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| RESEARCH ARTICLE

Mechanism of Life Cycle and Transmission of Babesia

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| ABSTRACT
Babesia is tick-borne apicomplexan protozoa which causes babesiosis. Babesiosis is an important tick-borne disease that affects a wide range of domestic and wild animals and occasionally humans in tropical and subtropical countries. So far, more than 100 different Babesia species have been identified in animals. Babesiosis occurs globally and can lead to significant economic losses, including mortality, decreased meat and milk production, and indirect costs associated with tick control measures. All species of Babesia has heteroxenous lifecycle. Ticks serve as definitive hosts for the sexual development of the organism, while mammals act as intermediate hosts by harboring the asexual stages. Mammals become infected with Babesia through the bite of infected ticks, which inject sporozoites into the bloodstream through their saliva. These sporozoites bind to red blood cells (RBCs), enter them via endocytosis and developing into trophozoites. They reproduce through binary fission, generating merozoites that break open infected red blood cells and invade new ones. Some merozoites develop into gamonts, which engage in sexual reproduction in the tick's gut, resulting in the creation of zygotes that invade the midgut epithelial cells. Zygotes change into motile ookinetes and move to the tick's salivary glands, where they develop into sporozoites. This review topic aims to provide useful informa¬tion about the mechanism of life cycle, transmission, Economic importance, history and timed of intracellular of Babesia species.

| KEYWORDS

Tick, transmission. Life cycle, mammals, Babesia

| ARTICLE INFORMATION

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1. Introduction

The phylum Apicomplexa includes significant parasites affecting humans and animals, such as the pathogens responsible for malaria, babesiosis, theileriosis, toxoplasmosis, cryptosporidiosis, and coccidiosis. Within Apicomplexa, the order Piroplasmida encompasses three genera: *Babesia* spp., *Theileria* spp., and *Cytauxzoon* spp. Here, we will discuss *Babesia* spp.(Elsworth & Duraisingh, 2021). Babesia is a genus of intraerythrocytic protozoan parasites (Montero-Clemente et al., 2022) which infect many domestic and wildlife animals as well as humans resulting in an intraerythrocytic infection (Abi, 2018; Al-Abedi & Al-Amery, 2021). There are more than 100 known species of this genus which cause babesiosis. Babesiosis is a worldwide tick-borne hemoprotozoosis affecting many mammalian species (Alain Chauvin et al., 2009). These animals are like cattle, Buffalo, Horse, donkey, Pig, Sheep, goat, Dog, Cat and etc. (Cozma, 2013).

The life cycle of *Babesia* complete via two kind of hosts. Hard ticks are as an intermediate host while bovine is as a definitive host (Abi, 2018). The life cycle of *Babesia* can be completed in three main stages, which two stage of them occur in hard ticks and one of them takes place in vertebrate: one, Gametogony: fusion and formation of gametes occur in the gut of the ticks. Second, Sporogony: It is asexual reproduction taking place in the salivary gland of tick and the Merogony of *Babesia* take place in the Vertebrates (Abdela & Jilo, 2016).

Babesia species are biologically transmitted by vectors through transovarial transmission (to the first generation) and transstadial transmission (the transfer of infection from the egg to the adult stage) (Demessie & Derso, 2015a). Babesia species is transmitted by hard ticks, where it is passed transovarially through the egg from one generation of ticks to the next. Ticks become infected by consuming parasites present in the blood of infected cattle. *B. bigemina* and *B. bovis* are transmitted transovarially by *boophilus* ticks, but only tick larvae transmit *B. bovis*, whereas nymphs and adults transmit *B. bigemina* and *B. divergens* (Esmaeilnejad et al., 2015). In an infected Tick, the *Babesia* parasite develops and spreads throughout the Tick's organs, eventually invading the salivary glands or eggs. When the infected Tick bites vertebrate animals, the parasites are injected into the bloodstream where they enter red blood cells (Hajdušek et al., 2013). It can also be transmitted mechanically through contaminated needles and syringes, blood transfusions, and surgical instruments (Montero et al., 2022). Transplacental transmission of *Babesia* species in cattle has been shown to occur as well (Aranda et al., 2017).

