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P2X7 receptor: A potential therapeutic target for autoimmune diseases

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A B S T R A C T

P2X7 receptor (P2X7R), a distinct ligand-gated ion channel, is a member of purinergic type 2 receptor family with ubiquitous expression in human body. Previous studies have revealed a pivotal role of P2X7R in innate and adaptive immunity. Once activated, it will meditate some vital cascaded responses including the assembly of nucleotide-binding domain (NOD) like receptor protein 3 (NLRP3) inflammasome, non-classical secretion of IL-1β, modulation of cytokine-independent pathways in inflammation such as P2X7R- transglutaminase-2 (TG2) and P2X7R-cathepsin pathway, activation and regulation of T cells, etc. In fact, above responses have been identified to be involved in the development of autoimmunity, specifically, the NLRP3 inflammasome could promote inflammation in massive autoimmune diseases and TG2, as well as cathepsin may contribute to joint destruction and degeneration in inflammatory arthritis. Recently, numerous evidences further suggested the significance of P2X7R in the pathogenesis of autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), multiple sclerosis (MS), etc. In this review, we will succinctly discuss the biological characteristics and summarize the recent progress of the involvement of P2X7R in the development and pathogenesis of autoimmune diseases, as well as its clinical implications and therapeutic potential.

1. Introduction

Purinergic signaling, a highly evolutionary conserved signaling system, which regards extracellular adenosine triphosphate (ATP), associated nucleotides and adenosine as transmitter molecules, acts a crucial role in considerable physiological processes and pathological reactions [1,2]. At present, two types and at least 24 subtypes of purinergic receptors have been described, among which P2X7 receptor (P2X7R) is the most extensively researched subtype from an immunological viewpoint [2,3]. Interestingly, the activation of P2X7R depends on the concentration and time of ATP stimulation, as well as the cell type [4]. Temporary treatment with low ATP concentration causes typical cation-selective channel opening that facilitates a prompt efflux of K^+ and influx of Na^+ and Ca^{2+} leading to changes in the ionic homeostasis of the cell, whereas prolonged challenge with higher concentration triggers formation of the large non-selective pore, which additionally allows the passage of molecules up to 900 Da via an uncertain mechanism [3,5].

The immune system comprises of innate and adaptive immunity, of which inappropriate or insufficient responses may result in visceral or systemic dysfunctions [6]. The first-line defense against challenge of pathogens is provided by the innate immune system, which encompasses varied cell types including macrophages, dendritic cells (DCs), etc. [4] through pathogen-associated molecular patterns (PAMPs) recognized by pattern recognition receptors (PRRs) [7]. As a starting point for inflammation, the P2X7R exerts an indispensable role in sensing the purinergic danger that is called “alarmins” and considered as a distinct subset of endogenous danger signals and leads to autoimmune responses [4,8–11]. Autoimmune diseases manifest a large quantity of conditions characterized by errant, chronic auto-inflammation against self-tissues, whose the well-known representations are systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS), Sjögren's syndrome (SS), systemic sclerosis (SSc), etc. [12]. P2X7R, as a particular P2X receptor for its downstream signaling that is coupled with pro-inflammatory cascades such as inflammasome assembly and maturation and non-classical secretion of IL-1β [5,13], plays a pivotal role in immunity and autoimmunity [3]. Current researches concerning P2X7R have partly revealed its essential mechanisms in inflammation-related disorders, which means that the P2X7R may open a brand-new door for anti-inflammatory therapy, naturally including autoimmune diseases [13–16].

In our review, we will succinctly summarize the immunological functions of P2X7R, as well as its role and significant therapeutic potential in autoimmune diseases.

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2. P2X7R and its immunological functions

P2X7R is a distinct member of P2X receptor subclass, which are ligand-gated ion channels belonging to the purinergic type 2 receptor family (P2) [13,17]. As a homomeric oligomer, it is formed by the assembly of the same three P2X7 subunit containing 595 amino acids, whose gene is located on human chromosome 12q24.31 with 53 kb spanning [3,18]. The structure of P2X7 subunit is two membrane spanning domains (TM1 and TM2) linked by an extracellular loop embracing ten conserved cysteine residues, an intracellular N termini, and a significantly longer intracellular C termini compared to that in the other P2X receptors [19]. TM1 and TM2 involve in the formation of the channel pore. The N and C termini determine the kinetics of receptor desensitization and pore expansion, as well as play a vital role in modulation of receptor functions by intracellular messengers, kinases, and reactive oxygen species (ROS), etc. [20]. Extracellular loop is thought to form disulfide bonds and serve as binding sites for transition metals that modulate P2X7R, as well as participate in the activation by ATP [19,21].

