated the most widely accepted name following the review by Nava *et al.* (58). However, notes on the systematic status of selected pathogens have been provided. Finally, Table 1 should be considered a "work in progress" because new descriptions of tick-borne pathogens will undoubtedly continued to be reported and characterized.

3. MOLECULAR BIOLOGY OF TICKS AND THE TICK-PATHOGEN INTERFACE

The impact of molecular studies in conjunction with conventional taxonomy on tick systematics and evolution are discussed by Nava *et al.* (58). These studies are important toward understanding the evolution of ticks, tick-pathogen interactions, and the validity of tick nomenclature in relation to latest worldwide list of ticks.

Climatic and environmental conditions impact ticks and tick-pathogen interactions (59). Characterization of the climatic niche used by various tick species, in combination with the modeling of tick-host-pathogen interactions, will be fundamentally important toward our

Table 1. Description of tick-borne pathogens, vectors, geographical distribution and host species affected

Pathogen	Disease	Tick vectors	Geographical distribution	Host species affected	References
Protozoa, genus *Babesia*					
B. beliceri		*Hyalomma* spp.	Russia	Cattle	1
B. bigemina	Cattle babesiosis	*Boophilus* spp., *Rhipicephalus* spp.	Africa, America, Asia, Australia	Cattle, buffalo	1
B. bovis	Cattle babesiosis	*Boophilus* spp.	Africa, America, Asia, Australia	Cattle, buffalo	1
B. major	Cattle babesiosis	*Haemaphysalis* spp.	Europe	Cattle	1
B. ovata		*Haemaphysalis* spp.	Asia	Cattle	1
B. occultans[1]		*Hyalomma* spp.	Africa	Cattle	1
B. divergens	Cattle babesiosis	*Ixodes* spp.	Europe	Cattle, Human[2]	1
B. microti[3]		*Ixodes scapularis*	USA, Canada	Human, rodents	1
B. canis	Dog babesiosis	*Rhipicephalus sanguineus*, *Dermacentor reticulatus*, *D. marginatus*	Tropical and semitropical worldwide	Dogs	1, 2, 3
B. vogeli	Dog babesiosis	*Rhipicephalus sanguineus*	Tropical and semitropical worldwide	Dogs	1
B. rossi	Dog babesiosis	*Haemaphysalis leachi*	Southern Africa	Dogs	1, 2
B. gibsoni	Dog babesiosis	*Haemaphysalis bispinosa, H. longicornis*, *Rhipicephalus sanguineus*	Africa, Asia, USA, southern Europe	Dogs	1, 2, 3
B. ovis	Sheep babesiosis	*Rhipicephalus bursa, R. turanicus*	Africa, Asia, Europe	Sheep	1
B. motasi	Sheep babesiosis	*Haemaphysalis* spp.	Africa, Asia, Europe	Sheep	1
B. caballi	Horse babesiosis	*Dermacentor* spp., *Rhipicephalus evertsi evertsi*	Africa, America, Asia, Europe	Horses, mules, donkeys	1, 3
B. felis		Unknown	Africa	Cats	1
B. bicornis		Unknown	Southern Africa	Black rhinoceros (*Diceros bicornis*)	5
B. odocoilei		*Ixodes scapularis*	America	Cervidae and wild Bovidae	6
Protozoa: genus *Theileria*					
T. annulata	Tropical theileriosis	*Hyalomma* spp.	Eurasia, Africa, Central Asia	Cattle, Camels	7
T. orientalis		*Haemaphysalis* spp.	Asia	Cattle, Asian buffalo	8
T. parva	East Coast Fever	*Rhipicephalus appendiculatus*	Africa	Cattle	9
T. lawrencei	Corridor disease	*Rhipicephalus zambeziensis*	Africa	Cattle	10
T. velifera	Apathogenic	*Amblyomma* spp.	Africa	Cattle, African buffalo	11
T. buffeli	Apathogenic	*Haemaphysalis* spp.	Asia	Cattle, Asian buffalo	11
T. mutans	Benign Theileriosis	*Amblyomma hebraeum, A. lepidum, A. variegaum*, *A. cohaerens*, *A. gemma*	Africa	Cattle	3, 10
T. taurotragi	Benign Theileriosis	*Rhipicephalus appendiculatus, R. pulchellus, R. zambeziensis*	Africa	Cattle	8
T. ovis	Sheep theileriosis	*Hyalomma* spp., *Rhipicephalus bursa*	Africa, Asia	Sheep	12
T. lestoquardi[4]	Sheep theileriosis	*Hyalomma* spp.	Mediterranean region, Asia, Middle East, India	Sheep, Goats	11
T. separata	Non-pathogenic	*Rhipicephalus evertsi*	Sheep, goats	Africa	11
T. bicornis	Not named	Unknown	Black rhinoceros (*Diceros bicornis*)	Southern Africa	5
T. equi	Equine biliary fever	*Dermacentor* spp., *Rhipicephalus* spp., *Hyalomma* spp., *Boophilus* spp.	Horses, mules, donkeys	Southern Europe, Africa, Asia	3, 11
T. cervi	Non-pathogenic	*Amblyomma americanum*	White-tailed deer (Odocoileus virginianus)	Nearctic	76
Protozoa: genus *Hepatozoon*					
H. canis	Hepatozoonosis	*Rhipicephalus sanguineus, Haemaphysalis longicornis*	Southern Europe, Middle East, Far East, Africa	Dogs	13
H. americanum	Hepatozoonosis	*Amblyomma maculatum*	Southern USA	Dogs	13
Protozoa: genus *Cytauxzoon*					
Cytauxzoon felis	Cytauxzoonosis[5]	*Dermacentor variabilis*	USA, Brazil	Domestic cats and wilds felids	15, 16
Bacteria: genus *Aegyptianella*					
A. pullorum[6]	Aegyptianellosis	*Argas walkerae, A. persicus, A. reflexus*	Africa, southern Europe, Middle Asia, Indian subcontinent	Domestic poultry	3, 17
Bacteria: genus *Rickettsia*					
R. rickettsii	Rocky Mountain spotted fever	*Dermacentor andersoni, D. variabilis, Amblyomma cajennense, A. aureolatum, Rhipicephalus sanguineus*	Americas	Human, dog	18, 19, 20