Clinical signs of babesiosis include weight loss, ataxia, decreased appetite, cessation of rumination, loss of body weight, progressive hemolytic anemia, jaundice (icterus), yellowing of the conjunctival and vaginal mucous membranes in advanced cases, hemoglobinuria, cardiac and respiratory issues, as well as reduced milk production (Tsuji et al., 2007). Babesiosis is the second most prevalent blood-borne parasitic infection, next to trypanosomiasis (Hajdušek et al., 2013). The major economic impact of babesiosis is on the cattle industry and the two most important species in cattle are *B. bovis* and *B. bigemina*) *(*Zintl et al., 2003).But *B. bovis* can cause more severe disease than *B. bigemina* (Wodaje, Adudna, et al., 2019*)*. Bovine babesiosis is the most important arthropod borne disease of cattle worldwide that causes significant morbidity and mortality (Schnittger et al., 2012). This review topic provides useful information about the mechanism of life cycle's *Babesia* species of Veterinary and describes the way of transmission from ticks to animals.

2. History

The earliest documented case of an epidemic caused by the *Babesia* genus likely involved cattle mortality. In 1888, Victor Babes described intraerythrocytic microorganisms responsible for the death of 50 thousand cattle in Romania and classified them as Bacteria. In 1893, Kilborne and Smith identified a causative agent of Texas cattle fever, categorizing it as a genus and naming it *Babesia*, thus classifying it as a protozoan. (Kjemtrup & Conrad, 2000; Uilenberg, 2006). They also proved that ticks are a crucial factor in the spread of this disease (Razmi, 2022). This was the first description of an arthropod-transmitted, pathogen of vertebrates. Babes later observed a similar organism in sheep blood (Babeș, 1892). After these microorganisms discovered in cattle and sheep because of these, they were named *Babesia bovis* and *Babesia ovis***.** Shortly after these findings in ruminants, the first describtion of *Babesia* spp. infection in dogs was reported in Italy in 1895. Lignieres described two forms of *Babesia* as *B. bigemina* and *B. bovis* in cattle in Argentina in 1903. The first human babesiosis was reported in a splenectomized Yugoslavian farmer in 1957. After the initial case in Europe, a case caused by *B. microti* was diagnosed in a splenectomized patient from California, USA, in 1966 (Razmi, 2022). Currently, these protozoan diseases occur worldwide (Malinovská, 2024). Since then, newly recognised *Babesia* with zoonotic potential continue to emerge around the world and the substantial economic impact of babesiosis on livestock and companion animals especially in the tropics and subtropics is ongoing (Hunfeld et al., 2008).

3. Etiology and classification

Protozoan parasites of the genus of *Babesia* belongs to the phylum apicomplexa, the class sporozoasida,su-bclass Haematozoea, order Piroplasmida, sub order Piroplasmorinae, and family Babesiidae cause babesiosis in domestic animals (Chandran, 2021; Hunfeld et al., 2008) . The *Babesia* genus includes over 100 *Babesia* species have been identified in vertebrate hosts. Of those, eighteen species have been found to cause babesiosis in domestic mammals, including pigs, horses, sheep, goats, cats, and dogs. Most *Babesia* species have been reported in rodents, cattle, and carnivores (A. Chauvin et al., 2009; Sivakumar et al., 2016). The most *Babesia* species which infect domestic animals has named in (table-1).

Historically, *Babesia* were classified by two methods, (1) the relative size and shape of trophozoites in the erythrocytes and the number of merozoites and (2) the host of origin. Based on size, there were two groups (small *babesia* has 1.0-2.5 µm length while large *Babesia* has 2.5-.5.0 µm) (Alain Chauvin et al., 2009). But this division is not associated with phylogenetic relatedness. Identification based on host origin was based on the assumption that these parasites are host-specific, which we now know is not the case for many species. Molecular characterization of multiple gene targets indicates that the piroplasms should be divided into at least five or six groups: one that includes small *Babesia* from various wild rodents, felids, canids, and mesomammals (called archaeopiroplas mids or Microti group); one that includes parasites from cervids, dogs, and people (called the western piroplasms, Duncani group or prototheilerids); one that includes primarily canine, bovine, and cervine species (babesids); another that includes primarily bovine, equine, and ovine species (unguilibabesids); and a final group that includes the *Theileria* and *Cytauxzoon* spp. (theilerids) (theilerids) (Wodaje, Adugna, et al., 2019; Yabsley & Shock, 2013).

Table (1): Named species of *Babesia* parasitic in domestic animals (Cozma, 2013).

