nature portfolio

https://doi.org/10.1038/s41579-020-00507-2

Supplementary information

Cells within cells: Rickettsiales and the obligate intracellular bacterial lifestyle

In the format provided by the authors and unedited

	Organism	Disease (human unless otherwise stated)	Host cells in mammals	Reservoir	Vector	Evidence of transovarian transmission	Currently known geographic distribution	Genome size (Mbp)	Genome repeat (%)	Genome coding (intact proteins and RNA) (%)	Plasmids	Predicted CDS (genome + plasmid)	Hypothetical proteins	%GC (genome)
Anaplasmataceae														
	Anaplasma marginale subsp. *centrale*	Bovine anaplasmosis	Erythrocytes	Cattle, wild ruminants	*Rhicephalus* spp., *Amblyomma variegatum* (ticks)	no	South America, Africa, Middle East	1.20	-	-	-	962	207	50.0
	Anaplasma marginale	Bovine anaplasmosis	Erythrocytes	Cattle, wild ruminants	*Rhicephalus microplus, Dermacentor* (ticks)	no	Worldwide in tropical/subtropical regions	1.20	5.6	-	-	961	200	49.8
	Anaplasma phagocytophilum	Human granulocytotropic anaplasmosis	Neutrophils	Deer, rodents, ruminants, horses, dogs, cats	*Ixodes scapularis, Ixodes pacificus, Ixodes ricinus* (ticks)	no	North America, Europe, Asia	1.48	12.7	-	-	1,110	263	41.6
	Candidatus Neoehrlichia mikurensis	Neoehrlichiosis	n.d.	Mammals and birds	*I. ricinus* (ticks)	no	Europe	-	-	-	-	-	-	-
	Ehrlichia canis	Canine monocytic ehrlichiosis	Monocytes and macrophages	Dogs	*Rhipicephalus sanguineus* (ticks)	no	Worldwide	1.31	-	-	-	967	206	29.0
	Ehrlichia chaffeensis	Human monocytotropic ehrlichiosis	Monocytes and macrophages	Deer, goats, dogs	*Amblyomma americanum* (ticks)	no	North America, Africa, Asia	1.18	3.8	-	-	934	162	30.1
	Ehrlichia ewingii	Canine and human granulocytotropic ehrlichiosis	Neutrophils	Dogs	*A. americanum* (ticks)	no	Worldwide	-	-	-	-	-	-	-
	Ehrlichia muris eauclairensis	Human ehrlichiosis	n.d.	unknown	*I. scapularis* and *Peromyscus leucopus*	no	Worldwide	-	-	-	-	-	-	-
	Ehrlichia muris muris	Human ehrlichiosis	n.d.	unknown	*Ixodes scapularis* and *Peromyscus leucopus* (ticks)	no	North America, possibly elsewhere	1.20	-	-	-	912	160	29.7
	Ehrlichia ruminantium	Bovine heartwater or cowdriosis	Endothelial cells	Ruminants	*Amblyomma* spp. (ticks)	no	Africa and Caribbean	1.51	-	-	-	943	193	27.5
	Neorickettsia sennetsu	Sennetsu fever and glandular fever	Monocytes and macrophages	Fish	unknown	yes	Asia	0.86	0.4	-	-	747	127	41.1
	Wolbachia pipientis wMel	none known	-	Arthropods	NA	yes	Worldwide	1.27	10.1	81	-	1,245	281	35.2
	Wolbachia sp. wBm	River blindness (via filarial nematode)	-	Nematod *Brugia malayi*	NA	yes	Worldwide in tropical/subtropical regions	1.08	5.4	67.4	-	990	243	34.2
Rickettsiaceae														