R. amblyommii	Spotted fever rickettsiae group; no disease name	*Amblyomma americanum, A. neumanni, A. cajennense, A. coelebs*	Americas	Human	77-79
R. conorii conorii	Mediterranean spotted fever	*Rhipicephalus sanguineus*	Europe, Africa, Asia	Human, dog	18, 19, 20
R. conorii israelensis	Israeli spotted fever	*Rhipicephalus sanguineus*	Israel	Human	19, 20
R. conorii caspia	Astrakhan fever	*Rhipicephalus sanguineus, R. pumilio*	Africa, Asia	Human	19, 20
R. conorii indica	Indian tick typhus	*Rhipicephalus sanguineus*	India	Human	23
R. sibirica sibirica	Siberian or North Asian tick typhus	*Dermacentor nuttalli, D. marginatus, D. silvarum, D. sinicus, Haemaphysalis concinna*	Asia	Human	18, 19, 20
R. sibirica mongolotimonae	Unnamed	*Hyalomma asiaticum, H. truncatum, H. anatolicum excavatum*	Africa, China, France	Human	18, 19, 20
R. australis	Queensland tick typhus	*Ixodes holocyclus, I. tasmani*	Australia	Human	18, 19, 20
R. japonica	Oriental or Japanese spotted fever	*Ixodes ovatus, Dermacentor taiwanensis, Haemaphysalis longicornis, H. flava*	Japan	Human	18, 19, 20
R. africae	African tick-bite fever	*Amblyomma hebraeum, A. variegatum*	Africa, Reunion Island, West Indies	Human	18, 19, 20
R. honei	Flinders island spotted fever	*Bothriocroton hydrosauri, Amblyomma cajennense, Ixodes granulatus*	Australia, USA, Thailand	Human	18, 19, 20
R. slovaca	TIBOLA, DEBONEL[7]	*Dermacentor marginatus, D. reticulatus*	Europe, Asia	Human	18, 19, 20
R. helvetica	Pathogenicity suspected in humans	*Ixodes ricinus*	Europe	Human	24
R. heilongjiangensis	Unnamed	*Dermacentor silvarum*	China	Human	23
R. aeschlimannii	Unnamed	*Hyalomma marginatum marginatum, H. m. rufipes, Rhipicephalus appendiculatus*	Europe, Africa	Human	18, 19, 20
R. parkeri	Unnamed	*Amblyomma. maculatum, A. triste, A. dubitatum*	USA, Uruguay, Brazil	Human	19, 23, 25
R. massiliae	Unnamed	*Rhipicephalus sanguineus, R. turanicus, R. muhsamae, R. lunulatus, R. sulcatus*	Europe, Asia, Argentina, USA	Human	19, 26, 27, 28
R. marmionii	Australian spotted fever	*Haemaphysalis novaeguineae, Ixodes holocyclus*	Australia	Human	19, 23
R. monacensis	Unnamed	*Ixodes ricinus*	Europe	Human	19, 29
Bacteria, genus *Ehrlichia*					
E. chaffeensis	Human monocytic ehrlichiosis	*Amblyomma americanum, Dermacentor variabilis*	USA	Human and various mammals	2, 20
E. ewingii	Canine granulocytic ehrlichiosis, Human ehrlichiosis	*Amblyomma americanum*	USA	Human, dogs	2, 18
E. ruminantium	Heartwater	*Amblyomma hebraeum, A. astrion, A. cohaerens, A. gemma, A. marmoreum, A. lepidum, A. pomposum, A. variegatum A. americanum*[8]	Africa, Caribbean	Mainly cattle[9]	3, 30
E. canis	Canine ehrlichiosis	*Rhipicephalus sanguineus*	Southern USA, southern Europe, Africa, Middle East, eastern Asia	Dogs	2
Bacteria, genera *Anaplasma, Francisella* and *Coxiella*					
Anaplasma phagocytophilum	Human granulocytic anaplasmosis	*Ixodes scapularis, I. pacificus, I. ricinus, I. hexagonus*	USA, Europe	Human and various mammals	20, 33, 34
A. marginale	Bovine Anaplasmosis	Various	Worldwide	Cattle	35
A. centrale	Bovine Anaplasmosis	Various	Worldwide	Cattle	35
A. ovis	Ovine Anaplasmosis	Various	Worldwide	Sheep	35
A. platys	Canine ehrlichiosis	*Rhipicephalus sanguineus*		Dog	36
F. tularensis	Tularemia	Various	Eurasia, Nearctic	Human and various mammals	18
C. burnetii	Q fever	Various[10]	Worldwide	Human and various mammals	18
Bacteria, genus *Borrelia*[11]					
B. burgdorferi	Lyme disease	*Ixodes pacificus, I. persulcatus, I. ricinus, I. scapularis*	USA, Canada, Europe, Asia, northern Africa	Human	18, 33
B. garinii	Lyme disease	*Ixodes persulcatus, I. ricinus*	Europe, Asia, northern Africa	Human	33
B. afzelii	Lyme disease	*Ixodes persulcatus, I. ricinus*	Europe, Asia, northern Africa	Human	33
B. valaisiana	Lyme disease	*Ixodes ricinus*	Europe, Asia	Human	18, 33
B. lusitaniae		*Ixodes ricinus*	Europe		33
B. spielmani	Lyme disease	*Ixodes ricinus*	Europe	Human	80

