ABSTRACT

Classical swine fever (CSF) is a disease caused by RNA virus, *Flaviviridae* family, genus *Pestivirus*, known as *Pestivirus C*. Its worldwide distribution is now known and causes large economic losses in pig production. Its only natural reservoirs are pig and wild boar. The objective of this review is to present an update on some relevant epidemiological and immunopathological aspects of CSF. CSF is a notifiable disease for Colombia and persistently infected animals are the key to its dissemination and endemicity. CSF virus infection is characterized by disseminated intravascular coagulation, thrombocytopenia and immunosuppression, depending on the severity of the virulence of the different strains. The virus has an affinity for monocytes/macrophages and vascular endothelial cells where it can induce different cellular mechanisms that allow it to proliferate and persist in the animal, such as: oxidative stress by increasing the levels of reactive oxygen species generating decrease of the bioavailability of nitric oxide; mitochondrial fission that allows cell survival by inhibiting apoptosis; and immunosuppression due to the depletion of T and B lymphocytes created by pyroptosis based on gasdermin-D in peripheral lymphoid organs that reduces the humoral and cellular immune response. Immunopathological understanding from molecular explanation in CSF is important in the conceptual contribution of the development of new prophylactic and therapeutic strategies that allow to control/eradic this disease.

Keywords: Communicable diseases; immunology; oxidative stress; pyroptosis; virology (Source: DeCS).

RESUMEN

La peste porcina clásica (PPC) es una enfermedad causada por un virus ARN de la familia *Flaviviridae*, genero *Pestivirus* conocido como *Pestivirus C*. En la actualidad se conoce su distribución mundial y es causante de grandes pérdidas económicas en las producciones porcícolas. Sus únicos reservorios naturales son el cerdo y el jabalí. El objetivo de esta revisión es presentar una actualización sobre algunos aspectos relevantes epidemiológicos e inmunopatológicos de la PPC. La PPC es una...
enfermedad de notificación obligatoria para Colombia y los animales persistentemente infectados son la clave para su diseminación y endemicidad. La infección por el virus de la PPC se caracteriza por coagulación intravascular diseminada, trombocitopenia e inmunosupresión, dependiendo en severidad por la virulencia de las distintas cepas. El virus tiene afinidad por monocitos/macrófagos y células endoteliales vasculares donde tiene la capacidad de inducir diferentes mecanismos celulares que le permiten proliferar y persistir en el animal como lo son: el estrés oxidativo al incrementar los niveles de especies reactivas de oxígeno que genera una disminución de la biodisponibilidad de óxido nítrico; la fisión mitocondrial que permite una supervivencia celular por la inhibición de la apoptosis; y la inmunosupresión debida a la depleción de linfocitos T y B creada por la piroptosis en función de la gasdermina-D en órganos linfoides periféricos que reduce la respuesta inmune humoral y celular. El entendimiento inmunopatológico desde la explicación molecular en la PPC es importante en el aporte conceptual del desarrollo de nuevas estrategias profilácticas y terapéuticas que permitan controlar/erradicar esta enfermedad.

Palabras clave: Enfermedad transmisible; inmunología; estrés oxidativo; piroptosis; virología (Fuente: DeCS).

INTRODUCTION

Classical swine fever (CSF) is a severe acute hemorrhagic swine disease characterized by disseminated intravascular coagulation, thrombocytopenia and immunosuppression, causing fever, leukopenia, abortion, hemorrhage and high mortality in its host, associated with significant economic losses in world pig production (1). This disease is caused by a single-stranded RNA virus belonging to the Flaviviridae family, genus Pestivirus, known as Pestivirus C (2). The enveloped virus particle has a diameter of approximately 40-60 nanometers and a nucleocapsid with an icosahedral characteristic (2). The most characteristic pathological findings in swine with CSF are kidney, urinary bladder, and lymph node haemorrhages (3). The infection can alter metabolic pathways such as glycolysis, the tricarboxylic acid cycle, amino acid, and lipid metabolism (4). In addition, the classical swine fever Virus (CSFV) inhibits the transcription of immune response genes (5).

Currently, CSFV is known to be of global distribution, presenting strains of different virulence that cause a great impact on the economy of pig production due to its high of morbidity and mortality rate and the consequent health risks associated with this disease listed in the diseases of mandatory reporting of the International Organization for Animal Health (OIE) (6) and of course adopted as a mandatory notification disease in Colombia (ICA Resolution No. 02129 of 2002).