Spotted fever group	*Rickettsia africae*	African tick bite fever	Endothelial cells	*Amblyomma* ticks	*Amblyomma hebraeum* and *A. variegatum* (ticks)	yes	Africa and the West Indies	1.28	-	-	1	2,055	414	32.4
	Rickettsia buchneri	none known	n.d.	*Ixodes scapularis*	*I. scapularis* (ticks)	yes	North America	1.82	20	78	4	2,340	374	31.0
	Rickettsia conorii	Boutonneuse fever	Endothelial cells, macrophages	Dogs	*R. sanguineus, Rhipicephalus pumilio* (ticks)	yes	Southern Europe, Africa, Southern Asia	1.27	0.65	81	-	1,374	439	32.5
	Rickettsia heilongjiangensis	Far eastern spotted fever	Endothelial cells	Rodents	*Dysmicoccus sylvarum* (ticks)	no	Asia	1.28	-	-	-	1,504	447	32.3
	Rickettsia helvetica	Aneruptive fever*	n.d.	Rodents	*Dermacentor reticulatus, Ixodes* spp. (ticks)	yes	Asia	1.37	-	-	1	1,620	396	32.2
	Rickettsia honei	Flinders Island spotted fever, Thai tick typhus	n.d.	Rodents, reptiles	*B. hydrosauri, Ixodes* spp. *Hae. novaeguineae* (ticks)	yes	Australia, Asia	1.27	-	-	-	1,205	136	32.4
	Rickettsia japonica	Japanese spotted fever	n.d.	Rodents	*Haemophilus* spp., *Ixodes ovatus, Dermacentor taiwanensis* (ticks)	yes	Asia	1.28	-	-	-	1,502	449	32.4
	Rickettsia massiliae	Mediterranean spotted fever-like disease	Endothelial cells	unknown	*Rhipicephalus* spp., *I. ricinus, Haemaphysalis paraleachi* (ticks)	yes	Europe, Africa, USA	1.28	-	-	1	1,495	399	32.6
	Rickettsia monacensis	Spotted fever	n.d.	unknown	*Ixodes* spp. (ticks)	yes	Europe, North Africa	1.35	-	-	-	1,560	288	32.4
	Rickettsia montanensis	limited reports of pathogenicity*	n.d.	Lizards, possibly birds	*Dermacentor* spp., *A. americanum* (ticks)	yes	North and Central America	1.28	-	-	-	1,425	387	32.6
	Rickettsia parkeri	Maculatum disease	Endothelial cells, macrophages	Dogs, cattle, *Amblyomma* ticks	*Amblyomma maculatum, Amblyomma triste, Dermacentor variabilis* (ticks)	yes	North and South America	1.30	-	-	-	1,477	426	32.4
	Rickettsia peacockii	none known	NA	unknown	*Dermacentor andersoni* (ticks)	yes	North and Central America	1.29	-	-	1	1,577	440	32.6
	Rickettsia raoultii	tick-borne lymphadenopathy (SENLAT)	n.d.	unknown	*Dermacentor* spp., *I. ricinus, Haemaphysalis* spp., *Amblyomma testudinarium* (ticks)	yes	Europe, Asia, North Africa	1.34	-	-	3	1,671	536	32.5
	Rickettsia rickettsii	Rocky Mountain spotted fever	Endothelial cells	Rodents	*Dermacentor variables, D. andersoni, R. sanguineus, Amblyomma cajennense, Amblyomma aureolatum* (ticks)	yes	North and South America	1.3	-	-	-	1,567	438	32.5