B. japonica	Lyme disease	*Ixodes ovatus*	Japan	Human	33
B. lonestari		*Amblyomma americanum*	USA	Human	37
B. theileri	Bovine borreliosis	*Boophilus* spp., *Rhipicephalus evertsi*	Africa, Central and South America, Australia	Cattle	38
B. turcica		*Hyalomma aegyptium*	Parts of Turkey[12]		39
B. miyamotoi		*Ixodes persulcatus*	Asia		40
B. hermsii	New World tick-borne relapsing fever	*Ornithodoros hermsi*	USA, Canada	Human	18, 33, 38
B. turicatae	New World tick-borne relapsing fever	*Ornithodoros turicata*	USA, Mexico	Human	18, 33, 38
B. parkeri	New World tick-borne relapsing fever	*Ornithodoros parkeri*	USA	Human	18, 33, 38
B. mazzottii	New World tick-borne relapsing fever	*Ornithodoros talaje*	USA, Mexico		18, 38
B. venezuelensis	New World tick-borne relapsing fever	*Ornithodoros rudis*	Central and South America	Human	18, 33, 38
B. duttonii	Old World tick-borne relapsing fever	*Ornithodoros moubata*	Africa	Human	18, 33, 38
B. crocidurae	Old World tick-borne relapsing fever	*Ornithodoros erraticus*[13]	Europe, Africa	Human	18, 33, 38
B. persica	Persian relapsing fever	*Ornithodoros tholozani*	Asia	Human	18, 33, 38
B. hispanica	Old World tick-borne relapsing fever	*Ornithodoros erraticus*	Spain, Portugal	Human	18, 33, 38
B. latyschevii	Old World tick-borne relapsing fever	*Ornithodoros tartakovskyi*	Iran, Central Asia	Human	18, 33, 38
B. caucasica	Old World tick-borne relapsing fever	*Ornithodoros aspersus*	Asia (Caucasus and Iraq)	Human	18, 33, 38
B. graingeri		*Ornithodoros graingeri*	Africa	Human	18
B. anserina	Avian borreliosis	*Argas* spp.	Worldwide	Birds	38
B. tillae		*Ornihodoros zumpti*	Africa	Human	42
B. coraciae	Bovine epizootic abortion	*Ornithodoros coriaceus*	USA	Cattle	33, 38
B. parkeri		*Ornithodoros parkeri*	USA	Human	42
Bacteria, genus *Dermatophilus*					
D. congolensis	Dermatophilosis	*Amblyomma variegatum*[14]	Africa	Ruminants	3
Viruses					
Bunyaviridae, Nairovirus	Crimean-Congo Hemorrhagic Fever virus	*Hyalomma marginatum, Hy. a. anatolicum, Hy. truncatum, Amblyommma variegatum, Haemaphysalis punctata, Ixodes ricinus, Dermacemtor* spp., *Rhipicephalus* spp.	Africa, Asia, Europe	Human	3, 33, 43, 44
Bunyaviridae, Nairovirus	Nairobi Sheep Disease	*Rhipicephalus appendiculatus, R. pulchelus, Amblyomma variegatum*	Kenya, Uganda, Rwanda, Tanzania, Somalia	Sheep, goats	45
Bunyaviridae, Nairovirus	Soldado virus	*Ornithodoros maritimus*, *O. capensis*, *O. denmarki*	Trinidad, Hawaii, Seychelles, Ethiopia, South Africa, Morocco, France, United Kingdom	Human	33, 44
Bunyaviridae, ungrouped	Issyk-Kul fever virus	*Argas vespertilionis, A. pusillus, Ixodes vespertilionis*[15]	Tadzhikistan, Kyrgyzstan, Turkmenistan	Bats, human	46
Reoviridae, Orbivirus	Eyach virus	*Ixodes ricinus, I. ventalloi*	Europe	Human	44
Reoviridae, Orbivirus	Colorado tick fever	*Dermacentor andersoni, D. occidentalis, D. albipictus*	Nearctic	Human	44
Reoviridae, Orbivirus	Mono Lake virus	*Argas monolakensis*, *A. cooleyi*	USA	Human	33, 47, 48, 49
Orthomyxoviridae Thogotovirus		*Amblyomma* spp., *Boophilus* spp., *Hyalomma* spp., *Rhipicephalus* spp.	Central and East Africa, southern Europe	Sheep, human	44, 50
Flaviviridae, Flavivirus	Omsk Hemorrhagic fever	*Dermacentor reticulatus*	Omsk and Novosibirsk regions of western Siberia (Russia)	Human	33, 44
Flaviviridae, Flavivirus	Tick Borne Encephalitis	*Ixodes ricinus, I. persulcatus, Haemaphysalis concinna, H. punctata*	Europe, Asia	Human	33, 44
Flaviviridae, Flavivirus	Langat virus	*Ixodes granulatus, Haemaphysalis papuana*	Malaysia	Wild rodents	51
Flaviviridae, Flavivirus	Louping ill	*Ixodes ricinus*	United Kingdom	Sheep	52
Flaviviridae, Flavivirus	Powassan Encephalitis	*Ixodes cookie, I. marxi, I. scapularis, Dermacentor andersoni*	Canada, USA, Russia	Human, rodents	3, 44, 53
Flaviviridae, Flavivirus	Kyasanur Forest disease	*Haemaphysalis* spp. (mainly *H. spinigera* and *H. turturis*)	Forested areas of the Kyasanur district in India	Human, monkeys	54
Asfaviridae, Asfavirus	African Swine Fever	*Ornithodoros moubata, O. erraticus, O. turicata, O. coriaceus, O. puertoricensis*[16]	Africa, southern Europe, Caribbean (outbreaks in Brazil, likely imported)	Domestic pigs	44, 55
Nematoda:					