Although vaccination has been stipulated as a key pillar of CSF prevention plans, CSFV has evolved to the point of generating persistently infected hosts that immortalize the possibility of disease outbreaks within the pig production system (7). For this reason, it is essential to study the immunopathological processes of CSFV, to support the developmental bases of new drugs and specific vaccines for the prevention, control and eradication of this disease.

The objective of this article is the presentation of a general context of the Colombian and global CSF epidemiology, in the same way and with a special emphasis on understanding the immunopathological mechanisms currently studied of CSFV focused on the generation of persistently infected animals.

General aspects of the classical swine fever virus: Biology and epidemiology

CSFV is single-stranded RNA and consists of a nucleocapsid with a lipid envelope. Its genome encodes 4 structural proteins: C, Ern, E1 and E2 that are components of the virion and 8 non-structural proteins p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B that play different roles in viral pathogenesis (8). Its genetic typing is done using the 5-UTR, E2 or NS5B regions; this is how CSFV is classified into 3 genotypes, which are divided into 3 or 4 subgenotypes (9). However, Ríos et al (10) proposed a reclassification with 5 genotypes and 14 subgenotypes, as follows: Genotype 1 (subgenotypes 1.1, 1.2, 1.3, 1.4, 1.5, 1.6 and 1.7), genotype 2 (subgenotypes 2.1, 2.2, 2.3, 2.4, 2.5, 2.6 and 2.7), genotype 3, genotype 4 and genotype 5. It is important to know the genetic diversity of CSFV, as well as its global distribution for understanding the dynamics of the disease (11).
Genotype 1 has mainly been described in Latin America, subgenotype 1.1 in Colombia (12), also in Peru, Ecuador, and Brazil (13). In addition, in Brazil subgenotypes 1.5 and 1.6 were isolated (14). Genotype 2 is generally present in Europe and Asia, with subgenotype 2.1 being predominant in China and the one with the greatest genetic variability (15). Genotype 3 is also present in Asia, initially subgroup 3.4 was identified in Taiwan; However, this was evolving to other genotypes, a similar case occurred in South Korea (16).

The natural reservoirs of CSFV are exclusively domestic pigs, feral pigs, and wild boar (17). The transmission routes are mainly through the oral and nasal route, either by direct contact with the secretions of infected animals, this being the most efficient, or by indirect contact with contaminated implements, artificial insemination, with surrounding wild boar or feral pigs (18). It is also possible to transmit it by air, by contact with contaminated people and food (19,20). The last route of transmission is especially alarming from the perspective of the zoosanitary status of countries and transportation facilities of not allowed food on air, river, or land passengers between countries, given that the CSFV remains active in food (products and by-products of pig origin) up to 37 days (21).

Another important source of intra-species transmission is the vertical transplacental route, mainly by low and medium virulence strains, causing persistently infected animals (22); by the activity of myeloid derived suppressor cells, a population of immature myeloid cells capable of decreasing the cellular response to interferon gamma (IFN-Y) against antigens (23). As well, persistently infected piglets have been evidenced after postnatal exposure, these piglets do not show symptoms, do not develop innate or adaptive immune responses, but can spread high viral load through their secretions within the production, infecting other animals and putting the farm at risk (24).

CSF is a disease that is present worldwide, it was initially identified in the United States in the late nineteenth century, although it was established that the virus originated when the Tunisian Sheep Virus jumped into pigs approximately 225 years ago (25). According to the OIE, the disease is endemic in certain places on the Asian and European continents, in Central and South America. However, there are several countries have successfully achieved their control and / or eradication; these OIE member countries are recognized as free of the CSFV, including: United States, Australia, the European Union, Canada; and in South America: Argentina, Uruguay, Paraguay, and Chile (Figure 1).

In Colombia, the CSF was first notified in 1942. In 1980, its great impact on pig production was evident and raised the concerns of national authorities (26), for this reason and according to Law 623 of November 21, 2000, the Eradication of Classic Swine Fever of Colombian territory was declared “National Social Interest”. Two years later, Decree 930 of May 10, 2002, in which “Concertation and co-management programme between the public and private sectors for the eradication of Classical Swine Fever throughout the national territory” was established. In turn, that same year, the state zoosanitary authorities: the Colombian Agricultural Institute (ICA) generated ICA Resolution No. 02129 of September 11, 2002 “By which sanitary measures are established for the eradication of Classical Swine Fever”.

