ОБЗОРЫ ЛИТЕРАТУРЫ

УДК 579.25, 579.61

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OVERVIEW OF TICK-ASSOCIATED RICKETTSIALES BACTERIA IN JAPAN

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Rickettsiales bacteria are obligatory intracellular parasites in vertebrates and/or invertebrates, and some cause severe febrile illness in humans as well as livestock. In Japan, "Rickettsia japonica" and "Orientia tsutsugamushi" are well known as causative agents for "Japanese spotted fever" transmitted by ticks and "Tsutsugamushi disease" transmitted by mites, respectively. In recent years, many researchers have reported the presence of several tick-associated Rickettsiales bacteria in Japan, mostly by molecular-based analyses. Some of these might be public health or veterinary significance. Such Rickettsiales bacteria include spotted fever group rickettsiae other than R. japonica, Ehrlichia spp., Anaplasma spp., and Neoehrlichia sp. We will summarize and introduce the representatives of these Rickettsiales bacteria present in Japan.

Key word: *Rickettsiales, Rickettsia, Ehrlichia, Anaplasma, Neoehrlichia*

ОБЗОР БАКТЕРИЙ ПОРЯДКА RICKETTSIALES, АССОЦИИРОВАННЫХ С ИКСОДОВЫМИ КЛЕЩАМИ В ЯПОНИИ

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Бактерии порядка Rickettsiales являются облигатными внутриклеточными паразитами позвоночных и беспозвоночных животных и некоторые из них вызывают тяжелые лихорадочные заболевания у человека и домашних животных. В Японии хорошо известны микроорганизмы Rickettsia japonica и Orientia tsutsugamushi, которые являются возбудителями Японской пятнистой лихорадки, переносимой иксодовыми клещами и лихорадки Цуцугамуши, переносимой соответственно краснотелковыми клещами. В последние годы появляется много сообщений о выявлении, преимущественно молекулярно-генетическими методами, в Японии нескольких новых бактерий порядка Rickettsiales, ассоциированных с клещами. Некоторые из этих бактерий могут иметь существенное ветеринарное или медицинское значение. Подобные бактерии включают риккетсий группы клещевых пятнистых лихорадок не относящихся к R. japonica, Ehrlichia spp., Anaplasma spp., и Neoehrlichia sp. В данном сообщении характеризуются основные представители этих групп, обитающие на территории Японии.

Ключевые слова: *Rickettsiales, Rickettsia, Ehrlichia, Anaplasma, Neoehrlichia*

The order *Rickettsiales* includes the genera *Rickettsia*, *Orientia*, *Ehrlichia*, *Anaplasma*, and *Neoehrlichia* etc. [1, 2]. In Japan, before the first report of "Japanese spotted fever (JSF)" caused by *Rickettsia japonica* in 1984 [3], "Tsutsugamushi disease" caused by *Orientia tsutsugamushi* had only been known as a rickettsiosis. *R. japonica* and *O. tsutsugamushi* are transmitted by ticks and mites, respectively. In recent years, many isolation and molecular analyses revealed the presence of tick-associated *Rickettsiales* bacteria such as spotted fever group rickettsiae other than *R. japonica, Ehrlichia* spp., *Anaplasma* spp., and *Neoehrlichia* sp. in ticks or wild mammals. The representatives of these *Rickettsiales* bacteria in Japan are summarized as below.

SPOTTED FEVER GROUP (SFG) *RICKETTSIAE*

So far, SFG rickettsiae which were identified in Japan are *R. japonica* [4], *R. helvetica* [5], *R. tamurae* [6], *R. asiatica* [7], *Candidatus* R. tarasevichiae [8], and *R. heilonjiangensis* [9]. *Rickettsia japonica* was isolated from tick species of *Haemaphysalis histricis*, *H. cornigera*, *H. flava*, *H. longicornis*, *Dermacentor taiwanesis*, and *Ixodes ovatus* [10]. *R. helvetica* was also isolated from ticks of *Ixodes ovatus*, *I. persulcatus*, and *I. monospinosus* [5] and also detected from Sika deer (*Cervus nippon yesoensis*) in Hokkaido, a northern part of Japan [11]. *R. tamurae* was isolated from *Amblyomma testudinarium* ticks [6]. *R. asiatica* was isolated from *I. ovatus* ticks [7]. *Candidatus* R. tarasevichiae was detected by PCR from *I. persulcatus* ticks in Hokkaido [8]. *R. heilonjiangensis* was isolated from *H. concinna* ticks [9]. Of these, *R. japonica* cause severe febrile illness in humans frequently in Japan [12]. Human infection by *R. heilonjiangensis* has recently been confirmed [9]. Additionally, *R. tamurae* was found to cause rickettsiosis, but it seems to be rare. The immunecompromised hosts are probably more sensitive to *R. tamurae* infection [13].