Host	Species	Distribution
Cattle	*B. bovis*	Worldwide
	B. bigemina	Worldwide
	B. divergens	Europe
	B. major	Asia, Europe
	B. occultans	Africa
	B. ovata	Asia
Buffalo	*B. bovis*	America, Asia
	B. bigemina	America, Asia
	B. orientalis	Asia
Horse, donkey	*B. caballi*	Africa, America, Asia, Europe
Pig	*B. trautmanni*	Africa, Europe
Sheep, goat	*B. crassa*	Asia
	B. motasi	Africa, Asia, Europe
	B. ovis	Africa, Asia, Europe
Dog	*B. canis*	Europe
	B. conradae	North America
	B. gibsoni	Asia, Africa, America, Europe
	B. rossi	Africa
	B. vogeli	Worldwide
Cat	*B. felis*	Africa
	B. presentii	Asia

4. Life cycle

All species of *Babesia* has heteroxenous lifecycle (figure -1). The sexual development takes place in ticks, because of this situation, ticks are considered as a definitive host while Mammals are intermediate hosts as they are harboring the asexual stages.

The infective sporozoites (figure 1-1) are injected through into blood stream of vertebrates by ticks of saliva (Cozma, 2013).

Sporozoites attach to erythrocytes (figure 1 - 2) and by endocytosis. they enter inside erythrocytes (figure 1 - 3). Inside the red blood cells, sporozoites start to feed, becoming trophozoites (1 - 4) which subsequently divide by binary fission resulting in the formation of two merozoites in each erythrocyte (figure 1 - 5). Merozoites lyse the infected RCBs and continue invading new RBCs. Some merozoites mature and turn into pre-gametocytes (beginning the gamogony phase) (Martínez-García et al., 2021).

Sometimes, one additional cell division results in the formation of four merozoites in each erythrocyte (figure 1 - 6). The size and location of the merozoites depend on both *Babesia* and the host species. *Babesia* spp. are divided into two groups with (1) large *Babesia* (2.5–5.0 μm long) which included (B. *bigemina*, *B. canis, B. major, B. motasi* etc). In which the merozoites are longer than the erythrocyte radius and (2) small *Babesia* (1.0–2.5 μm long) which included *(B. bovis, B. divergens, B. gibsoni, B. ovis* etc.) in which the merozoites are smaller than the erythrocyte radius (Laha et al., 2015). In order, merozoites rupture the infected erythrocytes (figure 1 - 7) and invade new ones (figure 1 - 8), repeating the merogony several times until many red blood cells are destroyed. During the course of infection, some merozoites are transformed into gamonts while still in the erythrocytes of the intermediate hosts. After, Conjugation of gametocytes occurs in the tick gut followed by multiplication by multiple fission and migration to various tissues including the salivary glands (Demessie & Derso, 2015b).

Once ingested *Babesia*-infected red-blood cells reach the tick midgut. Many parasites will be destroyed or degenerate, but a small number will evolve to gametocytes, essential for zygote fusion and penetration of the midgut peritrophic membrane(Sonenshine & Hynes, 2008).

When a new tick (figure 1-9,10.11) feeds on the infected blood of the intermediate host, the gametocytes enter the tick midgut lumen, and invade the epithelial cells (figure 1-12) and emerge from erythrocytes, in order, develop into polymorphic (spherical to pyramidal) strahlenkorper that go on to divide by multiple fission to form gamonts (Gray et al., 2019; Suarez et al., 2019). Eventually, start the gametogony process to produce gametes. It seems that the other stages (i.e. merozoites, sporozoites, trophozoites) ingested by the vector are not able to produce the intestinal infection in the tick. Then gamonts sexually join, the zygote is formed. Zygotes invade basophilic midgut epithelial cells. In this time, zygote has 8-10 μm length and look like as a spike-like arrowhead organelle, this shape facilitates cell penetration. Once across, the arrowhead touches the midgut cell membrane, which invaginates

around this organelle at the point of contact. No parasitophorous membrane is produced and the midgut cell membrane appears to be lysed at the point of entry, apparently due to the action of enzyme released from a coiled structure in the invading parasite. The function of the arrowhead appears to be very similar to that of rhoptries and micronemes in other protozoan parasites. when the *babesia* zygote has been internalized, the arrowhead organelle disintegrates and the zygote is then transformed into a motile stage, termed the ookinete. Meiosis, which indicates the beginning of sporogony in the apicomplexa life cycle, probably occurs at this stage because the ookinete appears to be haploid (A. Chauvin et al., 2009). The ookinete migrates to the tick's salivary glands a mobile oocyst-like structure called kinete (figure 1 - 13)(Santos et al., 2023). Through the hemolymph, the kinetes will invade all the tick's tissue, including ovaries (figure 1 - 15) and salivary glands (figure 1 - 14). When reaching the salivary glands, the kinetes start the sporogony with the formation of sporozoites. Kinetes from the ovaries will be responsible for the transovarial transmission to the eggs produced by the female tick and eventually part of the next generation larvae will be already infected when hatch. The sporozoites from the salivary gland will infect a new host when the tick feeds again(Cozma, 2013).