ATP, as the only known physiologic agonist for P2X receptors (P2XRs), can be released via non-physiological necrotic cell death or stress, plasma membrane injury and non-lytic pathways [3,4], such as pannexins [22], ATP-binding cassette (ABC) transporters [23], PRRs activation [24], secretory vesicles [25] and P2X7R itself [26]. Besides, several researches indicated that human cathelicidin-derived peptide LL-37 may be also a P2X7R agonist [13]. The P2X7R is widely expressed in numerous cells and nearly all tissues of the body including monocytes/macrophages [27,28], T cells [29], mast cells [30], fibroblasts [31], epithelial cells [32], microglia [33], endocrine and exocrine pancreas [34], etc., among which the distribution in the immune and inflammatory system cells of monocyte-macrophage lineage is the highest [28]. The activation of P2X7R requires three ATP molecules binding to its extracellular domain, reported by a series of electrophysiological data [35]. As mentioned above, compared to short-time treatment of low ATP concentration, prolonged stimulation with higher concentration leads to the channel-to-pore transition, which results in depolarization and permeability change of membrane, decreased cytosolic K^+, increased cytosolic Ca^{2+} and Na^+, as well as the flux of some other molecules such as bacterial products (PAMPs) entry and large-scale intracellular ATP release [5,36]. Though the exact molecular mechanism of channel-to-pore transition remains incompletely clear, several hypotheses have been convinced as following: a). intrinsic pore formation function via channel expansion. b). recruitment of membrane hemi-channels such as pannexin-1 [20,36–38]. Additionally, P2X7R activity is also regulated by cations and anions in extracellular medium [20,39]. Given that its ubiquitous expression on nearly all immune cell types [40], P2X7R is involved in both innate and adaptive immunity.

During innate immune responses, the key role of P2X7R is to activate the assembly of nucleotide-binding domain (NOD) like receptor protein 3 (NLRP3) inflammasome rapidly, which could consecutively facilitate caspase-1 meditated maturation and release of the pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18) [6,10]. The activation of NLRP3 inflammasome by P2X7R may result from decreased cytosolic K^+ [13,41] and increased cytosolic Ca^{2+} [42,43], which could be caused by P2X7R activation resulting in channel opening or pore formation. Mitochondrial DNA (mtDNA) from damaged mitochondrial caused by cellular change in ionic homeostasis [42,44,45]and ROS related to P2X7R activation and mitochondrial damage [46,47] are also well-established. Meanwhile, P2X7R activation induced-pore allows entry of bacterial products (PAMPS) and ATP leading to production of ROS to drive inflammasome formation, as well as passage of hydrophilic solutes into cytosol, which is thought to cause cell death resulting in more ATP release [17,36]. Moreover, the direct interaction between P2X7R and NLRP3 inflammasome should not be neglected [11]. From another perspective, to increase the several key genes products in inflammatory cascades including pro-IL-1β, pro-IL-18 and inflammasome components such as NLRP3 and apoptosis-associated speck-like protein (ASC), P2X7R stimulation is regarded as the second signal by inducing K+ efflux, inflammasome assembly, and caspase-1 activation while PRRs such as Toll-like receptor (TLR) mediated nuclear factor kappa B (NF-κB) pathway activation acts as the first signal [2]. Besides, IL-1β and IL-18 lack a signal sequence for classical cellular secretory vesicles, the P2X7R also plays a key role in the mechanism of non-classical secretion of IL-1β including the exosome pathway, microvesicle pathway and autophagy pathway, etc. [5,48]. Importantly, transglutaminase-2 (TG2) externalization in conjunction with thioredoxin-1 (Trx), which is meditated by P2X7R activation via member pore formation of P2X7R itself rather than ion channels or pannexin-1 channels, could modify immunogenic peptides to promote the activation and homing of T and B cells, thus contributes to several autoimmune conditions, such as inflammatory arthritis [49,50]. Additionally, P2X7R also modulates several intracellular signaling pathways such as MyD88/NF-κB pathway and activation of mitogen-activated protein kinase (MAPK) pathway proteins [51,52].

During adaptive immune responses, intercellular interactions between T cells and antigen-presenting cells (APC) through the immune synapse induces intracellular ATP release, which serves as a local autocrine or paracrine signaling molecule and the initiation of T cell activation [53,54]. By responding to T cell receptor (TCR)-meditated released ATP, P2X7R participates in the activation and proliferation of T cell via triggering Ca^{2+} influx, which is required for activation of nuclear factor of activated T cells (NFAT) leading to the expression of interleukin-2 (IL-2) [54,55]. Furthermore, P2X7R modulates the balance between the helper T 17 (Th17) and regulatory T (Treg) cells [29,56]. Activation of ATP-P2X7R pathway impairs the suppressive activity and stability of Treg cells and inhibits the differentiation of naive $CD4^+$ T cells into Treg cells, as well as promotes the conversion of Treg cells into Th17 cells [29].