EHRLICHIA SPP.

Ehrlichia muris have firstly been isolated from a wild mouse of *Eothenomys kageus* (synonym of *E. smithi*) and reported in 1995 in Japan [14]. Later, several nonclassified genetic variants of the genus *Ehrlichia* have been found in Japan. Of these, the *Ehrlichia* HF strain has well studied. The HF strain was initially isolated and described from *I. ovatus* tick in 2000 [15]. The genetic variants of HF strain were detected by molecular analysis from wild mice of *Apodemus argenteus*, *A. speciosus*, and *E.smithi* [16] and dogs [17]. These bacteria cause fetal infection to immunocompetent laboratory mice. Recently, the *Ehrlichia* variant closely related to *E. ewingii* was identified from *H. longicornis* ticks [18]. *E. chaffensis* which is well known as a human pathogen was detected from Sika deer (*Cervus nippon nippon*) and described in 2009 [19], although there is no report of human infection in Japan to date.

ANAPLASMA SPP.

We have initially detected *Anaplasma phagocytophilum*, a human pathogen, from *I. persulcatus* and *I. ovatus* ticks inhabiting Japan in 2005 [20]. Recently, we confirmed that *H. formosensis*, *H. longicornis*, and *H. megaspinosa* were also potential arthropod vectors for transmission of *A. phagocytophilum* [21]. The genetic variants of *A. phagocytophilum* have also been identified from Sika deer and boars in Japan [22, 23]. Besides *A. phagocytophilum*, *A. centrale* and *A. bovis* were detected from deer and *Haemaphysalis* ticks [22]. *A. platys* was identified from dog in Japan [24].

NEOEHRLICHIA SP.

Candidatus Neoehrlichia mikurensis and its genetic variants have firstly discovered from wild rodents (*Rattus norvegicus*) and *I. ovatus* ticks in Japan in 2004 [2]. Later, we and the others were also detected from wild mice of *A. argenteus*, *A. speciosus*, and *E. smithi* [25, 26]. Recently, the human cases of *Candidatus* N. mikurensis infection have been reported in Europe [27-29]. In the most cases, the disease developed in immunecompromised individuals. The vector candidates are *Ixodes* ticks such as *I. ricinus*, *I. persulcatus*, and *I. ovatus* in Europe and Asia [2, 30, 31].

ЛИТЕРАТУРА

1. Dumler J.S., Barbet A.F., Bekker C.P., Dasch G.A. et al. Reorganization of genera in the families *Rickettsiaceae* and *Anaplasmataceae* in the order *Rickettsiales*: unification of some species of *Ehrlichia* with *Anaplasma*, *Cowdria* with *Ehrlichia* and *Ehrlichia* with *Neorickettsia*, descriptions of six new species combinations and designation of *Ehrlichia equi* and 'HGE agent' as subjective synonyms of *Ehrlichia phagocytophila* // Int. J. Syst. Evol. Microbiol. — 2001, Nov. — Vol. 51 (Pt 6). — P. 2145—2465.

2. Kawahara M., Rikihisa Y., Isogai E., Takahashi M. et al. Ultrastructure and phylogenetic analysis of '*Candidatus* Neoehrlichia mikurensis' in the family *Anaplasmataceae*, isolated from wild rats and found in Ixodes ovatus ticks // Int. J. Syst. Evol. Microbiol. — 2004, Sep. — Vol. 54 (Pt 5). — P. 1837—1843.

3. Mahara F., Koga K., Sawada S., Taniguchi T. et al. The first report of the rickettsial infections of spotted fever group in Japan: three clinical cases // Kansenshogaku Zasshi. — 1985. — Vol. 59. — P. 1165—1171.