It was demonstrated that transmission of *B. microti* from the tick occurs 24 hours following its feeding. This process has not been studied with other *Babesia* species (Karbowiak et al., 2018).

In order to understand the ecological rationale behind the transmission of pathogens by ticks, it is essential to present some brief insights into the tick biology and mechanism of vectorial transmission. Ticks have three feeding developmental stages: larvae, nymphs and adults (male and females). Most ticks follow a so-called three host life cycle, meaning that each stage feeds on a different host. After larvae hatch from the eggs, they attach to a host, feed with blood and detach. After detachment, the larvae drop into their surroundings, where they experience their first molting and transform into nymphs. Nymphs search for a new host, they attach to it and feed again. After fully engorged they detach, fall into the environment and molt for the second time, becoming adults. Part of the nymphs become males, the others become females. Adult ticks attach to the third host, the feed and reproduce sexually. Fully engorged and fertilized females fall-off the host. After some time spent in the environment, they lay thousands of eggs and die. Males typically do not feed and are attached to the host solely to locate females. Given these factors, it is clear that each stage of the tick feeds only once and on a single host. The next time it will feed it will be already as another developmental stage. If a larva (figure 1 - L) feeds on a host infected with *Babesia*, it will acquire the infection (figure 1 - 9). The next time it will feed, it will be as a nymph, on another host. Hence, the maintenance of the infection from a stage to another (figure 1- 9') is a sine qua non prerequisite for the existence and transmission for any tick-borne disease. This essential event is known as transstadial passage (or less accurately, transstadial transmission). The same situation happens if a nymph (figure 1 - N) feeds on an infected host (figure 1 - 10). It will pass the infection to adults (figure 1 - 10') which will eventually infect a new host. If the infected stage is an adult female (figure 1 - F) (figure 1 - 11), the infection must be ecologically continuous, meaning the female must be able to transmit the acquired pathogen to her offspring (figure 1 - 11').(Cozma, 2013). This is possible in certain tick-borne pathogens (but not in all) because of the presence of anatomical structures which connect the digestive tube of the tick with the ovaries. This feature is known as transovarial transmission. Not all species of *Babesia* are able to pass by this transovarial route. It seems that *B. felis* from cats or *B. microti* from rodents are such species (Suarez et al., 2019).

