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Review

ATP signaling and NTPDase in Systemic Lupus Erythematosus (SLE)

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ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune and inflammatory disease with periods of exacerbation and remission. SLE is characterized by the irreversible breakdown of immunological self-tolerance, where there is deregulation of multiple aspects of the immune system. SLE immune dysfunction is characterized by activation of autoreactive T lymphocytes, and hyperactivity of B lymphocytes with consequent production of several autoantibodies. ATP is a purinergic mediator released into the extracellular space in response to cell and tissue damage which operates as a danger signal to modulate immune and inflammatory responses. ATP binds to P2 receptors and its levels are regulated by NTPDase (CD39). SLE patients exhibit increased levels of ATP which binds to P2X receptors resulting in activation of the inflammasome and consequent release of IL-1β and IL-18, cytokines associated with disease pathogenesis. CD39 is upregulated in SLE representing an important immunoregulatory mechanism by controlling inflammation and favoring the production of adenosine. The aim of this review is to clarify the effects of ATP on the modulation of the inflammatory process and immune responses via P2 receptors as well as the role of NTPDase in the immunopathogenesis of SLE.

1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem inflammatory autoimmune disease (Dias and Isenberg, 2014; Tsokos et al., 2016) characterized by loss of immunological tolerance and production of autoantibodies (Tsokos et al., 2016). Breakdown of immune tolerance may result from the accumulation of apoptotic cellswhich, under normal conditions, are rapidly cleared. Defects in the clearance of apoptotic cells and subsequent accumulation of these cells induce inflammation and immune responses (Wu et al., 2016). In patients with SLE, the immune system is widely compromised, but the causes of disease and autoimmunity remain unknown (Tsokos et al., 2016). Nevertheless, it is known that genetic, hormonal, and environmental factors are involved in the etiology of the disease (Dias and Isenberg, 2014) (Box 1).

The immune dysfunction characteristic of SLE is complex and involves both the innate and the adaptive immune responses which are regulated by a multiplicity of pathways. A key pathway involved in the immunopathogenesis of inflammatory and autoimmune diseases is the purinergic system (Idzko et al., 2014; Deaglio and Robson, 2011; Di Virgilio and Giuliani, 2016), which regulates a wide variety of cellular processes in immune cells, such as cytokine secretion, cell-cell interaction, generation of reactive oxygen species (ROS) and intracellular pathogen removal (Junger, 2011). Adenine nucleotides, name ATP (adenosine triphosphate), ADP (adenosine diphosphate) and AMP (adenosine monophosphate) and nucleoside derivative adenosine represent the primary components of the purinergic system. These molecules interact with specific purinergic receptors and are regulated by purinergic enzymes, that comprise the final regulatory component of the purinergic system (Bours et al., 2006) (Box 1).

A group of enzymes responsible for regulating the levels of adenine nucleotides and adenosine on the surface of the cell are called ectoenzymes. Purinergic enzymes include the E-NTPDases (Nucleoside Triphosphate Diphosphohydrolase), the family of E-NPPs (Nucleotide pyrophosphatases / phosphodiesterases), E-5'-nucleotidase and E-Adenosine Deaminase (E-ADA) (Yegutkin, 2008). These enzymes form an enzymatic chain that begins with E-NTPDase (CD39) and E-NPP, which hydrolyze ATP and ADP to AMP. Next, AMP is hydrolyzed by the enzyme E-5'-nucleotidase (CD73) to adenosine, which is ultimately converted to inosine by E-ADA (Bours et al., 2006).

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Box 1
Systemic lupus erythematosus.

The incidence rates varied from 0.3 to 23.7 per 100,000 person-years.
The prevalence rates ranged from 6.5 to 178.0 per 100,000 inhabitants.
The incidence is higher in women than in men at a ratio of 8-15: 1.
The peak incidence occurs during reproductive age, the mean age of diagnosis ranges from 17 to 32 years.
The frequency is higher in descendants of Africans, Hispanics, Chinese, and Asians; in general these patients present a greater number of hematological, neurological and renal manifestations.
The mortality rate is 2.6–3 times higher than in the general population, probably related to high rates of infections, cardiovascular disease and kidney disease.
Presents a heterogeneity of clinical manifestations where different organs and systems can be affected.
The diagnosis is based on clinical and immunologic criteria.
Disease control is complex, before planning the treatment it is necessary to determine the severity of the disease, including which organs are affected and the degree of inflammation.