4. Uchida T., Uchiyama T., Kumano K., Walker D.H. *Rickettsia japonica* sp. nov., the etiological agent of spotted fever group rickettsiosis in Japan // Int. J. Syst. Bacteriol. — 1992, Apr. — Vol. 42 (2). — P. 303—305.

5. Fournier P.E., Fujita H., Takada N., Raoult D. Genetic identification of rickettsiae isolated from ticks in Japan // J. Clin. Microbiol. — 2002, Jun. — Vol. 40 (6). — P. 2176—2181.

6. Fournier P.E., Takada N., Fujita H., Raoult D. *Rickettsia tamurae* sp. nov., isolated from *Amblyomma testudinarium* ticks // Int. J. Syst. Evol. Microbiol. — 2006, Jul. — Vol. 56 (Pt. 7). — P. 1673—1675.

7. Fujita H., Fournier P.E., Takada N., Saito T. et al. *Rickettsia asiatica* sp. nov., isolated in Japan // Int. J. Syst. Evol. Microbiol. — 2006, Oct. — Vol. 56 (Pt. 10). — P. 2365—2368.

8. Inokuma H., Ohashi M., Jilintai, Tanabe S. et al. Prevalence of tick-borne *Rickettsia* and *Ehrlichia* in *Ixodes persulcatus* and *Ixodes ovatus* in Tokachi district, Eastern Hokkaido, Japan // J. Vet. Med. Sci. — 2007, Jun. — Vol. 69 (6). — P. 661—664.

9. Ando S., Kurosawa M., Sakata A., Fujita H. et al. Human *Rickettsia heilongjiangensis* infection, Japan // Emerg. Infect. Dis. — 2010, Aug. — Vol. 16 (8). — P. 1306—1308.

10. Fujita H. Cell culture system for isolation of disease agents: 15 years of experience in Ohara Research Laboratory // Annual Report of Ohara General Hospital. Fukushima (Japan); Ohara General Hospital. — 2008. — P. 21—42.

11. Inokuma H., Seino N., Suzuki M., Kaji K. et al. Detection of *Rickettsia helvetica* DNA from peripheral blood of Sika deer (*Cervus nippon yesoensis*) in Japan // J. Wildl. Dis. — 2008, Jan. — Vol. 44 (1). — P. 164—167.

12. National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare. Scrub typhs and Japanese spotted fever in Japan, as of December 2006 // Infectious Agents Surveillance Reprot. — 2006. — P. 27—32.

13. Imaoka K., Kaneko S., Tabara K., Kusatake K. et al. The First Human Case of *Rickettsia tamurae* infection in Japan // Case Rep. Dermatol. — 2011. — Vol. 3 (1). — P. 68—73.

14. Wen B., Rikihisa Y., Mott J., Fuerst P.A. et al. *Ehrlichia muris* sp. nov., identified on the basis of 16S rRNA base sequences and serological, morphological, and biological characteristics // Int. J. Syst. Bacteriol. — 1995, Apr. — Vol. 45 (2). — P. 250—254.

15. Shibata S., Kawahara M., Rikihisa Y., Fujita H. et al. New *Ehrlichia* species closely related to *Ehrlichia chaffeensis* isolated from *Ixodes ovatus* ticks in Japan // J. Clin. Microbiol. — 2000, Apr. — Vol. 38 (4). — P. 1331—1338.

16. Naitou H., Kawaguchi D., Nishimura Y., Inayoshi M. et al. Molecular identification of *Ehrlichia* species and '*Candidatus* Neoehrlichia mikurensis' from ticks and wild rodents in Shizuoka and Nagano Prefectures, Japan // Microbiol. Immunol. — 2006. — Vol. 50 (1). — P. 45—51.

17. Inokuma H., Ohno K., Onishi T., Raoult D. et al. Detection of ehrlichial infection by PCR in dogs from Yamaguchi and Okinawa Prefectures, Japan // J. Vet. Med. Sci. — 2001, Jul. — Vol. 63 (7). — P. 815—817.

18. Matsumoto K., Takeuchi T., Yokoyama N., Katagiri Y. et al. Detection of the new *Ehrlichia* species closely related to *Ehrlichia ewingii* from *Haemaphysalis longicornis* in Yonaguni Island, Okinawa, Japan // J. Vet. Med. Sci. — 2011, Nov. — Vol. 73 (11). — P. 1485—1488.