	Rickettsia sibirica	North Asian tick typhus, Siberian tick typhus	n.d.	Rodents	*Dermacentor* spp., *R. sanguineus, Ixodes persulcatus, Hyalomma* spp., *Rhizomucor pusillus* (ticks)	no	Europe, Africa, Asia	1.25	-	-	-	1,464	431	32.5
	Rickettsia slovaca	tick-borne lymphadenopathy (SENLAT)	n.d.	unknown	*Dermacentor* (ticks)	yes	Europe, Asia, North Africa	1.28	-	-	-	1,523	464	32.5
	Rickettsia tamurae	spotted fever	n.d.	unknown	*Ixodes* spp. (ticks)	no	Asia	1.45	-	-	-	1,664	518	32.5
Typhus group	*Rickettsia prowazekii*	Epidemic typhus/Brill-Zinsser disease	Endothelial cells	Humans, flying squirrels	*Pediculus humanus humanus* (louse), flying squirrel ectoparasites	no	Worldwide	1.11	0.3	76	-	872	99	29.1
	Rickettsia typhi	Murine typhus	Endothelial cells	Rats	*Xenopsylla cheopis, Ctenocephalides felis* (fleas)	no	Worldwide	1.11	0.29	-	-	835	88	28.9
Transitional group	*Rickettsia akari*	Rickettsialpox	Endothelial cells, macrophages	Mice	*Liponyssoides sanguinus* (mite)	yes	North America, Asia, Europe	1.23	-	-	-	1,287	310	32.3
	Rickettsia australis	Queensland tick typhus	Endothelial cells	unknown	*Ixodes holocyclus, Ixodes tasmani, Ixodes cornuatus* (ticks)	no	Australia	1.30	-	-	1	1,420	388	32.3
	Rickettsia felis	Flea-borne spotted fever*	n.d.	Fleas	*C. felis* (flea)	yes	Worldwide	1.59	4.3	83.6	2	1,721	451	32.5
Ancestral group	*Rickettsia bellii*	none known	NA	unknown	*Amblyomma* spp., *Dermacentor* spp., *Haemophysalis* spp., (ticks)	yes	North and South America	1.53	3.7	85.2	-	1,566	372	31.7
	Rickettsia canadensis	none known	NA	unknown	*Haemaphysalis leporispalustris* (tick)	no	North and Central America	1.16		-	-	1,106	195	31.1
Scrub typhus group	*Orientia tsutsugamushi*	Scrub typhus	Endothelial cells, dendritic cells, monocytes/macrophages	Trombiculid mites	*Leptotrombidium* spp. (mites)	yes	Asia, Oceania, Northern Australia	2.5	49	-	-	2,578	469	30.8
	Candidatus Orientia chiloensis	Scrub typhus	n.d.	unknown	n.d.	n.d.	Chilé	-	-	-	-	-	-	-
	Candidatus Orientia chuto	Scrub typhus	n.d.	unknown	n.d.	n.d.	United Arab Emirates	-	-	-	-	-	-	-

Supplementary Table 1. Overview of disease, growth and genome characteristics of pathogenic Rickettsiales species or those important for human health. The information provided in this table relates to the following strains: *Anaplasma centrale* Str. Israel, *Anaplasma marginale* str. St. Maries, *Anaplasma phagocytophilum* str. HZ, *Ehrlichia canis* str. Jake, *Ehrlichia chaffeensis* str. Arkansas, *Ehrlichia muris muris* str. AS145, *Ehrlichia muris eauclairensis* Wisconsin, *Ehrlichia ruminatum* str. Welgevonden, *Neorickettsia sennetsu* str. Miyayama, *Wolbachia* pipientis wMel endosymbiont of *Drosophila melanogaster, Wolbachia* sp. wBm endosymbiont of *Brugia malayi* isolate TRS, *rickettsia africae* str. ESF-5, *Rickettsia buchneri* str. REIS, *Rickettsia conorii* str. Malish 7, *Rickettsia heilongjiangensis* str.