On balance, IL-1β and IL-18, as the main products of P2X7R activation during innate immunity, contributing to differentiation of Th17 and Th1 cells [57], decrease of Treg cells [58], enhanced expression of IL-2 receptor in lymphocytes and increased production of antibody by B cell amplification [59], are main pro-inflammatory agonists in inflammatory cascade [60]. Treg cells account for the maintenance of immunological self-tolerance that inhabits autoimmune responses, whereas Th17 cells, a distinct $CD4^+$ T cell lineage, contribute to the induction and progression of inflammation by producing IL-17 [61,62]. IL-1β and IL-6, especially IL-6, could meditate the conversion from Treg cells to Th17 cells [58]. The disequilibrium between Th17 cells and Treg cells favoring pro-inflammatory Th17 cells has been reported to be involved in numerous autoimmune disorders including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), ankylosing spondylitis (AS), multiple sclerosis (MS), etc. [61]. Briefly speaking, P2X7R is implicated in recognizing endogenous danger signals and acting a vital role in inflammation-related disorders, as well as the immunity (Fig. 1).

3. P2X7R in autoimmune diseases

Autoimmune diseases comprise a cluster of at least 80 disorders with severe clinical syndromes, which share the common characteristic of insufficient self-tolerance contributing to an immune-mediated attack on the body's own cells, tissues and organs [61,63]. In spite of emerging target therapy progressing, the therapeutic effects and prognosis remains to be improved [64–66]. Accordingly, to explore an original and efficient therapeutic target for autoimmune patients is imperative. Based on the same hallmark of vitiated self-tolerance, the P2X7R has been reported to be implicated in the pathogenesis and progression of several autoimmune diseases, including SLE [67], RA [68], IBD [69], MS [70], and other disorders such as SS [71], psoriasis [72] and SSc [73] (Table 1).

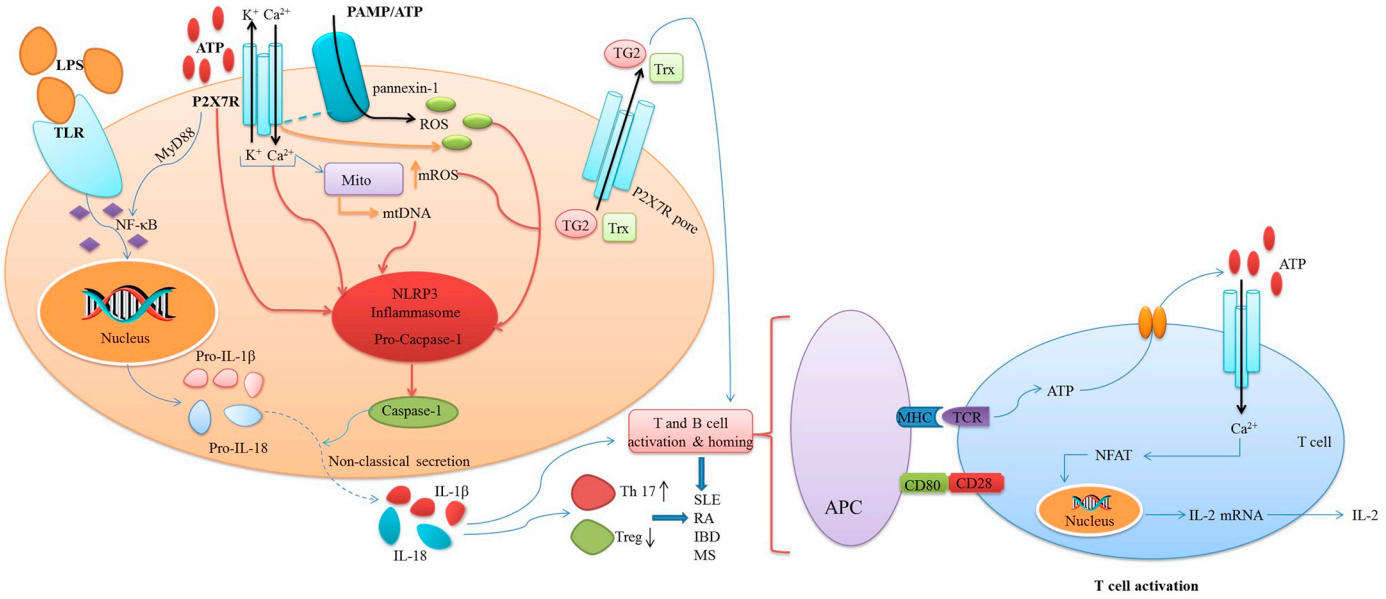

Fig. 1. Mechanisms of P2X7 receptor action.