genus *Acanthocheilonema*					
Acanthocheilonema viteae[17]		*Ornithodoros tartakovskyi*	Asia	Rodents	17
Acanthocheilonema dracunculoides[18]		*Rhipicephalus sanguineus*		Dogs	57

[1] No one has yet demonstrated that *B. occultans* is a different species from *B. beliceri* (1). [2] While *B. divergens* is primarily a species associated with cattle, it may cause disease in humans (4). [3] Most probably this is not a *Babesia sp.* (1). [4] A yet unnamed species has been reported from China transmitted by *Haemaphysalis qinghaiensis* and different from *T. lestoquardi* and *T. buffeli* (14). [5] *Cytauxzoon manul* and another probably new species have been described in wilds felids in Mongolia and Spain (21,22). [6] An *Aegyptianella* found in wild turkeys (*Meleagris gallopavo)* in the USA and describde as *A. pullorum* appears to be a different species, specific to turkeys. [7] There is not a total agreement on the name of the disease. While some authors prefer to use Tick-Borne-Lymphadenitis, others prefer to use Dermacentor-Borne-Necrosis-Erythema-Lymphadenopathy. [8] Other tick species endemic in the Neartic and Neotropics have been involved in the laboratory transmission of *E. ruminatum.* Even in the absence of the main vectors in these regions, it has been claimed that local ticks could spread the infection (31). [9] Many wild ruminants may act as hosts of *E. ruminatium* (32). [10] Transmission of *C. burnetti* by tick bite is very rare. [11] Species of *Borrelia* are herein arranged as transmitted by hard ticks or soft ticks. [12] This species has not been identified in humans but only in the tick *Hyalomma aegyptium*. However, Vatansever et al. (41) reported the high prevalence of *H. aegyptium* immature on humans in Istanbul, Turkey. Therefore, the possibility or a transmission to humans should be considered when analyzing cases of Borreliosis in this area. [13] It is not yet clear whether *O. erraticus* is the same species as *O. sonrai* and *O. marocanus*. The current point of view is that *O. erraticus* and *O. sonrai* are valid species, while *O.marocanus* would e a junior synonym of *O. erraticus.* [14] Associated with sever dermatophilosis of ruminants. [15] This is a primary disease of bats. However, several strains of the virus have been isolated from bat-biting ticks and these ticks have the ability to feed on humans. [16] The role in transmission by *O. turicata, O. coriaceus* and *O. puertoricensis* has been demonstrated under laboratory conditions (56) [17] Some authors prefer to place these species under the genus *Dipetalonema.*[18] Idem to "17"

ability to understand the impact of climate change on tick range and the epidemiology of tick-borne diseases (59). The impact of global climate change on the distribution of vector-borne diseases is increasingly acknowledged, and this emerging area of research will be receiving considerable attention in the future (60-62).

Developing an understanding of the molecular basis for tick reproduction (63) and immunity (64) is critically important for defining tick-host and tick-pathogen interactions. Recent advances in these areas have demonstrated the complexity of these systems and are providing novel approaches for the manipulation and study of tick biology. The diversity of molecular mechanisms that govern tick-pathogen and tick-host interactions are illustrated in recent research on the interface between ticks and selected pathogens, including *Anaplasma* (65), *Ehrlichia* (66), *Borrelia* (67), viruses (68), and piroplasms (69), as well as at the interface between ticks and vertebrate hosts (70). These reviews cover current knowledge on the most important groups of pathogens transmitted by ticks and emphasize the important role of tick salivary glands in tick feeding, pathogen infection and transmission.

