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Review

Babesia: A world emerging

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ABSTRACT

Babesia are tick-transmitted hemoprotozooans that infect mammals and birds, and which are acknowledged for their major impact on farm and pet animal health and associated economic costs worldwide. Additionally, *Babesia* infections of wildlife can be fatal if associated with stressful management practices; and human babesiosis, also transmitted by blood transfusion, is an increasing public-health concern. Due to the huge diversity of species reported to serve as *Babesia* hosts, all vertebrates might be potential carriers, as long as they are adequate hosts for *Babesia*-vector ticks. We here provide a comprehensive overview of the most relevant *Babesia* species, and a discussion of the classical taxonomic criteria. *Babesia*, *Cytauxzoon* and *Theileria* parasites are closely related and collectively referred to as piroplasmids. A possible scenario for the history of piroplasmids is presented in the context of recent findings, and its implications for future research avenues are outlined. Phylogenetic trees of all available 18S rRNA and hsp70 genes were generated, based on which we present a thoroughly revised molecular classification, comprising five monophyletic *Babesia* lineages, one *Cytauxzoon* clade, and one *Theileria* clade. Updated 18S rRNA and beta-tubulin gene trees of the *B. microti* isolates agree with those previously reported. To reconcile estimates of the origin of piroplasmids and ticks (~300 Ma, respectively), and mammalian radiation (60 Ma), we hypothesize that the dixenous piroplasmid life cycle evolved with the origin of ticks. Thus, the observed time gap between tick origin and mammalian radiation indicates the existence of hitherto unknown piroplasmid lineages and/or species in extant vertebrate taxa, including reptiles and possibly amphibians. The development and current status of the molecular taxonomy of *Babesia*, with emphasis on human-infecting species, is discussed. Finally, recent results from population genetic studies of *Babesia* parasites, and their implications for the development of pathogenicity, drug resistance and vaccines, are summarized.

Contents

Abbreviations: AFLP, amplified fragment-length polymorphism; BSC, biological species concept; CI, confidence interval; HPD, highest posterior density; ITS, intergenic spacer region; LD, linkage disequilibrium; Ma, million years ago; MLT, multilocus genotype; MOI, multiplicity of infection; MRCA, most recent common ancestor; PSC, phylogenetic species concept; RAPD, random amplification of polymorphic DNA.

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1. Introduction

Babesia are tick-transmitted protozoan hemoparasites, of great economic, veterinary and medical impact worldwide. They are considered to be the second most commonly found parasites in the blood of mammals after trypanosomes, and they have also been described infecting birds. In their vertebrate hosts they reproduce asexually inside erythrocytes, and together with *Theileria* spp. they are referred to as piroplasms or piroplasmids. The sexual phase of the *Babesia* life cycle typically takes place in Ixodid ticks, which acquire and transmit the parasites during their blood meals (Fig. 1) (Kakoma and Mehlhorn, 1994; Telford et al., 1993; Gray and Weiss, 2008).

Victor Babeş (1888) was the first to discover microorganisms inside bovine erythrocytes of Romanian cattle that presented hemoglobinuria; and he later observed a similar organism in sheep blood (Babeş, 1892). Five years later in the USA, Smith and Kilbour described that the presence of an intraerythrocytic parasite was the cause of tick-transmitted Texas Cattle Fever, a disease that had long stricken cattle ranchers in the Southern US states (Smith and Kilbourne, 1893). This turned out to be the first description of an arthropod-transmitted pathogen of vertebrates. The parasites described by Babeş, and Smith and Kilbour were later named *Babesia bovis*, *B. ovis* and *B. bigemina*, respectively (Starcovici, 1893; Mihalca, 2010). Soon afterwards, babesias parasitizing the blood of other domestic animals were observed, such as those that eventually became known as *B. canis* and *B. caballi*, described by Piana and Galli-Valerio (1895) and by Koch (1904), in dog and horse erythrocytes, respectively. Since these early findings, more than 100 different *Babesia* species have been discovered, and thanks to the advances in microscopy, cell biology and molecular biology techniques our knowledge of the *Babesia* world is rapidly expanding (Levine, 1988; Roncalli Amici, 2001; Criado-Fornelio et al., 2004; de Waal and Van Heerden, 2004; Uilenberg, 2006; Lack et al., 2012).