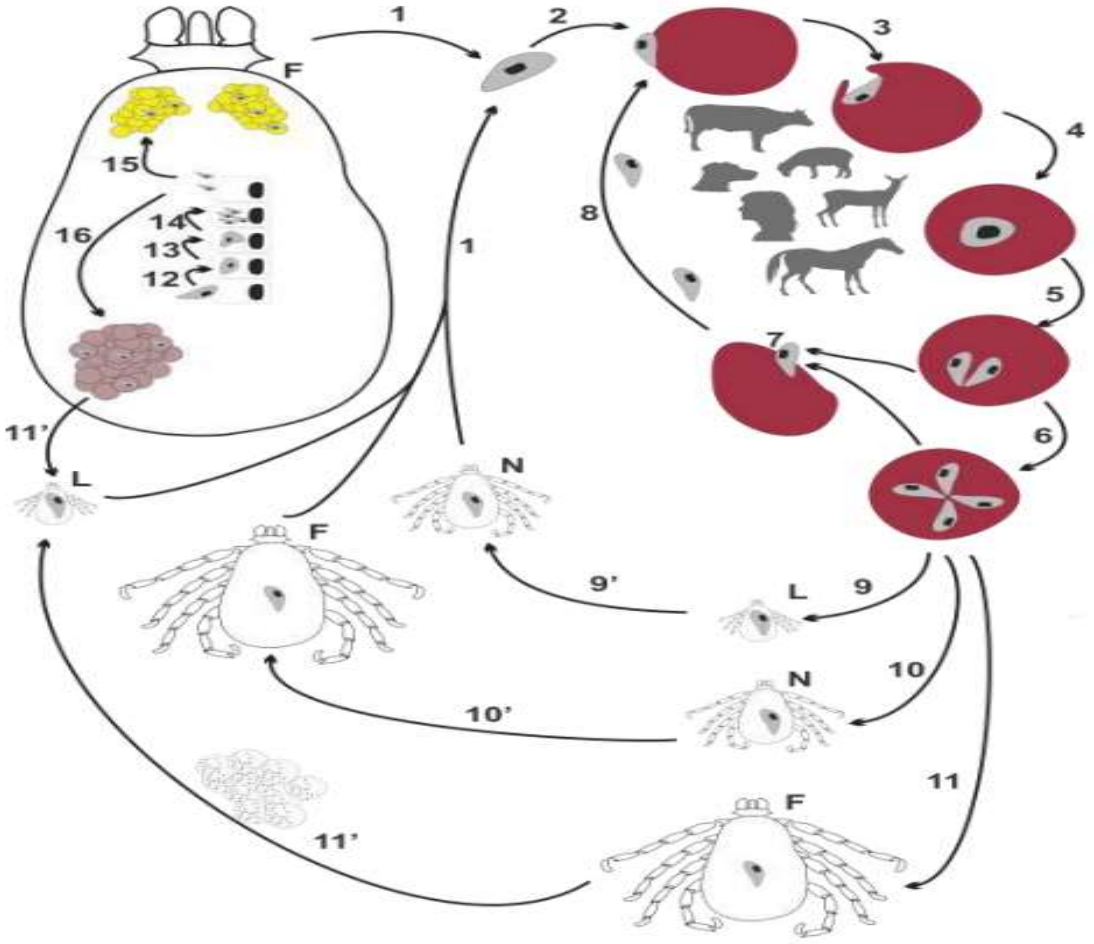
Considering the relatively strict host specificity of *Babesia*, an additional crucial barrier is not only the alternation of ecological hosts but also the specific host species involved. Not all the three hosts from a complete life cycle of a tick are belonging to the same species. For instance, in the case of *Dermacentor reticulatus* the larvae and nymphs feed usually on micromammals and only adult ticks use dogs. It is known that *D. reticulatus* is the vector of *Babesia canis*. If *Babesia canis* infects only dogs, it is evident that the only stages which acquire the infection from dogs are adults. It logically means that infected adults females pass the infection to the eggs. Infected larvae which hatch will feed on small mammals, possibly not infecting them. However, the larvae retain the infection in their bodies and transmit it to nymphs, which then pass it on to adults. As a result, the next generation of adults will be responsible for infecting a new dog, which can sometimes take years (Kasaija et al., 2021).

An intriguing method of transmission for species carried by one-host ticks (where all stages feed on the same host) involves males that move from one animal to another.

Another crucial factor in the transmission of tick-borne diseases is the infectivity of tick saliva during the initial hours or days after attachment. It was said before that *Babesia* moves from the intestine of the tick to the salivary glands where sporozoites will be formed. This in-tick migration takes place for most of the tick borne pathogens only after the ticks attaches to a host which is suitable for the pathogen's development. Factors from the vertebrate's blood will activate the migration of the pathogens to the salivary gland and eventually its transmission to the host. This key aspect is essential from practical point of view. If a tick dies due to antiparasitic treatment or is mechanically removed from the host before salivary migration occurs, the risk of pathogen transmission is limited (Neelakanta & Sultana, 2021).

A potential, though relatively uncommon, method of transmission for Babesia is vertical transmission in vertebrates, where an infected mother passes the pathogen to her fetus. Transplacental transmission has been reported in humans, cattle, horses and dogs. Transmission through infected needles or blood transfusion is also possible (Chandran, 2021; Ravindran, 2020).

Figure (1): The life cycle of *Babesia*



5. Groups of molecules in the tick midgut that play a role in acquiring *Babesia*

Recently, it was suggested that during the sexual phase of *Babesia* spp., certain specific proteins depicted in figure (2), which are known to play roles in recognition and adhesion, are expressed. These include glycosylphosphatidylinositol (GPI) anchored proteins that interact with specific targets in epithelial cells (Alzan et al., 2016; Bastos et al., 2013).