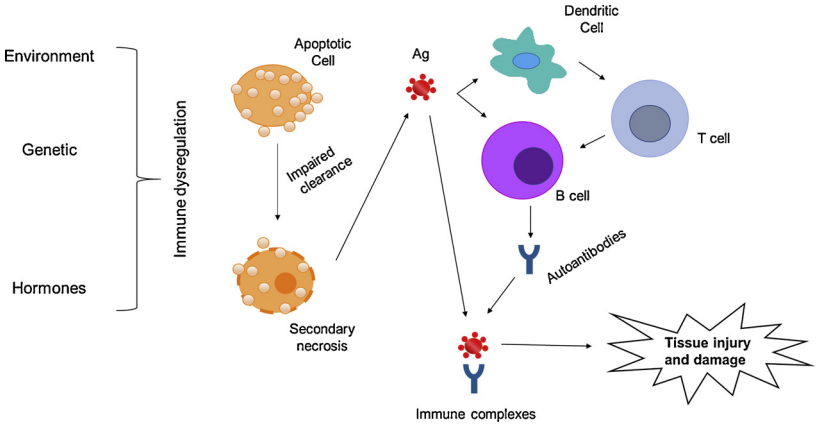

Fig. 1. Pathogenesis of systemic lupus erythematosus (SLE). Apoptotic cells undergo secondary necrosis, causing cells to lose membrane integrity and release intracellular content that will serve as a source of autoantigens, which are recognized by dendritic cells and activate T cells. T cells provide help for B cells to produce autoantibodies. The union of autoantibodies with autoantigens forms the immune complexes, which are deposited in tissues and organs causing inflammation and damage. Ag, autoantigens.

ATP is released from damaged tissues and dying cells, generating inflammatory responses (Di Virgilio, 2005). Extracellular ATP exerts inflammatory effects through the activation of purinergic P2 receptors (Yegutkin, 2008). Two P2 receptor subfamilies have been described: P2X and P2Y. P2X receptors are membrane cation channels whose opening causes Ca^{2+} and Na^{+} influx as well as K^{+} efflux; while P2Y receptors are G-protein-coupled (Cekic and Linden, 2016). ATP is metabolized to adenosine, a molecule with anti-inflammatory properties, by ectonucleotidases. E-NTPDase belongs to the family of ectonucleotidases, hydrolyzes ATP to AMP and regulates nucleotide signaling in the immune system (Vitiello et al., 2012).

In this review, we focus on ATP and its involvement in the modulation of the inflammatory process and immune responses via P2 receptors. We also discuss the role of enzyme E-NTPDase which is responsible for ATP hydrolysis, limiting its interaction with the receptors and favoring the downstream generation of adenosine. In this review, we assess the interplay between ATP signaling and SLE disease and the involvement of this nucleotide and E-NTPDase in the immunopathogenesis of this autoimmune disease.

1.1. Immunopathogenesis of SLE

SLE is characterized by aberrant innate and adaptative immune responses, where there is a break of tolerance, defects in clearance of apoptotic cells, generation of self-antigens and auto-antibodies, leading to inflammation, dysfunction, and tissue failure (Zharkova et al., 2017). Cells undergoing apoptosis secrete anti-inflammatory cytokines, such as IL-10 and TGF-β, and expose engulfment signals called “find me”, “eat me” and “stay away” signals to macrophages (Navratil and Ahearn, 2001).

The release of “find me” signals, which include ATP, lysophosphatidylcholine (LPC), fractalkine (CX3CL1) and sphingosine 1-phosphate (SIP), attract phagocytes that engulf apoptotic cells. Early apoptotic cells also express “eat me” signals, like phosphatidylserine (PS), to promote its recognition by phagocytes. In addition, dying cells release factors to prevent neutrophil migration, inflammation and immune response which are known as “stay away” signals (Podolska et al., 2015). Apoptotic cells prevent the release of its intracellular material by maintaining membrane integrity, whereas necrotic cells lose membrane integrity, releasing cellular contents and inducing immune and inflammatory responses (Herrmann et al., 2000).