Activation of PRR such as TLR mediated NF-κB or MAPK pathway up-regulates the expression of several key genes products in inflammatory cascade including pro-IL-1β, pro-IL-18 and inflammasome components.

Activated by ATP or LL-37, the P2X7R facilitates channel opening or pore formation resulting in efflux of K^+ and influx of Ca^{2+} or additional flux of other molecules such as bacterial products (PAMPs) and ATP. Two hypotheses of mechanism of channel-to-pore transition are convinced: (1) intrinsic pore formation function via channel expansion. (2) recruitment of membrane hemi-channels such as pannexin-1. The models of NLRP3 inflammasome activated by P2X7R are as following: (1) Decreased cytosolic K^+ and increased cytosolic Ca^{2+} trigger NLRP3 activation. (2) P2X7R stimulates the production of ROS, which contributes to the activation of NLRP3 inflammasome. (3) Changes of ionic homeostasis especially Ca^{2+} cause mitochondrial damage, including the release of mtDNA into the cytosol, increased production of mROS, and loss of membrane potential. Both mtDNA and mROS lead to NLRP3 activation. (4) The entry of bacterial products (PAMPS) and ATP via P2X7R activation-induced pore leads to ROS production to drive inflammasome formation. (5) P2X7R induces NLRP3 activation via direct mutual interaction. Activation of NLRP3 inflammasome converts pro-caspase-1 into mature caspase-1, which cleaves the pro-inflammatory cytokines such as IL-1β and IL-18.

TG2 externalization in conjunction with Trx is meditated by P2X7R activation via member pore formation of the P2X7R itself rather than ion channels or pannexin-1 channels.

By responding to TCR-meditated released intracellular ATP, P2X7R participates in the activation and proliferation of T cell via triggering Ca^{2+} influx, which is required for activation of NFAT leading to the expression of IL-2.

PRR: sensor-pattern-recognition receptor; TLR: Toll-like receptor; NF-κB: nuclear factor kappa B; MAPK: mitogen activated protein kinase; ATP: adenosine triphosphate; PAMPs: pathogen-associated molecular patterns; NLRP3: nucleotide-binding domain (NOD) like receptor protein 3; ROS: reactive oxygen species; mtDNA: mitochondrial DNA; mROS: mitochondrial ROS; TG2: transglutaminase-2; Trx: thioredoxin-1; TCR: T cell receptor; NFAT: nuclear factor of activated T cells; IL-2: interleukin-2; APC: antigen-presenting cells; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; IBD: inflammatory bowel disease; MS: multiple sclerosis.

3.1. Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder featured with anti-nuclear antibodies production, complement consumption and immune complex activation, which leads to immune responses against self-antigens and causes multiple organs damage [74]. Along with researches deepening, though the specific etiology and pathogenic mechanisms of SLE is still incompletely elucidated, P2X7R is thought to have a potential involvement in the pathogenesis and development of the disease [75].

As a wide-used experimental mouse model of SLE, MLR/*lpr* strain manifests a closely similar autoimmune syndrome to human SLE and progressive lymphoproliferation due to the *lpr* mutation leading to impairment of the Fas receptor [76]. Zhao et al. [77] reported significantly increased expression of P2X7R-NLRP3 inflammasome signaling molecules including P2X7R, NLRP3 and ASC, as well as caspase-l-p20 subunit that represents the highly active forms of processed caspase-1 in the kidneys of MLR/*lpr* mice. Kahlenberg et al. suggested that caspase-1 might be involved in SLE pathogenesis via a pristane-induced lupus (PIL) model. Caspase-$1^{-/-}$ mice showed decreased autoantibodies and reduced vascular damage compared to caspase-$1^{+/+}$mice [78]. Meanwhile, in lupus nephritis (LN) patients, Tuener et al. [79] showed that up-regulated P2X7R expression in glomeruli and renal tubules contributes to autoimmune-related glomerulonephritis through apoptosis or the regulation of pro-inflammatory cytokines. From another perspective, the phenomenon can be further confirmed by the fact that genetic deletion of P2X7R (P2X7R-KO) mice exhibited obvious protection against antibody-mediated glomerulonephritis [80]. Additionally, Kahlenberg et al. [81] also demonstrated that neutrophil extracellular traps (NETs) and LL-37-mediated activation of the inflammasome leading to autoimmune syndromes are increased in macrophages of lupus patients, and during above processes, P2X7R activation is required. At the gene level, human P2X7R gene locus at 12q24 called SLEB4 as a novel SLE susceptibility locus in Hispanic and European American families has been detected [74]. Besides, Chen et al. [82] also reported that single-nucleotide polymorphism (SNP) in the P2X7R gene (rs1718119) was associated with susceptibility to SLE in a Chinese population through a case-control study. However, the difference in the allele frequencies of 1513 AC SNP of P2X7R gene between sporadic SLE patients and controls was not found in Caucasian populations [83]. Interestingly, the 1513 AC SNP was also found to be associated with low expression of P2X7R in SLE patients, indicating an involvement of P2X7R in some other different mechanisms [75].