The sequence and annotation of the first tick genome, *Ixodes scapularis*, is rapidly progressing (71). The entire *I. scapularis* genome shotgun sequence data have now been generated and assembled, providing 3.8 fold coverage of the genome (GenBank project accession number ABJB010000000; VectorBase designation IscaW1). The knowledge gained from tick genomics (72), molecular biology of tick feeding, reproduction and immune response (63, 64, 70) and tick-pathogen (65-69) and tick-host (70) interactions will markedly contribute to our understanding of the tick-pathogen interface and may ultimately be expected to lead to development of new strategies for control of ticks and tick-borne pathogens (73, 74).

4. SUMMARY AND PERSPECTIVE

According to Dennis and Peisman (75), tick-borne pathogens are believed to be responsible for more than 100,000 cases of illness in humans throughout the world and are the most important vectors of disease-causing pathogens in domestic and wild animals. The control of tick infestations and the pathogens they transmit constitute a priority to improve human and animal health worldwide. Research on the characterization of the molecular events that mediate vital tick functions such as feeding, reproduction, immunity and the tick-pathogen interface, is still in its infancy. However, as summarized in the following chapters (58, 59, 63-70, 72-74), the recent application of molecular and systems biology approaches will contribute to our understanding of the biology of the tick-pathogen interface. Collectively, this information may be useful for the development of new and novel control methods for both tick infestations and the prevention of transmission of tick-borne pathogens (Figure 1).

5. ACKNOWLEDGEMENTS

We thank members of our laboratories for fruitful discussions and technical assistance. Ruth C. Galindo (IREC, Spain) is specially acknowledged for editorial assistance with manuscripts included in this book.

6. REFERENCES

1. G. Uilenberg: Babesia- A historical review. *Vet Parasitol* 138, 3-10 (2006)

2. S.E. Shaw, M.J. Day, R.J. Birtles, E.B. Breitschwerdt: Tick-borne infectious diseases of dogs. *Trends in Parasitol* 17, 74-80 (2001)

3. F. Jongejan, G. Uilenberg: The global importance of ticks. *Parasitology* 129, S1-S12 (2004)

4. J.S. Gray: Identity of causal agents of human babesiosis in Europe. *Int J Med Microbiol* 296, 131-136 (2006)

5. A.M. Nijhof, B.L. Penzhorn, G. Lynen, J.O. Mollel, P. Morkel, C.P. Bekker, F. Jongejan: *Babesia bicornis* sp. nov. and *Theileria bicornis* sp. nov.: tick-borne parasites associated with mortality in the black rhinoceros (*Diceros bicornis*). *J Clin Microbiol* 41, 2249-2254 (2003)

6. L. Schoelkopf, C.E. Hutchinson, K.G. Bendele, W.L. Goff, M. Willette, J.M. Rasmussen, P.J. Holman: New ruminant hosts and wider geographic range identified for *Babesia odocoilei* (Emerson and Wright 1970). *J Wildl Dis* 41, 683-690 (2005)

7. G. Uilenberg: Theilerial species of domestic livestock. In: Advances in the control of theileriosis. Eds. A.D. Irvin, M.P. Cunningham, A.S. Young. Martinus Nijhoff Publishers, The Hague, 4-37 (1981)

8. M.J. Gubbels, Y. Hong, M.V.D. Weide, Q. Bai, I.J. Nijman, L. Guangyuan, F. Jongejan: Molecular characterisation of the *Theileria buffeli*/*orientalis* group. *Int J Parasitol* 30, 943-952 (2000)

9. B.D. Perry, J.J. Curry, A.W. Mukhebi: Assessment of the impact of control measures against Theileriosis. In: Ticks and Tick-Borne Disease Control, Proceedings ofa Joint OAU, FAO and ILRAD Workshop Held in Kampala, Uganda. 32-34 (1991)

10. A.R. Walker, A. Bouattour, J-L. Camicas, A. Estrada-Peña, I. Horak, A. Latif, R.G. Pegram, P.M. Preston: Ticks of domestic animals in Africa: a guide to identification of species. Bioscience Reports, Edinburgh, UK (2003)

11. P. Preston, Theilerioses: In: The Encyclopedia of arthropod-transmitted infections of man and domesticated animals. Ed. N.W. Service. CABI Publishing, NY 487-502 (2001)

12. M. Aktas, K. Altay, N. Dumanli: PCR-based detection of *Theileria ovis* in *Rhipicephalus bursa* adult ticks. *Vet Parasitol* 140, 259-263 (2006)

13. G. Baneth: Hepatozoonosis, canine. In: The Encyclopedia of arthropod-transmitted infections of man and domesticated animals. Ed. N.W. Service. CABI Publishing, NY 215-220 (2001)

14. H. Yin, L. Schnittger, J. Luo, U. Seitzer, J.S. Ahmed: Ovine theileriosis in China: new look at an old story. *Parasitol Res* 101, 191-195 (2007)