Proteomic analysis of the *R. microplus* midgut has revealed a mitochondrial voltage-dependent anion-selective channel (BmVDAC) polypeptide, also referred to as mitochondria porin, which binds to the sexual stage proteins of *B. bigemina*. In ticks VDAC (Voltage-Dependent Anion Channel, has been linked to several physiological processes, including energy metabolism, osmoregulation, and stress responses. Given that ticks undergo long periods without feeding, their reliance on efficient mitochondrial function, particularly through proteins like VDAC, is critical for maintaining homeostasis during these periods (Couto, 2021). Under *Babesia* invasion this protein was found over-represented in the *R. microplus* midgut (Rodríguez-Hernández et al., 2012).

The tick receptor for outer surface protein A (TROSPA) was first discovered in the midgut epithelium of I. s*capularis* as a receptor for *B. burgdorferi*, indicating its potential role in regulating bacterial infections in ticks (Urbanowicz et al., 2016). In *R. annulatus*, an orthologue of trospa gene was over-expressed during *B. bigemina* infection and gene knockdown significantly reduced *B. bigemina* infection levels by 70 and 83% in *R. microplus* and *R. annulatus*, respectively (Antunes et al., 2012).

Other molecules present in the midgut that also protect the tick from pathogen invasion are the MD-2-related lipid recognition (ML)-domain containing proteins related with lipid recognition like: proteases and protease inhibitors (Hajdušek et al., 2013).

Eventually, other proteins which role in the mechanism of humoral The midgut defensin-like protein that is longicin. When this protein is inoculated in infected mice with *Babesia*. The *B. microti* parasitaemia reduced. Lack of longicin protein in *R. annulatus*, *B. gibsoni* parasitaemia is increased in the midgut, ovaries and eggs (Tsuji et al., 2007).

Bm86 is a glycoprotein, recognized for the first time in *R. microplus*, and present in midgut cells, that is likely to be involved in the endocytosis of the blood ingested by ticks (Bastos et al., 2013; Rodríguez-Hernández et al., 2012).

Subolesin, subolesin is also a kind of protein in the midgut of tick, suggesting its potential as a candidate antigen for an anti-tick and tick-borne pathogen (TTBP) vaccine (Antunes et al., 2017).