Indeed, Le Gall et al. [76] have found impaired P2X7R activity in T cells from autoimmune MRL/*lpr* mice. The converse situations of P2X7R expression are not mutually exclusive but contribute to similar autoimmune syndromes ultimately. As we know, autoimmune diseases could also be induced by defective homeostasis modulation of effector T cells [84]. In MRL/*lpr* mice, Le Gall et al. [76] identified that the loss of P2X7R expression on T cells was tremendously associated with the

Table 1
Linkages of several autoimmune diseases to P2X7R.

Disease	Publication year	Author	Subjects	Linkages to P2X7R	Ref
SLE	2004	Nath et al.	SLE patients	P2X7R gene locus at 12q24 (SLEB4) was a SLE susceptibility locus	[74]
	2007	Turner et al.	LN patients	Increased expression of P2X7R in the renal biopsy tissue	[79]
	2008	Forchap et al.	SLE patients	A loss-of-function of 1513 AC SNP of P2X7R gene was not a SLE susceptibility locus	[83]
	2009	Taylor et al.	P2X7R-KO mice	P2X7R deficiency attenuated renal injury in GN	[80]
	2010	Portales- Cervantes et al.	SLE patients	Low expression of P2X7R was associated with the 1513 AC SNP of P2X7R gene	[75]
	2012	Le Gall et al.	MLR/lpr mice	Impaired P2X7R activation in T cells was involved in a T-cell homeostatic pathway	[76]
	2013	Zhao et al.	MLR/lpr mice	Enhanced expression of P2X7R and related signaling pathway molecules in the kidneys	[77]
	2013	Chen et al.	SLE patients	SNP in the P2X7R gene (rs1718119) associated with susceptibility to SLE	[82]
	2013	Kahlenberg et al.	SLE patients and mice	Activation of P2X7R was required for the LL-37-meditated inflammasome activation	[81]
	2019	Faliti et al.	SLE patients	Reduction of P2X7R mRNA and impaired response of Tfh cells to P2X7R stimulation	[85]
RA	2002	Dell'Antoni et al.	CFA-induced mouse model	P2X7R meditated the transmission of the inflammatory pain in arthritis	[102]
	2002	Labasi et al.	Mice	P2X7R-deficient mice manifested reduced incidence and severity of arthritis	[135]
	2008	Caporali et al	RA patients	RA patients type B synoviocytes expressed functional P2X7R modulating IL-6 release	[93]
	2008	Christenson et al.	RA patients Human neutrophils	Increased neutrophils survival meditated by P2X7R promoted inflammation of RA	[101]
	2010	Portales- Cervantes et al.	RA patients	Increased expression of P2X7R in PBMCs from RA patients as compared to controls	[75]
	2010	Lopez- Castejon et al.	Human macrophages Mouse BMDM	P2X7R meditated cathepsins release as a cytokine-independent mechanism in pathogenesis of RA	[97]
	2011	Al-Shukaili et al.	RA patients	The SNP of P2X7R gene at position 1068 and 1513 conferred susceptibility to RA	[88]
	2012	Portales- Cervantes et al.	RA patients	The 489C > T SNP of P2X7R gene enhanced the function of P2X7R and may contribute to the pathogenesis of RA	[89]
	2012	Keystone et al.	RA patients	P2X7R inhibitor AZD9056 was not efficient for the treatment of RA	[136]
	2012	Stock et al.	RA patients	P2X7R antagonist CE-224,535 was not efficacious for the treatment of RA patients with an inadequate response to MTX.	[137]
	2014	Mclnnes et al.	Rat SCW model	P2X7R expression was detected in inflamed synovial tissue after onset of arthritis Inhibition of P2X7R reduced articular inflammation and erosive progression	[91]
	2016	Fan et al.	RA patients CIA mice	Increased expression of P2X7R in PBMCs from patients with RA Th17 cell differentiation induced by CII required P2X7R signaling in CIA mice	[86]
	2018	Chen et al.	RA patients	Elevated P2X7R level in the synovial tissue with a great diagnostic value for RA Levels of IL-1β and IL-6 were positively correlated with the levels of P2X7R in the synovial tissues	[92]
IBD	2010	Cesaro et al.	CD patients	Significantly down-regulated expression of P2X7R in intestinal epithelial cells of CD patients	[112]
	2012	Kurashima et al.	CD patients TNBS-induced mouse model	P2X7R -mediated mast cell activation in both the initiation and exacerbation of intestinal inflammation	[30]
	2012	Gulbransen et al.	Mice model colitis	P2X7R- pannexin-1 meditated inflammation-induced neuron cell death and contributed to colonic motor dysfunction	[111]
	2014	Marques et al.	TNBS-induced mouse model	Prophylactic systemic P2X7R blockade prevented experimental colitis effectively	[108]
	2014	Neves et al.	CD patients	The up-regulation of P2X7R in CD inflamed mucosa was consistent with the involvement of purinoceptors in inflammation and apoptosis	[106]
	2015	Hofman et al.	CAC model	P2X7R blockade promoted accumulation of Treg cells and production TGF-β	[109]
	2015	Eser et al.	CD patients	Evaluation of P2X7R inhibitor AZD9056 lacked potential anti-inflammatory effect but indicated a great value for the relief of chronic abdominal pain	[114]
	2015	Miller et al.	C57BL/6J mice P2X7R-KO mice	P2X7R inhibited inflammation in protozoan parasite Toxoplasma induced ileitis	[113]
	2016	Wan et al.	DSS induced model	P2X7R-NLRP3 inflammasome and P2X7R- NFκB pathway were crucial in pathogenesis of RA	[107]
MS	2005	Narcisse et al.	MS patients	High expression of P2X7R on reactive astrocytes.in autopsy brain tissues	[117]
	2007	Matute et al.	MS patients EAE model	Elevated P2X7R expression in normal-appearing axon tracts in MS patients ATP- P2X7R activation killed oligodendrocytes and contributed to the pathogenesis of EAE	[119]
	2010	Grygorowicz et al.	EAE model	Overexpression of P2X7R connecting to astrocytic pool of cells was detected at very early asymptomatic phase but relating to neurons emerged in the peak of neurological symptoms	[121]
	2011	Grygorowicz et al.	EAE model	P2X7R overexpression related to synaptosomal fraction in the symptomatic phase and to the glial fraction in the recovery phase of EAE P2X7R-mediated signaling in the pathomechanisms of EAE with the possible relevance of astrocytic pool of cells.	[122]
	2011	Oyanguren- Desez et al.	MS patients	Higher frequency of a gain-of-function P2X7R SNP (rs17525809) in MS patients compared to controls	[123]
	2015	Gu et al.	MS patients	A loss-of-function P2X7R SNP (rs28360457) encoding Arg307Gln conferred a protection against MS	[124]
	2017	Amadio et al.	MS patients	Inhibition of P2X7R on monocytes and up-regulation in astrocytes may sustain inflammatory mechanisms in MS	[118]