Early apoptotic cell clearance by macrophages is impaired in SLE, leading to their accumulation and secondary necrosis, a late post-apoptotic phase. The undigested apoptotic material can be taken up by dendritic cells (DCs), which activate T helper 1 cells (Th1) and T helper 2 (Th2) cells. Autoreactive B cells, with help from T cells, produce autoantibodies which combine with self-antigens to form immune complexes (IC) (Wu et al., 2016). IC are deposited in tissues causing activation of the complement system and immune cell infiltration, promoting acute and chronic inflammation and consequent tissue damage (Podolska et al., 2015) (Fig. 1). The presence of apoptotic debris reacting with autoantibodies leads to the production of IC, which may induce further apoptosis, creating a vicious cycle generating more autoantibodies and inflammation (Sarmiento et al., 2007).

1.2. ATP regulates immune responses

Extracellular ATP is an important regulator of inflammatory and immune responses and can be rapidly released by regulated exocytosis, upon stress, cell damage, or death (Di Virgilio et al., 2009). The release of ATP by necrotic cells is non-specific, whereas specific release includes vesicular exocytosis and release mediated by channels via

connexin or pannexin (Dosch et al., 2018). The release of ATP through exocytosis occurs with the fusion of the vesicle to the plasma membrane, this mechanism is dependent vesicular nucleotide transporter (VNUT) (Sawada et al., 2008).

The release of ATP by inflammatory cells occurs in a controlled manner via connexin or pannexin hemichannels (Junger, 2011), pannexin proteins form hemichannels whereas connexin proteins can form hemichannels and gap junctions (Sosinsky et al., 2011), under homeostatic conditions these channels remain predominantly closed (Dourado et al., 2014). Increased levels of ATP and its binding to purinergic receptors mobilize intracellular calcium signaling through the connexin gap junction in the endothelium and result in increased expression of adhesion molecules for leukocytes contributing to inflammation (Scheckenbach et al., 2011). Opening and activation of pannexin-1 (Panx1) channels can occur through various mechanisms, such as mechanical stress (Kienitz et al., 2011), histamine stimulation (Pinheiro et al., 2013), increased intracellular calcium (Locovei et al., 2006), and caspase-mediated cleavage of the portion of Panx1 (Sandilos et al., 2012). The latter mechanism results in irreversible channel opening and release of large amounts of ATP (Timóteo et al., 2014). During the activation of the inflammasome, the opening of Panx-1 can be coupled to the activation of purinergic receptors, such as P2X7 (Adamson and Leitinger, 2014) and P2Y6 (Timóteo et al., 2014).

The maintenance of homeostasis depends on the removal of the apoptotic cells by professional phagocytes in a silent and anti-inflammatory way (Ravichandran and Lorenz, 2007). During the late stages of apoptosis, the membrane integrity is lost and the cellular contents are released, contributing to the loss of immune tolerance (Muñoz et al., 2010). There are several differences between apoptosis and necrosis (Table 1), one of them is the amount of ATP released. During apoptosis, the amount of nucleotide released is regulated and lower than the amount seen during a damage-induced loss of membrane integrity (Chekeni and Ravichandran, 2011). ATP released from necrotic cells is recognized by inflammatory cells generating a proinflammatory microenvironment through the secretion of proinflammatory cytokines and recruitment of neutrophils (Dosch et al., 2018).

However, ATP may elicit either a proinflammatory or an anti-inflammatory response, depending on which P2 receptor subtype is activated. High concentrations of ATP activate P2X7 receptors, consequently opening the cation-specific channel, and allowing K^+ efflux and Na^+ and Ca^{2+} influx. P2X7 drives the activation of the NLRP3 inflammasome triggering mechanisms that support inflammation, and continuous stimulation of this receptor induces apoptosis (Morandini et al., 2014).

DAMPs (danger-associated molecular patterns) are a group of endogenous and heterogeneous molecules that can be released into the extracellular environment as a result of cellular damage, inflammation, secondary necrosis and necrosis (Pisetsky, 2011). ATP acts as a DAMP in response to cellular damage (Vitiello et al., 2012) and promotes inflammation through four distinct mechanisms: 1) inflammasome activation in a P2X7-dependent manner with consequent release of IL-1β and IL-18 (Di Virgilio, 2007); 2) T cell activation via P2X1, P2X4 and P2X7 receptors (through its role in calcium influx) (Woehrle et al., 2010); 3) inhibition of the suppressive activity and viability of regulatory T (Treg) cells through the activation of P2X7 receptors (Cekic and Linden, 2016); 4) increasing of neutrophil activity via P2X7 receptors (Vitiello et al., 2012).