2. Distribution and pathological effects of some relevant *Babesia* spp.

The remarkable impact of babesia infections in three host groups: domestic animals, humans and, most recently acknowledged, some wildlife species, has inspired a great amount of research efforts in recent decades.

In general, babesia infections course with varying degrees of severity that can often be associated to the host's age, immunological status, concurrent infections with other pathogens, and/or genetic factors. Common manifestations of acute babesia infections in different hosts can include fever, anemia, hemoglobinuria, jaundice, malaise, lethargy and anorexia, while the chronic status is generally asymptomatic. Among domestic animals, babesia infec-

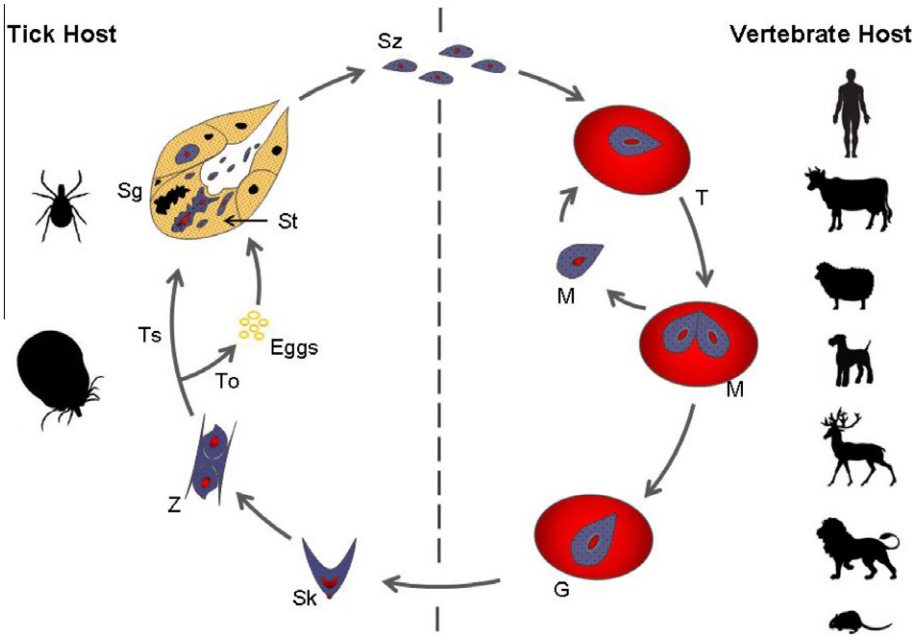

Fig. 1. Generic life-cycle of *Babesia* spp. *Babesia* sporozoites (Sz) are injected into the bloodstream of a vertebrate host with minute amounts of saliva, during the blood meal of an infected tick. After invading erythrocytes they differentiate into trophozoites (T), which divide asexually (merogony) into two or sometimes four merozoites (M). Merozoites exit the erythrocytes and invade new ones, continuing the replicative cycle in the host. A few merozoites stop division and transform into gamonts or pre-gametocytes (G). Gamogony and sporogony take place in the tick. When gamonts are taken up by a tick feeding on an infected host, they differentiate in the gut into gametes, also known as ray bodies or Strahlenkörper (Sk), that fuse forming a diploid zygote (Z, gamogony). Zygotes undergo meiosis giving rise to motile haploid kinetes, which multiply by sporogony and access the hemolymph, invading and continuing their replication in several tick organs, including the salivary glands (Sg). Here, a final cycle of differentiation and multiplication takes place, in which kinetes transform into sporozoites that will infect a vertebrate host after the tick has molted into the next stage, i.e. larvae to nymph or nymph to adult (transstadial transmission, Ts). In some *Babesia* spp. (*Babesia* sensu strictu), kinetes also invade the tick ovaries and eggs, and infective sporozoites are formed in the salivary glands of the next generation larvae (transovarial transmission, To) (Mehlhorn and Schein, 1984).