The effects of national regulations on CSF management became notable from 2008, when the first disease-free places are declared: the departments of Amazonas, San Andrés, and Providencia. Subsequently, in 2011 the departments with the highest pig production were declared CSF-free (Caldas, Quindío, Valle del Cauca, Risaralda, Antioquia). This was achieved by a joint effort, which included the modernization of farms and the implementation of biosecurity protocols (26).

During the period between 2013 and 2018, 134 CSF outbreaks were reported in Colombia, of which the majority occurred in the Caribbean region, with the Magdalena and Cesar departments being the most affected, it is known that 95% of these cases are known to have been documented in backyard pigs (27). According to the ICA epidemiological bulletin in 2020, epidemiological alerts were presented in Bolívar, Sucre, and Norte de Santander departments.
Classical swine fever: Immunopathology

Immunopathology brings together an ordered and systematic series of interaction phenomena between the infectious agent and its host, in relation to the immune system, response, regulation and systemic effects or in the agent's target organ systems; starting from the mechanisms of entry into the host cell in the case of viruses, to the detail of their direct or indirect deleterious effects (e.g. exacerbated immune response) (28).

CSFV infection in host cells

The CSFV has an affinity, especially, for the monocyte-macrophage (monocytotropic) cell line, but it can also be replicated in vascular endothelial cells, entering the cell through different endocytic pathways. Cluster of differentiation 46 (CD46) and heparan sulfate are the main binding receptors for viral entry (29). The caveolin-1-dependent endocytic pathway requires Ras-related proteins (Rab5 and Rab7, small GTPases) to be transported to endosomes, subsequently Rab 11 directs endosome recycling and is finally transferred to lysosomes mediated by an associated membrane protein to lysosome 1 (Lamp-1) where CSFV RNA is released (30).

Clathrin, pH and cholesterol dependent endocytosis, which requires Rab5 and Rab7, has also been evidenced in previous studies, and in addition, it has also been shown that Rab5 improves viral spread by interacting with Pestiviruses non-structural protein 4B (NS4B) (31). The interaction of protooncogene tyrosine kinase MER (MERTK) with viral E2 glycoprotein promotes the entry of CSFV and regulates the innate response of the host (32). Additionally, the tumor susceptibility gene 101 (Tsg101) in the pathway of the endosomal classification complex needed for transport (ESCRT-1) and its interaction with some non-structural proteins also regulates the entry and replication of CSFV (33). The importance of the interaction of Disintegrin and Metalloprotease 17 (ADAM17) with the Zinc-dependent Glycoprotein E2 in the entry of CSFV was recently determined (34). The mechanism of CSFV entry into the monocyte-macrophage is widely varied, supported by its highly evolutionary and adaptive process to its hosts.

After entering the host cell, CSFV replication induces oxidative stress by increasing levels of reactive oxygen species (ROS) intracellularly (35); In response to this situation, the infected cell increases the levels of antioxidants, such as thioredoxin (Trx), peroxiredoxin-6 (PRDX-6) and heme oxygenase-1 (HO-1), to attenuate increasing oxidative stress. However, these antioxidant mechanisms become insufficient against viral infection (36). In addition, high concentrations of cyclooxygenase-2 (COX-2) are added to this situation of cellular stress, and in turn, decrease in the gamma receptor activated by the proliferator of anti-inflammatory protein (PPAR-γ), actions that contribute to the inflammatory response disease and host cell (e.g., endothelial) dysfunction in the CSFV infectious process (37).

He et al (36) used oxidative stress inhibitors in cells infected by CSFV, where they found low concentrations of viral RNA, an action that demonstrated the importance of oxidative stress as a participatory factor in CSFV replication. An example of these inhibitors is the overexposure with Trx that creates an interaction with the viral protein E, which inhibits the replication of CSFV through the nuclear factor κ B (NF-κB) pathway, showing a possible therapeutic - immunoprophylactic strategy against the initiation of the molecular pathogenesis of CSFV (38).