Table 1
Differences between apoptosis and necrosis.

APOPTOSIS	NECROSIS
Physiological cell death	Pathological cell death
Plasma membrane integrity	Loss of plasma membrane integrity
Selective release of ATP	Total intracellular ATP content released
Efficient clearance of apoptotic cells by macrophages	Impaired clearance of apoptotic cells by macrophages
No release of DAMPs	Release of DAMPs
No inflammation and sequestering of autoantigens	Inflammation and accessibility of autoantigens

The P2Y11receptor has inhibitory effects on different immune cells since its the activation stimulates adenylate cyclase which causes the intracellular Ca^{2+} to rise as well as a raising in the cAMP concentration, a known immune cell negative regulator. ATP-induced P2Y11 activation inhibits T-cell proliferation and cytokine production (Vitiello et al., 2012).

ATP regulates various immune responses depending on its extracellular concentration and the receptor it interacts with. It may serve as a danger signal and drives inflammation if released in high concentrations. In low concentrations, ATP can suppress the secretion of inflammatory cytokines, consequently leading to an anti-inflammatory state (Di Virgilio et al., 2009).

1.3. ATP and the pathogenesis of SLE

Impaired or failed clearance of cells in the early phases of apoptosis is a characteristic of the etiology of SLE (Chen et al., 2014). In early apoptosis, ATP acts as a “find me” signal to attract phagocytes, promoting phagocytic clearance (Chekeni et al., 2010). The release of caspase-dependent ATP during apoptosis and consequent binding to P2Y2 receptors promotes the migration of monocytes to the sites where apoptosis occurred (Seye et al., 2003). In patients with SLE, there is a decreased phagocytic activity, which may affect the clearance of dying cells (Mahajan et al., 2016). Elliot et al. (2009) observed that a disturbance in the "find me" signaling, at the level of ATP or receptor (P2Y), impairs the clearance of apoptotic material, confirmed the relationship between "find me" signals (ATP) and clearance of dying cells. Nucleotides play a role in regulating the phagocytic activity, however, the mechanisms involved are still unknown.

Failure in apoptotic cell clearance may lead to autoimmunity and chronic inflammation, and nucleotides, through their participation in the modulation of phagocytic ability, may have a role in such conditions (Elliott et al., 2009). The efficient clearance of apoptotic cells is important for the maintenance of auto tolerance by preventing the accumulation of apoptotic cells and subsequent progression to secondary necrosis (Wu et al., 2016). Studies show that loss of tolerance and chronic inflammation associated with autoimmunity may be due to continued exposure to DAMP released after cell or tissue damage. An increase in the number of DAMPs has been associated with several autoimmune diseases, such as rheumatoid arthritis (RA), systemic sclerosis (SSc) and SLE (Álvarez and Vasquez, 2017). In a recently published study from our research group, we found that SLE patients showed increased serum levels of ATP (Becker et al., 2019).

The ATP-P2X7-driven efflux of potassium results in NLRP3 activation and the release of IL-1β and IL-18 pro-inflammatory cytokines (Babelova et al., 2009) (Fig. 2). IL-1β, together with IL-6 and IL-23, direct the differentiation of T helper 17 cells (Th17) (Yang and Chiang, 2015). SLE patients have increased serum IL-1β levels which correlate with disease activity (Cigni et al., 2014). Increased levels of IL-18 were also observed in SLE and are correlate with the severity of the disease and the presence of lupus nephritis (Kahlenberg et al., 2011; Hu et al., 2010). IL-18 enhances CD4 + T cell interferon-γ production, as it stimulates leukocyte chemotaxis and cartilage destruction (Volin and Koch, 2011). Although further studies clarifying the role of the NLRP3 inflammasome in autoimmune diseases are necessary, inhibition this inflammasome may be a promising therapeutic target for SLE (Shen et al., 2018; Deuteraiou et al., 2018; Kahlenberg and Kaplan, 2014).