(*continued on next page*)

Table 1 (*continued*)

Disease	Publication year	Author	Subjects	Linkages to P2X7R	Ref
SS	2012	Woods et al.	Mice	Activation of the P2X7R with ATP or BzATP stimulated the cleavage and release of α-fodrin	[129]
			SMG cell aggregates	ATP-P2X7R activation enhanced immune cell infiltration into the gland and initiated apoptosis of salivary epithelial cells	
	2013	Baldini et al.	pSS patients	Significantly higher P2X7R expression in salivary glands from pSS individuals	[128]
				P2X7R-inflammasome-caspase-1-IL-18 axis involved in the development of pSS exocrinopathy.	
	2014	Xie et al.	pSS patients	Substantially higher surface expression of P2X7R on PBMC in pSS patients than controls	[126]
	2015	Yu et al.	pSS patients	mRNA and protein levels of P2X7R on pSS PBMCs were significantly higher than in normal individuals	[127]
	2017	Khalafalla et al.	CD28 − / −,IFNγ − / −,NOD.H-2 h4 mouse model	Treatment of the P2X7R antagonist A438079 in vivo ameliorated salivary gland inflammation and improved saliva secretion.	[125]
Psoriasis	2013	Killeen et al.	Psoriasis patients	Increased expression of P2X7R in non-lesional and lesional psoriatic skin	[72]
				mRNA level of P2X7R was significantly higher in non-lesional psoriatic samples	
				ATP-P2X7R-miR21 pathway served as a potential pathogenic mechanism for the initiation of psoriasis	
	2017	Geraghty et al.	IMQ-induced psoriasis mice	P2X7R was not essential for development of IMQ-induced psoriasis-like inflammation	[130]
SSc	2017	Gentile et al.	SSc patients	Increased P2X7R surface expression with enhanced Ca2+ influx in SSc dermal fibroblasts	[73]
				Activation of P2X7R leaded to pro-fibrotic effects	

SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; IBD: inflammatory bowel disease; CD: Crohn's disease; CAC: colitis-associated cancer; MS: multiple sclerosis; SS: sjögren's syndrome; pSS: primary sjögren's syndrome; SSc: systemic sclerosis; LN: lupus nephritis; GN: glomerulonephritis; CFA: complete Freund's adjuvant; CII: type II collagen; CIA: collagen-induced arthritis; BMDM: bone marrow-derived macrophages; SCW: streptococcal cell wall; TNBS: 2,4,6-trinitro-benzene-sulfonic acid; DSS: dextran sulphate sodium; EAE: experimental autoimmune encephalomyelitis; SMG: submandibular gland; IMQ: imiquimod; NF-κB: nuclear factor kappa B; SNP: single-nucleotide polymorphism; PBMCs: peripheral blood mononuclear cells; MTX: methotrexate; Th 17 cell: T helper 17 cell; TGF-β: transforming growth factor-β; NLRP3: nucleotide-binding domain (NOD) like receptor protein 3; BzATP: 3′-O-(4-benzoyl)benzoyl-ATP.

overexpression of B220, which could damage the T cells homeostatic regulation and cloak the response of normal $B220^-$ T-cell subgroups to P2X7R stimulation resulting in drastically decreased sensitivity to ATP-mediated stimulation of P2X7R in T cells, thereby, they were protected from death arising from extracellular ATP. Along with the accumulation of the effector T cells, there will lead to autoimmune syndromes such as LN and T-cells meditated lymphoproliferation. In another study, Faliti et al. [85] revealed that down-regulation of P2X7R that possibly caused by observed reduction of P2X7R mRNA might contribute to a selective T follicular helper (Tfh) cell dysfunction associated with SLE. By using a PIL model characterized by peritoneal lipogranulomas, production of antinuclear antibodies (ANAs) and glomerulonephritis, Faliti et al. also demonstrated that P2X7R deletion significantly exacerbated immunopathology and worsened the disease by enhancing the secretion of autoantibodies. The over-production of these autoantibodies might result from down-regulation of immune checkpoint function during B cell differentiation [85].

3.2. Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is a chronic autoimmune disease with elusive etiology that is characterized by chronic synovial inflammation, joint destruction and progressive articular damage, which leads to joint deformity, reduced quality of life and even impaired function of some other organ systems [68,86]. It has been shown that P2X7R acts as a potential site in the participation and regulation of the inflammation in RA [49,87]. The polymorphism at position 1068 and 1513 in the P2X7R gene may serve as a susceptibility gene locus for RA [88]. Another similar study has also demonstrated that 489C > T SNP of P2X7R gene enhanced the function of P2X7R in RA patients and may contribute to the pathogenesis of RA [89]. Interestingly, perhaps due to genetic polymorphism in the P2X7R, the sensitivity of RA patient mononuclear cells to ATP stimulation is higher than healthy controls [90].

Substantially increased P2X7R expression in peripheral blood mononuclear cells (PBMCs) from RA patients as compared to normal controls has been observed in several studies [75,86]. By using the rat streptococcal cell wall (SCW) arthritis model, P2X7R expression was detected in inflammatory synovial tissue after onset of arthritis [91]. In RA patients, Chen et al. [92] have also shown elevated P2X7R level in the synovial tissue with a great diagnostic value for RA. Specifically, functional P2X7R is expressed in human type B synoviocytes from rheumatoid joints, and it may regulate IL-6 release into synovial fluid [93]. Moreover, in the presence of LPS, obviously higher amounts of IL-1β was detected in PBMCs from RA patients in response to ATP [90], which may arise from increased levels of P2X7R. In fact, Chen et al. [92] further reported that the expression levels of IL-1β and IL-6 were positively correlated with the levels of P2X7R in the synovial tissues of RA patients.

In addition, accumulating evidence indicates that inflammatory T cells especially IL-17 producing Th17 cells are crucial in pathogenesis of RA [94,95]. Induced by immunization with an emulsion of complete Freund's adjuvant (CFA) and type II collagen (CII), collagen-induced arthritis (CIA) is the most extensively studied model of RA to explore the potential mechanisms of autoimmune disease [96]. Fan et al. [86] found that P2X7R signaling was required for CII-regulated the Th17 cell differentiation both in vivo and in vitro. Using the CIA mice, blocking the P2X7R signaling could reduce the production of IL-17A, ameliorate the hind paw swelling and attenuate CII-mediated joint damage [86].