19. Kawahara M., Tajima T., Torii H., Yabutani M. et al. *Ehrlichia chaffeensis* infection of sika deer, Japan // Emerg. Infect. Dis. — 2009, Dec. — Vol. 15 (12). — P. 1991—1993.

20. Ohashi N., Inayoshi M., Kitamura K., Kawamori F. et al. *Anaplasma phagocytophilum*-infected ticks // Emerg. Infect. Dis. — 2005, Nov. — Vol. 11 (11). — P. 1780—1783.

21. Gaowa, Wuritu, Wu D., Yoshikawa Y. et al. Detection and characterization of *p44/msp2* transcript variants of *Anaplasma phagocytophilum* from naturally infected ticks and wild deer in Japan // Jpn J. Infect. Dis. — 2012. — Vol. 65 (1). — P. 79—83.

22. Kawahara M., Rikihisa Y., Lin Q., Isogai E. et al. Novel genetic variants of *Anaplasma phagocytophilum*, *Anaplasma bovis*, *Anaplasma centrale*, and a novel *Ehrlichia* sp. in wild deer and ticks on two major islands in Japan // Appl. Environ. Microbiol. — 2006, Feb. — Vol. 72 (2). — P. 1102—1109.

23. Masuzawa T., Uchishima Y., Fukui T., Okamoto Y. et al. Detection of *Anaplasma phagocytophilum* from Wild Boars and Deer in Japan // Jpn J. Infect. Dis. — 2011. — Vol. 64 (4). — P. 333—336.

24. Inokuma H., Fujii K., Matsumoto K., Okuda M. et al. Demonstration of *Anaplasma* (*Ehrlichia*) *platys* inclusions in peripheral blood platelets of a dog in Japan // Vet. Parasitol. — 2002, Dec. — Vol. 110 (1—2). — P. 145—152.

25. Naitou H., Kawaguchi D., Nishimura Y., Inayoshi M. et al. Molecular identification of *Ehrlichia* species and '*Candidatus* Neoehrlichia mikurensis' from ticks and wild rodents in Shizuoka and Nagano Prefectures, Japan // Microbiol. Immunol. — 2006. — Vol. 50 (1). — P. 45—51.

26. Tabara K., Arai S., Kawabuchi T., Itagaki A. et al. Molecular survey of *Babesia microti*, *Ehrlichia* species and *Candidatus* Neoehrlichia mikurensis in wild rodents from Shimane Prefecture, Japan // Microbiol. Immunol. — 2007. — Vol. 51 (4). — P. 359—367.

27. Welinder-Olsson C., Kjellin E., Vaht K., Jacobsson S. et al. First case of human "*Candidatus* Neoehrlichia mikurensis" infection in a febrile patient with chronic lymphocytic leukemia // J. Clin. Microbiol. — 2010, May. — Vol. 48 (5). — P. 1956—1959.

28. von Loewenich F.D., Geissdörfer W., Disqué C., Matten J. et al. Detection of "*Candidatus* Neoehrlichia mikurensis" in two patients with severe febrile illnesses: evidence for a European sequence variant // J. Clin. Microbiol. — 2010, Jul. — Vol. 48 (7). — P. 2630—2635.

29. Fehr J.S., Bloemberg G.V., Ritter C., Hombach M. et al. Septicemia caused by tick-borne bacterial pathogen *Candidatus* Neoehrlichia mikurensis // Emerg. Infect. Dis. — 2010, Jul. — Vol. 16 (7). — P. 1127—1129.

30. Rar V.A., Epikhina T.I., Livanova N.N., Panov V.V. et al. Study of the heterogeneity of 16s rRNA gene and groESL operone in the dna samples of *Anaplasma phagocytophilum*, *Ehrlichia muris*, and "*Candidatus* Neoehrlichia mikurensis" determined in the *Ixodes persulcatus* ticks in the area of Urals, Siberia, and far east of Russia // Mol. Gen. Mikrobiol. Virusol. — 2011. — Vol. 2. — P. 17—23.

31. Carpi G., Cagnacci F., Wittekindt N.E., Zhao F. et al. Metagenomic profile of the bacterial communities associated with *Ixodes ricinus* ticks // PLoS One. — 2011. — Vol. 6 (10). — e25604.

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