P2X7, via NLRP3 activation, is a key feature in the maturation and release of pro-inflammatory cytokines IL-1β and IL-18. This receptor has three subunits to which three molecules of ATP bind and, when it is

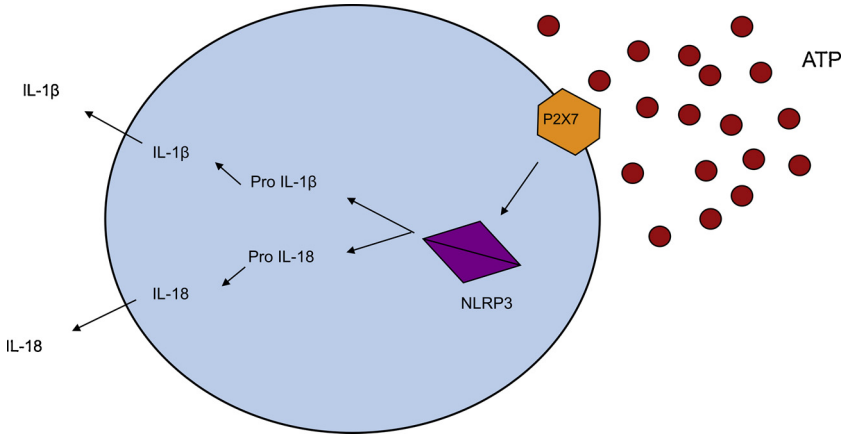

Fig. 2. Activation of the inflammasome via P2X7 receptors.

stimulated by low concentrations of ATP, causes the opening of cation-selective channels, whereas high concentrations of ATP drive the formation of a large non-selective pore (Khakh and Alan North, 2006). Activation of P2X7 stimulates the assembly of the NLRP3 inflammasome, leading to an increase of IL-1β release and polarization towards a Th17 immune response, contributing to lupus nephritis. Upregulated expression or activity of P2X7 in SLE may serve as fuel for the pro-inflammatory state (Di Virgilio and Giuliani, 2016). In contrast, the use of antagonists of P2X7 has been shown to limit the tissue damage associated with autoimmune diseases (Arulkumaran et al., 2011). The study Zhao et al. (Zhao et al., 2013) showed that inhibition of P2X7 reduces the development of anti-dsDNA antibodies, immune complex deposition and renal inflammation in a model of lupus nephritis. Genetic deletion of P2X7 also confers protection against antibody-mediated glomerulonephritis (Taylor et al., 2009).

1.4. ATP signaling in the subsets of immune cells involved in SLE

1.4.1. Monocytes/macrophages

Monocytes/macrophages regulate inflammation and induce immunity. Monocytes enter the bloodstream and differentiate into resident tissue macrophages and acquire distinct phenotypes and functions depending on the microenvironment (Katsiari et al., 2010).

Macrophages from patients with SLE show a defective phagocytic activity and aberrant accumulation of apoptotic debris leading to the autoimmunity phenomenon (Kuroiwa and Lee, 1998). ATP has an inhibitory effect on phagocytes mediated by the P2X7 receptor, but the mechanism responsible for this effect is still not completely understood (Di Virgilio and Vuerich, 2015).

1.4.2. Dendritic cells

Dendritic cells (DC) process and present phagocytosed antigens to naïve T cells and are essential for immunity and tolerance (Podolska et al., 2015). In physiologic conditions, DCs are found in tissues in an immature state, present autoantigens to autoreactive T cells and maintain the tolerance through mechanisms like anergy, silencing of detrimental effector T cells or the activation of Treg. DCs polarizes naïve T cells into Th1, Th2, Th17 or Treg cells in a manner dependent on the secretion of cytokines (Steinman et al., 2003). Extracellular nucleotides exert various effects on DC through P2, such as maturation, control of cytokine release and induction of cell death (Idzko et al., 2002). ATP, through the activation of P2Y11 receptors, induces DC semi-maturation, increasing the expression of costimulatory molecules and decreased IL-12 production, which is associated with Th2 response or tolerance. However, prolonged exposure to high concentrations of ATP can activate P2X7 receptors, mediating apoptosis and inducing NLRP3 inflammasome signaling in DCs, directing the maturation of these cells and leading to the secretion of pro-inflammatory cytokines such as IL-1β and IL-18 (Burnstock and Boeynaems, 2014), which are extremely important cytokines in SLE (Cigni et al., 2014; Kahlenberg et al., 2011).