15. A.J. Birkenheuer, H. Marr, A.R. Alleman, M.G. Levy, E.B. Breitschwerdt: Development and evaluation of a PCR assay for the detection of *Cytauxzoon felis* DNA in feline blood samples. *Vet Parasitol* 137, 144-149 (2006)

16. P.V. Peixoto, C.O. Soares, A. Scofield, C.D. Santiago, T.N. França, S.S. Barros: Fatal cytauxzoonosis in captive-reared lions in Brazil. *Vet Parasitol* 145, 383-387 (2007)

17. H. Hoogstraal: Argasid and nuttalliellid ticks as parasites and vectors. *Adv Parasitol* 24, 135-238 (1985)

18. P. Parola, D. Raoult: Ticks and tickborne bacterial disease in humans: an emerging infection threat. *Clin Infect Dis* 32, 897-928 (2001)

19. P. Parola, C.D. Paddock, D. Raoult: Tick-borne rickettsioses around the world: emerging diseases challenging old concepts. *Clin Microbiol Rev* 18, 719-756 (2005)

20. P. Parola, B. Davoust, D. Raoult: Tick- and flea-borne rickettsial emerging zoonoses. *Vet Res* 36, 469-492 (2005)

21. M.V. Reichard, R.A. Bussche van den, J.H. Meinkoth, J.P. Hoover, A.A. Kocan: A new species of *Cytauxzoon* from Pallas' cats caught in Mongolia and comments on the systematics and taxonomy of piroplasmids. *J Parasitol* 91, 420-426 (2005)

22. J.Millán, V. Naranjo, A. Rodríguez, J.M., Pérez de la Lastra, A.J. Mangold, J. de la Fuente: Prevalence of infection and 18S rRNA gene sequences of *Cytauxzoon* species in Iberian lynx (*Lynx pardinus*) in Spain. *Parasitology* 134, 995-1001 (2007)

23. P. Parola, D. Raoult: Tropical rickettsioses. *Clin Dermatol* 24, 191-200 (2006)

24. P.E. Fournier, C. Allombert, Y. Supputamongkol, G. Caruso, P. Brouqui, D. Raoult: Aneruptive fever associated with antibodies to *Rickettsia helvetica* in Europe and Thailand. *J Clin Microbiol* 42, 816-818 (2004)

25. I.Silveira, R.C. Pacheco, M.P.J. Szabó, H.G.C. Ramos, M.B. Labruna: *Rickettsia parkeri* in Brazil. *Emerg Infect Dis* 13, 1111-1113 (2007)

26. G.L. Cicuttin, M. Rodríguez, I. Vargas, P. Jado: Anda Primera detección de *Rickettsia massiliae* en la ciudad de Buenos Aires Resultado preliminares. *Rev Arg Zoon* 1, 8-10 (2004)

27. M.E. Eremeeva, E.A. Bosserman, L.J. Demma, M.L. Zambrano, D.M. Blau, G.A. Dasch: Isolation and Identification of *Rickettsia massiliae* from *Rhipicephalus sanguineus* Ticks Collected in Arizona. *Appl Env Microbiol* 72, 5569-5577 (2006)

28. G. Vitale, S. Mansuelo, J.M. Rolain, D. Raoult: *Rickettsia massiliae* human isolation. *Emerg Infect Dis* 12, 174-175 (2006)

29. I. Jado, J.A. Oteo, M. Aldámiz, H. Gil, R. Escudero, V. Ibarra, J. Portu, M.J. Lezaun, C. García-Amil, I. Rodríguez-Moreno, P. Anda: *Rickettsia monacensis* and human disease, Spain. *Emerg Infect Dis* 13, 1405-1407 (2007)

30. J.B. Walker, A. Olwage: The tick vectors of *Cowdria ruminatium (*Ixodoidea: Ixodidae, genus *Amblyomma*) and their distribution. *Onderstepoort J Vet Res* 54, 353-379 (1987)

31. M.J. Burridge, L.A. Simmons, B.H. Simbi, T.F. Peter, S.M. Mahan: Evidence of *Cowdria ruminantium* infection (Heartwater) in *Amblyomma sparsum* ticks found in tortoises imported into Florida. *J Parasitol* 86, 1135-1136 (2000)

32. T.F. Peter, M.J. Burridge, S.M. Mahan: *Ehrlichia ruminantium* infection (heartwater) in wild animals. *Trends in Parasitol* 18, 214-218 (2002)

33. A.Estrada-Peña, F. Jongean: Ticks feeding on humans: a review of records on human - biting Ixodoidea with special reference to pathogen transmission. *Exp Appl Acarol* 23, 685-715 (1999)

34. A. Grzeszczuk, G. Karbowiak, S. Ziarko, O. Kovalchuk: The root-vole *Microtus oeconomus* (Pallas, 1776): a new potential reservoir of *Anaplasma phagocytophilum*. *Vec Bor Zoon Dis* 6, 240-243 (2006)

35. K. Kocan: Anaplasmosis. In: The Encyclopedia of arthropod-transmitted infections of man and domesticated animals. Ed. N.W. Service. CABI Publishing, New York. 28-33 (2001)