054, *Rickettsia helvetica* str. C9P9, *Rickettsia honei* str. RB, *Rickettsia japonica* str. YH, *Rickettsia massiliae* str. AZT80, *Rickettsia monacensis* str. IrR/Munich, *Rickettsia montanensis* str. OSU 85-930, *Rickettsia parkeri* str. Portsmouth, *Rickettsia peacockii* str Rustic, *Rickettsia raoultii* str. Khabarovsk, *Rickettsia rickettsii* str. Iowa, *Rickettsia sibirica* str. 246, *Rickettsia slovaca* str. 13-B, *Rickettsia tamurae* str. AT-1, *Rickettsia prowazekii* str. Madrid E, *Rickettsia typhi* str. Wilmington, *Rickettsia akari* str. Hartford, *Rickettsia australis* str. Cutlack, *Rickettsia felis* str. URRWXCal2, *Rickettsia bellii* str. RML369-C, *Rickettsia canadensis* str. McKiel, *Orientia tsutsugamushi* str. Karp, *Candidatus* Orientia *chuto* str. Dubai. *pathogenicity in humans not confirmed. NA, not available; n.d., not determined; SENLAT, scalp eschar and neck lymphadenopathy after tick bite; CDS, coding DNA sequence. Table adapted from refs[1-8]

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Organism	Surface protein	Protein family	Described role	Antigenic variation	Reference
Anaplasma marginale	MSP1a, MSP1b	MSP1	Surface antigen	MSP1a: single copy gene with strain-specific differences in tandem repeats, MSP1b: possible recombination between 5 pseudogenes	1
	MSP2	Outer membrane porin (pfam01617, superfamily cl21487)	Surface antigen	Recombination using donor DNA from ~5-7 pseudogenes (strain St. Maries) into a hyper variable region leads to antigenic variation and immune evasion. Alternating expression with MSP3 confers further variation.	1
	MSP3	Outer membrane porin (pfam01617, superfamily cl21487)	Surface antigen	Recombination using donor DNA from ~5-7 pseudogenes (strain St. Maries) into a hyper variable region leads to antigenic variation and immune evasion. Alternating expression with MSP2 confers further variation.	1
	MSP4	Outer membrane porin (pfam01617, superfamily cl21487)	Surface antigen	-	2
	MSP5	Outer membrane porin (pfam01617, superfamily cl21487)	Surface antigen	-	2
	OmpA	OmpA (pfam00691, superfamily cl30079)	Adhesin, unknown receptor	-	3
Anaplasma phagocytophilum	AipA	Unknown	Required for invasion, unknown receptor	-	4
	Asp14	Unknown	Required for invasion, but not adhesion. Binds to protein disulfide isomerase	-	5
	HSP70	HSP70	Adhesin	-	6
	MSP2 (P44)	Outer membrane porin (pfam01617, superfamily cl21487)	Major surface antigen, role in adhesion to host cells, unknown receptor	Recombination using donor DNA from ~100 pseudogenes (strain HZ) into a hyper variable region leads to antigenic variation and immune evasion.	5
	MSP4	Outer membrane porin (pfam01617, superfamily cl21487)	Adhesin	-	6
	OmpA	OmpA (pfam00691, superfamily cl30079)	Adhesin, binds to sialyl Lewis x-capped P-selectin glycoprotein ligand-1	-	7
Ehrlichia chaffeensis	EtpE (ECH1038)	Unknown	Adhesin and invasin, binds to DNaseX, also involved in inhibition of reactive oxygen species in macrophages	-	8,9
	OmpA	OmpA (pfam00691, superfamily cl30079)	Possible adhesin	-	10
	P28 (OMP-1)	Outer membrane porin (pfam01617, superfamily cl21487)	Surface antigen	Differential expression of multiple P28 genes arranged in tandem array	11
	TRP32	Type 1 secreted tandem repeat proteins similar to repeats-in-toxin family of exoproteins	Secreted and surface exposed protein. Surface antigen, effector protein	-	12
	TRP47	Type 1 secreted tandem repeat proteins similar to repeats-in-toxin family of exoproteins	Secreted and surface exposed protein. Surface antigen, effector protein	-	13
	TRP120	Type 1 secreted tandem repeat proteins similar to repeats-in-toxin family of exoproteins	Secreted and surface exposed protein. Adhesin. Surface antigen, effector protein	-	14
Wolbachia pipientis wMel	WSP	Outer membrane porin (pfam01617, superfamily cl21487)	Surface antigen, role in adhesion to host cells	Variation in hypervariable region driven by mutations and intra- and inter-genic recombination	15