1.4.3. Neutrophils

Neutrophils are essential effector cells in the immune defense, responsible for the initial clearance of pathogens through phagocytosis, degranulation, and release of neutrophil extracellular traps (NETs). NETs are networks of extracellular decondensed chromatin fibers decorated with histones. After stimulation, neutrophils can undergo NETosis, a type of cell death which releases NETs (Fuchs et al., 2007). Increased NETosis and/or defective clearance of NETs in SLE is involved in the pathogenesis of this disease since NETs are a potential source of autoantigens found in renal and skin biopsies in these patients (Bonanni et al., 2015).

Receptors on the surface of neutrophils recognize DAMPs during inflammation, including nucleotides. ATP triggers proinflammatory responses in neutrophils such as the release of arachidonic acid, phagocytosis and also the induction of degranulation (Bours et al., 2006). The activation of neutrophils can also stimulate the NLRP3 inflammasome via ATP/P2X receptors (Tan and Weninger, 2017). ATP is also capable of preserving the survival of neutrophils, delaying apoptosis, thus regulating the duration of the inflammatory response. These effects of ATP on neutrophil survival are mediated via activation of the P2Y11 receptor and may compromise the immune function of these cells by increasing their longevity (Vaughan et al., 2007). However, SLE patients neutrophils exhibit abnormal characteristics, such as increased infiltration, impaired phagocytosis, and increased apoptosis (Ren et al., 2003). For a better understanding of the role of ATP in neutrophils in SLE patients, further studies are necessary.

1.4.4. T cells

T cells play an important role in the development of tolerance, and loss of this tolerance is implicated in the development of autoimmune diseases. Several T cell abnormalities have been described in SLE patients, emphasizing the involvement of these cells in SLE pathogenesis. T cells are key to B cell hyperactivity and consequent autoantibody production, which contributes to tissue damage in patients with SLE (Crispín et al., 2007). ATP is involved in the activation of the T cells by increasing TCR-mediated responses (Cekic and Linden, 2016). TCR stimulation causes the release of ATP by pannexin-1 hemichannels (Schenk et al., 2008) and vesicular exocytosis (Tokunaga et al., 2010). ATP increases the activation of the effector T cell during inflammation, through P2X receptors stimulation of Ca^{2+} influx (Cekic and Linden, 2016). During the immune response, activated T cells may also express P2Y receptors, such as P2Y6 (Giannattasio et al., 2011), but there is

limited information on this receptor.

During the activation of T cells in patients with SLE, the T cell receptors (TCR) exhibit an overtly abnormal response, leading to an increased cytoplasmic Ca^{2+} influx and cytosolic protein tyrosine phosphorylation (Crispín et al., 2010). After stimulation, T cells proliferate and differentiate into different subsets (Th1, Th2, Th17 or Tregs). Tregs regulate the course of the protective immune response contributing to homeostasis and tolerance and limiting tissue damage (Walter Sifuentes Giraldo et al., 2012). ATP inhibits the suppressive activity and the viability of Treg cells, stimulating apoptosis due to pore formation by P2X7 (Cekic and Linden, 2016). Studies have reported abnormalities in Treg cell suppression abilities in SLE patients (Miyara et al., 2005; Lin et al., 2007; Alvarado-Sánchez et al., 2006; Dal Ben et al., 2014). In addition to deficiency or loss of function of Tregs, SLE patients display an imbalance in the Th17/Treg ratio, with an increased number of Th17 cells, which are involved in the loss of immune tolerance, in detriment of Tregs (Kleczynska et al., 2011).

1.4.5. B cells

Abnormalities in B-cell signaling in patients with SLE have been observed, evidencing the critical role of B cells in the pathogenesis of this disease (Peng, 2009). The loss of B cell tolerance is key in SLE pathogenesis since B cells of SLE patients produce autoantibodies mainly against nuclear antigens (Dörner et al., 2011). Activation of B cells occurs via binding of the antigen to the antigen receptor (BCR), inducing signaling that controls phagocytosis, migration, proliferation, cytokine release, and production of autoantibodies (Reth and Wienands, 1997).