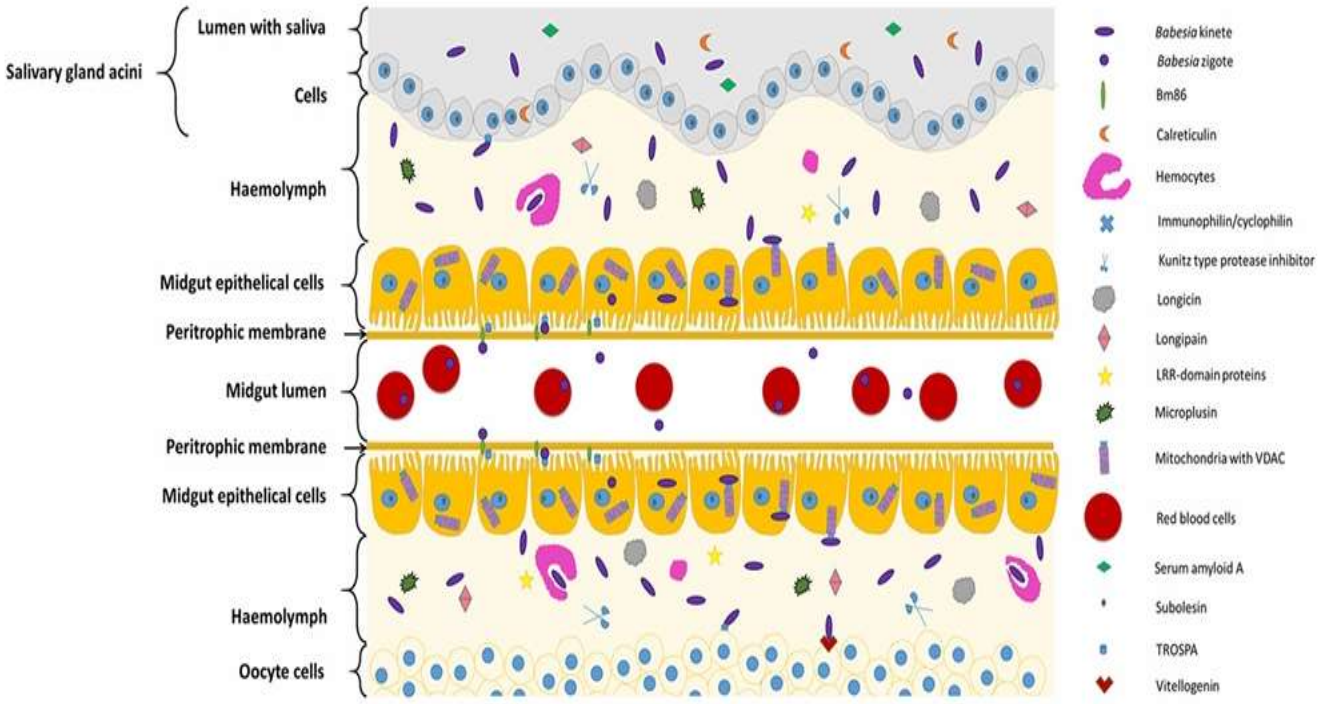


Figure (2) Diagram representing tick molecules implicated in *Babesia* spp. acquisition and transmission by the vector. When ticks feed on *Babesia*-infected animals,parasites within red blood cells reach and penetrate the tick midgut per trophic membrane to invade the epithelial cells (in the figure center). Once these cells are infected, transcriptional factors, such as subolesin, can regulate protein expression in several cellular pathways, facilitating *Babesia* infection. In the microvilli of the midgut cells, parasite zygotes will probably interact with a tick glycoprotein (Bm86) and a tick receptor of the outer surface protein A (TROSPA). Inside the epithelial cells, mitochondria porins (VDAC) can bind to *Babesia* kinete proteins promoting plasminogen activation in the cell surface, allowing their passage to the haemolymph. Once here, the haemocytes can phagocyte circulating parasites and the tick antimicrobial molecules such as, longicin, micropulsin, longipain, LRR-domain and Kunitz-type protease inhibitors are activated potentially reducing the infection in the vector. If the infectious parasites surpass these barriers of defense, they will be capable to spread across the tissues and invade ovaries (represented in the bottom of the figure) and SGs (represented in the top of the figure). In the ovary, the interaction of *Babesia* molecules with tick vitellogenin and TROSPA receptors may contribute for the occurrence of transovarial transmission; while in the SGs, *Babesia* interacts with TROSPA and calreticulin) Antunes et al., 2017).

6. Babesia importance in the field of veterinary

Babesia spp. are tick-borne parasites that multiply within and ultimately destroy the red blood cells (RBCs) of their mammalian hosts, resulting in serious or fatal illness. *Babesia* spp. infect a wide-array of mammalian and tick hosts and cause disease in animals of economic importance, predominantly cattle, as well in companion animals. *Babesia* spp. of veterinary importance are dispersed globally in both high- and low- socioeconomic countries. However, there is not a research which shows the global economic burden of *Babesia* spp. Infection accurately, but based on, study in Tanzania provides an example, which is estimated to be ~$50 million USD a year in 2006 (Karbowiak et al., 2018).

Bovine babesiosis causes most serious economic loss to the livestock industry, endangering half a billion cattle across the world (Suarez et al., 2019). On the other hand, research shows which *Babesia* becomes the most widespread parasite due to exposure of 400 million cattle to infection through the world. Recently, Babesia has emerged as the most widespread parasite, leading to significant economic losses, including increased mortality, decreased meat and milk production, and indirect costs associated with tick control measures. Babesiosis especially in cattle has great economic importance because unlike many other parasitic diseases it affects adults more severely than young cattle leading to direct losses through death and the restriction of movement of animals by quarantine laws (Onoja et al., 2013). The disease is also a barrier to improving productivity of local cattle by cross-breeding due to the high mortality of genetically superior but highly susceptible cattle, especially dairy cattle, imported from *Babesia*-free areas. As a result, the quality of cattle in endemic areas remains poor, hindering the growth of the cattle industry and negatively affecting the wellbeing of producers and their families (Demessie & Derso, 2015b).

7. Impact of *Babesia* in the field of Public health

Naturally, there are not any known *Piroplasm* spp. Which indicate human is the host, however, several *Babesia* spp. are increasingly recognized as emerging zoonotic pathogens, including *B. microti, B. divergens,* and *B. duncani,* as well as other poorly characterized *Babesia* spp. (Elsworth & Duraisingh, 2021).