Wolbachia wBm	WSP	Outer membrane porin (pfam01617, superfamily cl21487)	Surface antigen, role in adhesion to host cells	Variation in hypervariable region driven by mutations and intra- and inter-genic recombination	5
Rickettsia conorii /*Rickettsia rickettsii*/*Rickettsia parkeri* (spotted fever group)	Adr1	Predicted beta barrel protein	Adhesin	-	16
	Adr2	Predicted beta barrel protein	Adhesin	-	16
	RickA	Contains WH2 (Wiscott-Aldrich homology region 2) domain (pfam02205)	Arp 2/3-mediated actin-based motility (short tails, slow movement)	-	17
	ScaO (rOmpA)	Surface cell antigen family of autotransporters (pfam03797)	Role in adhesion to host cells and entry. Binds to integrin and fibroblast growth factor receptor 1	-	18,19
	Sca1	Surface cell antigen family of autotransporters (pfam03797)	Role in adhesion to host cells	-	18,19
	Sca2	Surface cell antigen family of autotransporters (pfam03797)	Actin polymerization (long tails, fast movement) and escape from cytoplasm. Role in adhesion to host cells and invasion	-	18,19
	Sca4	Surface cell antigen family of autotransporters (pfam03797)	Vinculin binding and cell to cell transfer of bacteria (no autotransporter domain)	-	18,19
	Sca5 (rOmpB)	Surface cell antigen family of autotransporters (pfam03797)	Role in adhesion to host cells and entry. Receptor is Ku70.	-	18,19
Rickettsia typhi/*Rickettsia prowazekii* (typhus group)	Adr1	Predicted beta barrel protein	Adhesin	-	16
	Adr2	Predicted beta barrel protein	Adhesin	-	16
	Sca1 (pseudogene in *R. prowazekii*)	Surface cell antigen family of autotransporters (pfam03797)	Role in adhesion to host cells and entry	-	18
	Sca2	Surface cell antigen family of autotransporters (pfam03797)	Role in adhesion to host cells and entry	-	18
	Sca4	Surface cell antigen family of autotransporters (pfam03797)	Vinculin binding and cell to cell transfer of bacteria (no autotransporter domain)	-	18
	Sca5 (rOmpB)	Surface cell antigen family of autotransporters (pfam03797)	Role in adhesion to host cells and entry. Receptor is Ku70.	-	18
Orientia tsutsugamushi	ScaA	Surface cell antigen family of autotransporters (pfam03797)	Surface antigen	-	20
	ScaB (only some strains)	Surface cell antigen family of autotransporters (pfam03797)	Unknown	-	20
	ScaC	Surface cell antigen family of autotransporters (pfam03797)	Adhesin. surface antigen	-	20
	ScaD	Surface cell antigen family of autotransporters (pfam03797)	Unknown	-	20
	ScaE	Surface cell antigen family of autotransporters (pfam03797)	Unknown	-	20
	TSA22	Unknown	Surface antigen	-	21
	TSA47 (HtrA)	Peptidase domain (pfam13365) and PDZ domain (pfam13180)	Surface antigen. Role in budding exit from host cells	-	21

	TSA56	Unique to *Orientia,* unknown structure *(*pfam03249)	Surface antigen. Role in adhesion to host cells and entry. Interacts with fibronectin	Variation in 4 hypervariable regions driven by mutations and intragenic recombination between distinct genotypes	22

Supplementary Table 2. Summary of major surface proteins in Rickettsiales. This table summarizes the best characterized surface proteins in selected Rickettsiales species, showing the protein family (where known), the described role of the surface protein, and any described antigenic variation.

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