B cells express P2X and P2Y receptors (Jacob et al., 2013). ATP regulates B cell activation, adhesion, migration, and IgE secretion (Przybyła et al., 2018). ATP-driven P2X7 activation is crucial for secretion of IgM, indicating that this receptor plays a key role in the humoral response (Sakowicz-burkiewicz et al., 2013).

B cells from SLE patients show increased intracytoplasmic Ca^{2+} influx in response to BCR stimulation, resulting in overactivation of these cells (Pugh-bernard and Cambier, 2006). The increased expression of P2X7 in T and B lymphocytes of SLE patients seems to be positively correlated with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), showing that this receptor is directly associated with the clinical manifestations of SLE (Li et al., 2012).

1.5. NTPDase and control of the cellular immune response

E-NTPDases hydrolyze extracellular tri- and diphosphonucleosides to monophosphonucleosides, requiring millimolar concentration of Ca^{2+} and Mg^{2+} for maximal activity (Yegutkin, 2008). Several studies show the importance of NTPDase in inflammation and immune responses, since the proinflammatory signaling of ATP, via P2X7, can be terminated by the action of this enzyme (Deaglio and Robson, 2011) (Antonioli et al., 2013). NTPDase1 (CD39) is the prototype E-NTPDase family and is the dominant ectoenzyme in the immune system (Mizumoto et al., 2002). In order to improve the understanding of the mechanisms involved in the immune response, Leal et al. (Leal et al., 2005) characterized the activity of NTPDase1 (CD39) in lymphocytes and standardized a colorimetric method to determine the activity of this enzyme.

The expression and activity of CD39 undergo changes according to the pathophysiological context, this enzyme has been found to be altered in autoimmune diseases such as multiple sclerosis (MS) (Spanevello et al., 2010), rheumatoid arthritis (RA) (Jaques et al., 2013; Moncrieffe et al., 2010) and SLE (Becker et al., 2019; Loza et al., 2011). The study by Spanevello et al. (2010) showed that the activity of NTPDase in lymphocytes of patients with MS is increased in relation to the control, suggesting that this enzyme modulates of the immune and inflammatory response in MS. The work of Jaques et al. (2013) evaluated the activity of NTPDase in lymphocytes of patients with RA, which is increased in relation to the control group, evidencing an organic mechanism to decrease the levels of inflammatory ATP and increase the levels of adenosine, an anti-inflammatory molecule.

In the study by Moncriefffe et al. (2010), increased CD39 expression was found in synovial fluid T cells from juvenile arthritis patients, suggesting that this increase in CD39 in the inflamed regions could represent an immunomodulatory mechanism through the hydrolysis of ATP. The study by Loza et al. (Loza et al., 2011) analyzed the expression of CD39 in Treg cells of patients with SLE and found a decreased expression of CD39 in these patients. This defect has a functional impact on the regulation of T cells and may represent a potential biomarker of SLE (Loza et al., 2011). On a previous study, we evaluated the expression and activity of CD39 in lymphocytes of SLE patients, both of which were found to be increased and were significantly correlated. These increases in both expression and activity could represent a compensatory mechanism to control inflammation since this enzyme has anti-inflammatory effects (Becker et al., 2019).

Extracellular ATP has several proinflammatory effects through binding to P2X7 receptors, including the release of IL-1β and IL-18 (Ferrari et al., 2006), cytokines linked to various diseases including SLE (Areas et al., 2007). CD39 prevents the secretion of IL-1β and IL-18 (Ferrari et al., 2006), the breakdown of ATP by CD39 and consequent generation of adenosine represents an important immunoregulatory mechanism (Mandapathil et al., 2010). CD39-null mice show an impaired B-cell response to T-dependent antigens, suggesting that CD39 contributes to the maturation of the antibody response (Dwyer et al., 2007).