In endothelial cells infected with increased ROS levels, the bioavailability of nitric oxide (NO) is reduced through biochemical reactions that lead to the formation of peroxynitrite. This metabolite uncouples the enzyme endothelial nitric oxide synthase (eNOS) resulting in the formation of the superoxide anion (37). Although the reduced NO finally causes several reactions related to endothelial dysfunction responsible for the main clinical consequences of the infection (Figure 2), its lower concentration could also represent weaker innate immune responses of the host against CSFV. In addition, Zaffuto et al (38) demonstrated that low levels of NO and high levels of arginase-1 (inhibitor of NO production) are also present in infected macrophages, potentiating oxidative stress and CSFV activity.

**Virulence factors of CSFV and host immunocompromise**

Apart from the effects of oxidative stress per se due to viral replication inside the infected cell, CSFV has a series of virulence factors of relevance for its pathogenic process that directly affect the immune system of its host. Starting with the effects on the innate immune system, where NS4B suppresses Toll-like receptor 3 (TLR 3) signaling, therefore the transcription of various nuclear transcription factors is affected (eg TRIF, IRF3 and NF-κB) that are essential in orchestrating the protective response from interferon (INF) and other cytokines (39) (Figure 3.2). NF-κB is a family of transcription factors that regulate a large number of important genes in the innate and adaptive immune system activity as a mediator of the inflammatory response, some viruses use the NF-κB activation in favor of viral replication while other viruses inhibit their activation as a useful mechanism to evade the immune response (40). Chen et al (40) demonstrated from studies with in vitro and in vivo cell models with mononuclear cells from infected animals, that CSFV infection does not activate NF-κB, possibly as a mechanism of viral evasion from the immune system, thus promoting the viral spread. Additionally, more recent studies by Dong and Tang (41) showed that the viral NS5A protein probably suppressed cellular pro-inflammatory activity by inhibiting NF-κB signaling pathways.

Another important signal transduction pathway in the immune system is the route of signal transducers / Janus kinase and transcription activators (JAK-STAT) involved in the activation of approximately 40 cytokines (42). In studies conducted by Wang et al (43) demonstrated in porcine kidney cells the interaction of CSFV protein E2 with the mitogen-activated protein kinase (MEK) that, by a mechanism yet to be clarified, can generate inhibition of the JAK-STAT route resulting greater replication of CSFV.

While the CSFV inactivates some cellular signaling pathways, it can activate others; thus, high concentrations of interleukin (IL) 1 (IL-1), IL-6 and IL-8 expression were present in CSFV-infected cells, high concentrations of expression were presented, with a higher peak after 2 hours of exposure. Where IL-1 is highly relevant in the activation of several pro-inflammatory cytokines secreted by endothelial cells and mainly infected monocytes / macrophages (44). Jinghan et al (45) demonstrated with strains of different virulence of CSFV, that viral infection induces the secretion of different cytokines such as tumor necrosis factor (TNF-α), IL-2, IL-4, IL-6 and IL-10 with differences in their expressions due to the response to infection between the different strains.
Figure 2. Mechanisms of oxidative stress in the endothelial cell infected by the classical swine fever virus (CSFV). Source: authors.

CSFV can enter the endothelial cell through caveolin-1 mediated endocytosis. Viral replication induces oxidative stress, where the mitochondria play a preponderant role and antioxidant enzymes (eg Trx, PRDX-6 and HO-1) are exceeded in their vital detoxification capacity. The accumulation of ROS and RNS generates alteration in the functionality of the NOse resulting in a fall in the concentration of NO. The alteration in the bioavailability of NO, added to the low enzymatic activity of COX-2 and lower expression of PPAR-γ in the arteriolar endothelium, aggravated by the functional alteration of Guanylate cyclase (lower concentration of cGMP), it is associated with endothelial dysfunction disease and its various clinical consequences of classical swine fever: thrombosis, arterial hypertension, and platelet aggregation.

On the other hand, CSFV infection stimulates the secretion of IL-1β and IL-18, cytokines that are important components of the innate immune system against viral invasion. The maturation of pro-IL-1β is mediated by the enzyme caspase 1, which is processed by the activation of the inflammasome NLRP3 in infected monocytes / macrophages (46, 47). According to Lin et al (46), this mechanism of IL-1β secretion by the CSFV host cell is induced by viral viroporin P7, which acts as a calcium-dependent ion channel in the endoplasmic reticulum, its most studied function is to generate a permeabilization of the cell membrane to facilitate the output of infectious viral particles (Figure 3.3).