36. E. Aguirre, M. Tseouro, R. Ruiz, I. Amusátegui, A. Sainz: Genetic characterization of *Anaplasma* (*Ehrlichia*) *platys* in dogs in Spain. *J Vet Med B Infect Dis Vet Public Health* 5, 197-200 (2006)

37. A.S. Varela, M.P. Luttrell, E.W Howerth, V.A. Moore, W.R. Davidson, D.E. Stallknecht, S.E Little: First culture of *Borrelia lonestari*, agent of southern tick-associated rash illness. *J Clin Microbiol* 42, 1163-1169 (2004)

38. A.G. Barbour, S.F. Hayes: Biology of *Borrelia* Species. *Microbiol Rev* 50, 381-400 (1986)

39. E.S. Guner, M. Watanabe, N. Hashimoto, T. Kadosaka, Y. Kawamura, T. Ezaki, H. Kawabata, Y. Imai, K. Kaneda, T. Masuzawa. *Borrelia turcica* sp. nov., isolated from the hard tick *Hyalomma aegyptium* in Turkey. *Int J Syst Evol Microbiol* 54, 1649-1652 (2004)

40. M. Fukunaga, Y. Takahashi, Y. Tsuruta, O. Matsushita, D. Ralph, M. McClelland, M. Nakao: Genetic and phenotypic analysis of *Borrelia miyamotoi* sp. nov., isolated from the ixodid tick *Ixodes persulcatus*, the vector for Lyme disease in Japan. *Int J Syst Bacteriol* 45, 804-810 (1995)

41. Z. Vatansever, A. Gargili, N.S. Aysul, G. Sengoz, A. Estrada-Peña: Ticks biting humans in the urban area of Istanbul. *Parasitol Res* DOI 10.1007/s00436-007-0809-z (2008)

42. S. Rebaudet, P. Parola: Epidemiology of relapsing fever borreliosis in Europe. *FEMS Immunol Med Microbiol* 48, 11-15 (2006)

43. PA. Nuttall: Crimean-Congo haemorrhagic fever. In: The Encyclopedia of arthropod-transmitted infections of man and domesticated animals.CABI Publishing, NY 126-132 (2001)

44. M. Labuda, P.A. Nuttall: Tick-borne viruses. *Parasitology* 129, S221-245 (2004)

45. F.G. Davis: Nairobi sheep disease. *Parassitologia* 39, 995-98 (1997)

46. I.N. Gavrilovskaya: Issyk-Kul virus disease. In: The Encyclopedia of arthropod-transmitted infections of man and domesticated animals. CABI Publishing, NY 231-234 (2001)

47. T.G. Schwan, M.D. Corwin, S.J. Brown: *Argas (Argas*) *monolakensis*, new species (Acari: Ixodoidea: Argasidae), a parasite of California gulls on islands in Mono Lake, California: description, biology, and life cycle. *J Med Entomol* 29, 78-97 (1992)

48. C. Vermeil, M. Marjolet, C. Chastel: Argas et arbovirus actualités. *Bull Soc Path Ex* 89, 363-365 (1996)

49. C.H. Calisher, T.G. Schwan, J.S. Lazuick, R.B. Eads, D.B. Francy: Isolation of Mono Lake virus (Family Reoviridae, Genus Orbivirus, Kemerovo serogroup) from *Argas cooleyi* (Acari: argasidae) collected in Colorado. *J Med Entomol* 25, 388-390 (1988)

50. J. Woodall: Thogotovirus. In: The Encyclopedia of arthropod-transmitted infections of man and domesticated animals. CABI Publishing, NY 504-506 (2001)

51. E.A. Gould: Langat virus. In: The Encyclopedia of arthropod-transmitted infections of man and domesticated animals, CABI Publishing, NY 265-268 (2001)

52. H.W. Reid: Epidemiology of louping-ill. In: Vector Biology. Academic Press, London*,* 161-178 (1984)

53. D.D. McLean: Powassan encephalitis. In: The Encyclopedia of arthropod-transmitted infections of man and domesticated animals. CABI Publishing, NY 409-416 (2001)

54. M.G.R. Varma: Kyasanur forest disease. In: The Encyclopedia of arthropod-transmitted infections of man and domesticated animals. CABI Publishing, NY 254-260 (2001)

55. E.P.J. Gibbs: African Swine Fever. In: The Encyclopedia of arthropod-transmitted infections of man and domesticated animals. CABI Publishing, NY 7-13 (2001)

56. W.R. Hess, R.G. Endris, T.M. Haslett, M.J. Monahan, P. McCoy: Potential arthropod vectors of African swine

fever virus in North America and the Caribbean basin. *Vet Parasitol* 26, 145-155 (1987)

57. A.S. Olmeda-Garcia, J.A. Rodriguez-Rodriguez, F.A. Rojo-Vazquez: Experimental transmission of *Dipetalonema dracunculoides* (Cobbold 1870) by *Rhipicephalus sanguineus* (Latreille 1806). *Vet Parasitol* 47, 339-342 (1993)