Human babesiosis was first identified in 1957 and is now recognized as being present worldwide. The increase in reported cases is likely due to increases in actual incidence as well as increased awareness of the disease (Gray et al., 2010; Yabsley & Shock, 2013). In order, *B. microti* can affect healthy people but *B. divergens* causes serious disease in humans who have had splenectomies and immunocompromised. *B. divergens* infections in humans who are medical emergency. They usually progress very rapidly and most cases in the past ended in death within a week. The disease is marked by a sudden onset of severe hemolysis, hemoglobinuria, jaundice, persistent high fever, chills, sweating, headaches, muscle pain, and pain in the lower back and abdomen, along with occasional vomiting and diarrhea. Shock and kidney failure may also occur. With modern, antiparasitic drugs and supportive therapy, the case fatality rate is approximately 40%. Mild cases may resolve with drug treatment alone (Couto, 2021; Gray et al., 2019).

To Prevent infection with *B. divergens*, immunocompromised individuals should exercise caution when traveling to areas where babesiosis is common, particularly during tick season. Exposure to ticks should be prevented by wearing appropriate clothing (e.g., long-sleeved shirts and long pants) and tick repellents. Skin and clothing should be inspected for ticks after being outdoors and any ticks found should be removed (Spickler et al., 2010).

8. Pathogenesis

The severity of Babesia spp. infections varies significantly based on factors such as the virulence of the strain or species, the age of the host, the host's immune status, and the presence of concurrent infections with other pathogens. The pathogenesis of *Babesia* spp. was studied in different animal models. The parasite invades the erythrocytes and lyse them, causing hemolytic anemia (Krause et al., 2007). The host's immune response is a key factor in the disease's pathogenesis, leading to immune-mediated effects (Fanelli, 2021; Ord & Lobo, 2015).

9. Timed intracellular cycles of *Babesia*

The replication timed intracellular cycle of *Babesia* in RBC depends on the species of *Babesia*. Based on research, One replication of *B.bovis* takes typically Takes ~12 hours. This time belongs to some parameter of hosts. Kinases, including CDKs and CRKs, control many aspects of the cell cycle in eukaryotes, including apicomplexans. Phosphosignaling in *Babesia* spp. was first demonstrated using phosphorylation-specific antibodies in combination with small molecules, which identified the presence of calcium and lipid responsive kinase activity in *B. bovis*.(Zhang, 2020).

The development of synchronization methods for B. divergens allowed the detailed analysis of life cycle parameters of the parasite. Surprisingly, it has been found that unlike other Apicomplexan parasites, population control measures are adopted by the parasite in which, at high parasitemia, options to prolong the RBC cycle are taken, whereas at lower parasitemia, exiting the RBC is chosen to invade new cells and increase population numbers. This developmental choice is unique for Babesia compared with other Apicomplexans like P. falciparum and Toxoplasma gondii, which have precisely timed intracellular cycles. P. falciparum typically spends 48 h in each erythrocytic cycle, while tachyzoite of T. gondii has a 6 h growth and replication period inside the host cell before egress. Multiple definitions of the intra-erythrocytic lifecycle for B. divergens have been laid out in keeping with the complex morphological presentation of the parasites inside the RBC. Historically, an 8 h lifecycle was attributed to the parasite, although no clear rationale for this important chronological hallmark had been laid out. Based on the first events of egress, an 4h life cycle has also been proposed for B. divergens, within the RBC. Data from other laboratories confirm that 4–5 h is an accurate representation of the shortest cycle of the parasite. Thus, 5 h can be considered the smallest amount of time needed for one IEC (Intra- Erythrocytic Cycle) (Cursino-Santos et al., 2016; Menshawy et al., 2018).

Other research has shown which the timed intracellular cycle of *babesia* is 24 h. Thus, the flexibility of this phase of the B. divergens lifecycle allows for parasite persistence, depending on specific developmental choices that it adopts (Lobo et al., 2019; Zhang, 2020).

10. Conclusion

This review topic presents a comprehensive summary of identification, history, taxonomy, Pathogenesis, importance in the field of public health and veterinary, and life cycle of *Babesia* species. Among them, the most important which I have attended that is the life cycle. The life cycle of all *Babesia* is heteroxenous. They have two kinds of hosts, intermediate and definitive. The sexual development takes place in ticks, because of this situation, ticks are considered as a definitive host while Mammals are intermediate hosts as they are harboring the asexual stages. The sexual stage includes Gametogony which produce gamonts and asexual stage involves sporozoit, trophozoit and merozoit.

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