In vitro studies with dendritic cells found that CSFV does not alter the morphological or functional characteristics of this cell, and its ability to present antigen to T lymphocyte remains intact serving as a mechanism for spreading the virus to peripheral lymphoid tissues, where it usually induces post-entry into these cell lines, a pyroptosis of lymphoid cells, which sums up the lymphopenia and consequent immunosuppression of the host (48).

Consequently, animals infected with CSFV show a decrease in adaptive immune system response, both of the humoral immune response mediated by CD4+ T cells that recognize the antigen presented by the larger histocompatibility complex (MHC) class II (MHC II) that normally stimulates the activation, maturation and secretion of antibodies by B lymphocytes; as well as the cellular immune response mediated by CD8+ T cells or cytotoxic T cells, which by binding its receptor with the antigen presented by MHCI is responsible for the destruction of cells infected by the virus (45). This action associated with its virulence factors generates immunosuppression of the host, with a high predisposition to secondary infections, mainly in the respiratory and digestive system of bacterial origin.

**Immunopathological mechanisms of the CSFV responsible for persistently infected animals**

Mitochondrial fission generates a division of the mitochondria into two mitochondria daughters, being an essential mechanism for the normal functioning of the cell in situations of metabolic or environmental stress through the maintenance of bioenergetic mechanisms (49). Furthermore, this mechanism allows the segregation of protein, lipid, and DNA components of the mitochondria for their respective elimination in order to maintain a number of renewed mitochondria (50). CSFV induces this mechanism of mitochondrial fission and subsequent fragmentation and selective autophagy of mitochondria (mitophagy) regulated by the putative kinase 1 pathway induced by PTEN (PINK1) and E3 ubiquitin ligase (Parkin) (PINK1 / Parkin) in the activation of stress on the endoplasmic reticulum due to its dynamic contact with mitochondria (51). This situation causes in cells infected by CSFV an
inhibition of the intrinsic or mitochondrial pathway of apoptosis, generating a decrease in the release of pro-apoptotic proteins such as cytochrome C and therefore a decrease in the activation of caspases that would normally function in the apoptosis process (49, 50) (Figure 3.4).

Pei et al (52) suggest that this occurs due to a regulation in IFN type I production levels due to a limitation of signaling in retinoic acid-inducible gene I receptors (RIG-I) (RLRs), which are responsible for identifying RNA-like molecular patterns associated with viruses and their respective activation of the innate immune system (53), leading to inhibition of IFN-stimulated gene expression (ISG) associated with apoptosis. That is, CSFV-induced mitophagy inhibits the activation of apoptosis, a mechanism known as an important route of protection in infected cells, which when inhibited promotes cell survival by facilitating replication and persistence of viral infection in the animal (52)(Figure 3.4).

Another action of CSFV to induce immunosuppression states of its host is the induction of pyroptosis in peripheral lymphoid organ T and B lymphoid lymphocytes, a mediated action through the activation of caspase 1(54). Likewise, the activation of gasdermin-D as a mediating factor for pyroptosis in the immunopathology of CSF has been determined. (55). Gasdermin-D, which is cleaved by capase-1 activity, induces this type of cell death when it rapidly targets the plasma membrane, binding to liposomes with the consequent formation of large permeability pores (56), this results in an alteration of cellular ion gradients leading to a flow of water, with cellular tumefaction and osmotic lysis, releasing cellular content (57) (Figure 3.5).