58. S. Nava, A.A. Guglielmone and J.A. Mangold: An overview of systematic and evolution of ticks. *Front Biosci*, in press (2008)

59. A. Estrada-Peña: Tick-borne pathogens, transmission rates and climate change. *Front Biosci*, in press (2008)

60. L. Eisen: Climate change and tick-borne diseases: A research field in need of long-term empirical field studies. *Int J Med Microbiol*, in press (2008)

61. J. Süss, C. Klaus, F.W. Gerstengarbe, P.C. Werner: What makes ticks tick? Climate change, ticks, and tick-borne diseases. *J Travel Med* 15, 39-45 (2008)

62. S. Kalluri, P. Gilruth, D, Rogers, M. Szczur: Surveillance of arthropod vector-borne infectious diseases using remote sensing techniques: a review. *PLoS Pathog* 3, 1361-1371 (2007)

63. R.Michael: The molecular basis of tick reproduction. *Front Biosci*, in press (2008)

64. D.E. Sonenshine and W.L. Hynes: Molecular characterization and related aspects of the innate immune response in ticks. *Front Biosci*, in press (2008)

65. K.M. Kocan, J. de la Fuente, E.F. Blouin : Molecular biology of the *Anaplasma*-tick interface: evidence of the role of pathogen and tick derived proteins. *Front Biosci*, in press (2008)

66. R.Reddy Ganta: Molecular characterization of tick-Ehrlichia interactions. *Front Biosci*, in preparation (2008)

67. A.M de Silva, K.R. Tyson and U. Pal: Molecular characterization of the tick-*Borrelia* interface. *Front Biosci*, in press (2008)

68. P.A. Nuttall: Molecular characterization of tick-virus interactions. *Front Biosci*, in press (2008)

69. M. Florin-Christensen and L. Schnittger: Piroplasms and ticks: a long-lasting intimate relationship. *Front Biosci*, in press (2008)

70. I.M.B Francischetti, A.Sá-Nunes, B.J. Mans, I.M. Santos and J.M.C. Ribeiro: The role of saliva in tick feeding. *Front Biosci*, in press (2008)

71. J. Pagel, V. Zee, N.S. Geraci, F.D. Guerrero, S.K. Wikel, J.J.Stuart, V.M. Nene, C.A. Hill: Tick genomics: the *Ixodes* genome project and beyond. *Int J Parasitol* 37, 1297-1305 (2007)

72. N. Vishvanath: Tick genomics - coming of age. *Front Biosci*, in press (2008)

73. J.de la Fuente, K.M. Kocan, C.Almazán, E.F. Blouin: Exploiting the molecular biology of the tick-pathogen interface for development of novel control strategies for both ticks and tick-borne pathogens. *Front Biosci*, in press (2008)

74. R. Rosario-Cruz, C. Almazán, R.J. Miller, D.I. Domínguez-García, R.Hernandez-Ortiz, J. de la Fuente: Genetic basis and impact of tick acaricide resistance. *Front Biosci*, in press (2008)

75. D.T. Dennis and J. Piesman: Overview of tick-borne infections of humans. In: Tick-borne Diseases of Humans. Eds. J.L Goodman, D.T. Dennis and D.E. Sonenshine. ASM Press, Washington 3–11 (2005)

76. J.S. Laird, A.A. Kocan, K.M. Kocan, S.M. Presley, J.A. Hair: Susceptibility of Amblyomma americanum to natural and experimental infections with Theileria cervi. *J Wildl Di* 24, 679-83 (1988)

77. S.A. Billeter, H.L. Blanton, S.E. Little, M.G. Levy, E.B. Breitschwerdt: Detection of Rickettsia amblyommii in association with a tick bite rash. *Vector Borne Zoonotic Dis* 7, 607-610 (2007)

78. M.B. Labruna, M.C. Horta, D.M. Aguiar, G.T. Cavalcante, A. Pinter, S.M. Gennari, L.M. Camargo: Prevalence of Rickettsia infection in dogs from the urban and rural areas of Monte Negro municipality, western Amazon, Brazil. *Vector Borne Zoonotic Dis* 7, 249-255 (2007)

79. M.B. Labruna, R.C. Pacheco, S. Nava, P.E. Brandao, L.J. Richtzenhain, A.A. Guglielmone: Infection by Rickettsia bellii and Candidatus "Rickettsia amblyommii" in Amblyomma neumanni ticks from Argentina. *Microb Ecol* 54,126-133 (2007)

80. D. Richter, D.B. Schelee, R. Allgöwer, F.R. Matuschka: Relationships of a novel Lyme disease spirochete, *Borrelia spielmani sp. nov*., with hosts in Central Europe. *Appl & Environ Microbiol* 70, 6414-6419 (2004)

Key Words: Tick, Pathogen, Rickettsia, Anaplasma, Borrelia, Ehrlichia, Virus, Review

Send correspondence to: Jose de la Fuente, Department of Veterinary Pathobiology, Center for Veterinary Health Sciences, 250 McElroy Hall, Oklahoma State University, Stillwater, OK 74078, Tel: 405-744-0372, Fax: 405-744-5275, E-mail: jose.de_la_fuente@okstate.edu

http://www.bioscience.org/current/vol13.htm