Treg cells are affected by ATP, through the activation of P2X7 receptors, which exerts an inhibitory effect on the function and generation of these cells inducing the conversion of these cells into Th17 cells, thereby tilting the balance towards the latest (Schenk et al., 2011). Corroborating to this data, the lack of CD39 leads to the expansion of the Th17 cell subset in a study with knockout CD39 in a murine model of lupus (Knight et al., 2018). The expression of CD39 in Tregs was found to prevent conversion to Th17 cells in humans, and suppress IL-17 production (Fletcher et al., 2009). The catalytic effect of CD39 on ATP favor the generation of adenosine, which boosts Treg numbers and their immunosupressive function (Ohta and Sitkovsky, 2014).

Although CD39, along with CD73, is not a classical marker of Tregs, such as CD25 and FOXP3, it is also recognized as a surface marker of these cells (Knight et al., 2018) and may indicate the severity of the immune tolerance loss (Gambichler et al., 2015). The role of CD39 in the maintenance of immune tolerance is associated with its capacity of degrading ATP and consequently inhibiting the production of IL-17, which stimulates B cells to produce autoantibodies (Knight et al., 2018). The activity of CD39 has two anti-inflammatory effects, the first is the removal of proinflammatory ATP, and the second is the amplification of adenosine production, a nucleoside that exhibits suppressive and anti-inflammatory activity (Borsellino et al., 2007). By degrading ATP, CD39 ensures the downstream production of adenosine, boosts the suppressive action of Tregs, and prevents the conversion of Tregs into Th17 cells, suppressing the production of IL-17 (Fletcher et al., 2009). Thus, this enzyme aids the maintenance of a balanced Th17/Treg ratio.

2. Concluding remarks

Systemic Lupus Erythematosus (SLE) is a debilitating and potentially fatal autoimmune disease. The lack of a specific diagnostic test and the complexity of the treatment make the management of this disease even more challenging. A better understanding of the immunopathogenic mechanisms involved in SLE may help uncover crucial information to clarify its origin, find useful diagnostic and disease progression biomarkers and enable the development of treatment targets.

ATP acts as a danger signal and exerts a variety of effects on immune cells (Fig. 3), via P2 receptors. This nucleotide is involved in three

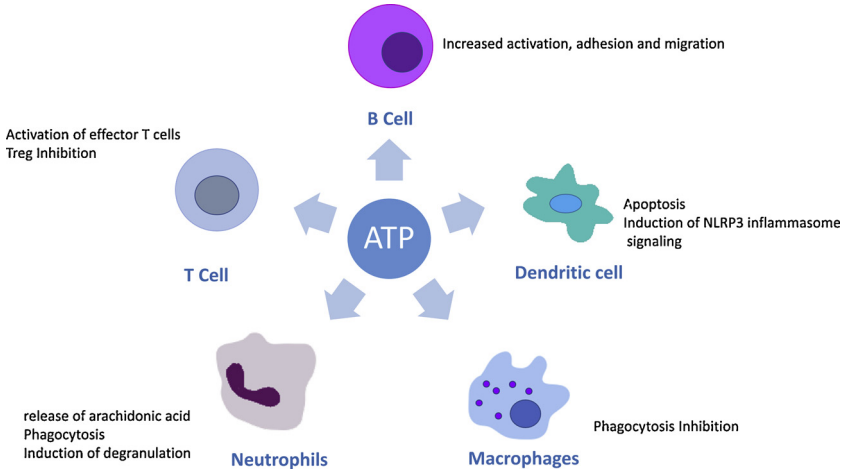

Fig. 3. Signaling of ATP in some immune cells involved in SLE.

major features of SLE: loss of immune tolerance, continuous antibody release, and inflammation, in the ATP-driven P2X7/inflammasome activation which is associated with inflammation and consequent systemic manifestations of the disease. Thus, the P2X7 receptor and the NLRP3 inflammasome could be used as treatment targets for SLE.

While activation of P2X7 receptors seems to contribute to the pathogenesis of the disease, CD39 exerts a protective effect against SLE. In addition, the expression of this enzyme may indicate the severity of the immune dysfunction associated with autoimmunity. To date, there are only a few studies specifically correlating SLE and the purinergic system. For a better understanding of the dysregulation of the immune system in this pathology more studies involving the purinergic system are needed.

Conflict of interest

The authors declare that they have no conflict of interest.

Declaration of interest

We wish to confirm that there are no known conflicts of interest associated with this publication.

We confirm that the manuscript has been read and approved by all named authors.

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