Figure 3. Immunopathological mechanisms of classical swine fever virus (CSFV). 1. Source: authors. CSFV presents different endocytic pathways for entry into the host cell, through CD46 and HS as classic endocytosis pathways, among others (Tsg101 - ESCRT-1, ADAM17, MERTK) to Mn / Mcf cells, given their monocytes/tropism. 2. NS4B as a virulence factor of CSFV play a preponderant role in infected Mn / Mcf, since it inhibits TRL3, without the activation of this innate immunity pathway, the activation of transcription processes is impossible (eg. TRIF, IRF3, NF-kB) associated with cellular response pathways to viral infection (IFN, Ct). 3. For its part, vipoirine P7 induces in Mn/Mcf the secretion of cytokines, among these the most important IL-1B, which will stimulate the inflammation NLRP3 and its subsequent inflammatory response. 4. In the infected Mn/Mcf CSFV through inhibition of RLRs goes unnoticed by foreign RNA recognition processes to the host cell, which promotes a production inhibition of IFN 1 and ISG, in addition to this, the mitochondrial fission and mitophagy mechanisms generate a decrease in pre-apoptotic proteins (Cit.C and Caspasas) concluding in infected and immortal Mn/Mcp. 5. In lymph nodes, DCs infected with CSFV interact with lymphoid cells (e.g., CD4 +) in the antigen presentation process, a situation that favors viral dissemination in other host cells, in addition to promoting pyroptosis mechanisms in exposed lymphocytes mediated by caspase 1 and gasdermina D. (Ct) cytokines; (CD46) cluster of differentiation 46; (CD4 +) CD4 + lymphocyte; (Ct. C) cytochrome C; (DC) dendritic cell; (NF-kB) nuclear factor kappa B; (TRIF, IRF3) nuclear transcription factors; (IL) interleukins; (IL-1B) interleukin 1B; (IFN) interferon; (IFN 1) type 1 interferon; (Mn/Mcp) monocytic-macrophages; (ISG) gene stimulated by IFN; (NF-kB) nuclear factor kappa B; (NS4B) non-structural protein 4B of Pestiviruses; (NLRP3) NLRP3 inflammasome; (MERTK) protooncogene tyrosine kinase MER (Tsg101) tumor susceptibility gene 101; (ESCRT-1) endosomal sorting complex required for transport; (ADAM17) metalloprotease 17; Retinoic acid inducible gene I type receptors (RLRs); (PINK1 / Parkin) pathway putative kinase 1 induced by PTEN and E3 ubiquitin ligase; (CSFV) classical swine fever Virus.
FINAL CONSIDERATIONS

In animals infected with CSFV, the innate immune response is exploited by CSFV for replication and persistence in the host by induction of different cellular mechanisms such as: oxidative stress, inhibition of transduction routes, mitochondrial fission with subsequent mitophagy and consequent inhibition of apoptosis that allows cell survival and the possibility of generating persistently infected animals, these being crucial for viral endemicity within the porcine production system and future outbreaks of CSF in immune windows even under rigorous vaccination schemes (50).

One of the immunopathological consequences of CSFV in its hosts is immunosuppression, which is caused by the mechanism of pyroptosis in peripheral lymphoid organs generated by infected immunocompromised animals, a situation that sometimes hinders its diagnosis or can exacerbate CSF when concomitant with other infections, for example, porcine respiratory and reproductive syndrome Virus, porcine Circovirus and secondary infections, such as Glaesserela parasuis, Pasteurella multocida, among others (54).

The high morbidity and mortality rate of CSFV is associated with large economic losses, both in countries where most swine production is industrialized, and in countries where this productive line is maintained by family and cross-country production; thus, affecting the marketing – export of its meat products and derivatives, as well as the family economy, respectively. Therefore, the implementation of different CSF control strategies from strict surveillance, zoning processes, preventive immunization, slaughter of infected animals and compliance with relevant health regulations is crucial (58).

The need to develop new vaccines that are more efficient against CSFV has led to research around the importance of differentiating infected animals from vaccinated animals, making this activity impossible to develop through serological diagnostic tests. From there the creation of marker vaccines for inoculated animals: such as E2 subunit vaccines with molecular adjuvant, chimeric vaccines, replicate vaccines and viral vectors. In addition, in the future the development of epitope vaccines could cover a high group of viral strains, up to those emerging beyond the current vaccine response. These emerging strains are the result of an evolutionary process influenced by viral selective pressure associated with extensive vaccination processes in different regions of the world (59). Other antiviral strategies based on knowledge of these immunopathological mechanisms are the development of new technologies involving CSF-resistant transgenic pigs with the ability to transmit this characteristic to offspring (60).

Finally, the different advances in research for the immunopathological understanding of CSF, which similarly ask questions for possible future studies, are of total importance in providing new strategies for disease prevention and control through different immunoprophylactic mechanisms or other therapeutic means from the molecular understanding of pathogenesis.

Conflict of interest

The authors declare that they have no conflict of interests for the submission of this manuscript.

REFERENCES


42. Tizard IR. Introducción a la inmunología veterinaria, octava edición. capítulo sexto; señalización celular: las citocinas y sus receptores; ruta de transducción de señales: La ruta de JAK-STAT. ELSEVIER; 2009.