During the inflammation process in RA, several other cytokine-independent pathways meditated by P2X7R also manifest a pivotal role, including P2X7R-TG2 and P2X7R-cathepsins pathway [49,97]. Accumulation of extracellular TG2 driven by P2X7R could meditate protein modification and crosslinking reactions that involve in the pathogenesis, indicating a potential pathogenic mechanism of RA [49]. Dzhambazov et al. [98] also reported that the presence of active TG2 significantly increases severity of disease in the CIA model. Instead of

inflammasome assembly, P2X7R-TG2 pathway depends on the membrane pore formation of the receptor, which is suggested to be more important than the ion channel activity in inflammation based on recent evidences, elucidating that selectively targeting this activity of the receptor is likely to be more therapeutic effectively with lower risk of side effects [49]. As for P2X7R-cathepsins pathway, cathepsins are lysosomal proteases, which could effectively degrade collagen extracellular matrix leading to joint destruction and involve in the inflammation and degeneration of arthritis [99]. Lopez-Castejon et al. [97] reported that P2X7R activation of human macrophages and mouse bone marrow-derived macrophages (BMDM) induced the release of cathepsin B, K, L, and S resulting in joint damage, which was independent of the presence of the cytokines IL-1β and IL-18.

Of note, neutrophil apoptosis is important for the regulation of inflammation, P2X7R may also play an indirect role in promoting inflammation of RA via anti-apoptotic signaling in neutrophils [13]. Serum amyloid A (SAA) protein, an acute phase reactant correlating with active joint inflammation, was found to be elevated in circulation and tissues of RA patients [100]. In vitro experiment manifested that SAA purified from plasma of RA patients effectively inhibited α-CD95 (FAS) mAb-induced human neutrophil apoptosis [101]. Furthermore, administration of the P2X7R antagonist oxidised ATP (oATP) completely abrogated the anti-apoptotic effect of SAA, which indicated that SAA could increase neutrophil survival via a P2X7R-dependent mechanism [101].

Interestingly, experiment in CFA-induced arthritis mouse model revealed that P2X7R could meditate the transmission of inflammatory pain based on its expression in peripheral nerve endings and endothelial cells rather than the recruitment of immune cell [102].

3.3. Inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD), a complicated and multifactorial disorder characterized by chronic relapsing intestinal inflammation, which acts a critical risk factor for colitis-associated cancer (CAC), mainly includes Ulcerative Colitis (UC) and Crohn's Disease (CD) [103,104]. Although the exact etiology remains undetermined, accumulating studies have revealed that P2X7R participated in the pathogenesis of IBD via regulating various cellular behaviors [69] (Fig. 2). Furthermore, genetic factors contribute to IBD, however, the P2X7R polymorphisms His155Tyr, Arg307Gln and Glu496Ala appeared not to be susceptibility factors for CD [105].

Neves et al. [106] demonstrated up-regulated expression of P2X7R colocalizing more with macrophages and dendritic cells in inflamed CD epithelium and lamina propria, as well as higher IL-1β level. Animal experiment in dextran sulphate sodium (DSS) induced mouse model of colitis showed significantly increased and consistent levels of caspase-1-p10 and IL-1β. Importantly, subsequent research showed that blockade of P2X7R decreased levels of above factors, which indicated that P2X7R meditated NLRP3/Caspase-1 inflammasome pathway was involved in the initiation of IBD [107]. Additionally, based on the similar levels change of NFκB and tumor necrosis factor (TNF), Wan et al. [107] also suggested that P2X7R-NFκB pathway plays a pivotal role in the pathogenesis of IBD. Using the 2,4,6-trinitro-benzene-sulfonic acid (TNBS) induced model, the findings that decreased TNF level in concordance with lower activation of NFκB of Marques et al. [108] also supported the role of P2X7R-NFκB pathway.

In CD patients, besides elevated expression of P2X7R, higher level of IL-17 and lower level of IL-10 were detected compared to controls, which were mainly produced by Th17 and Treg cells respectively [106]. Another study in CAC model by Hofman et al. [109] found that P2X7R blockade promoted the accumulation of Treg cells within lesions of the intestine and increased the production of transforming growth factor-β (TGF-β). These all pointed to that the balance between Th17 and Treg cells regulated by P2X7R activation was a crucial pathogenic mechanism in IBD. Meanwhile, increased TGF-β in the case of P2X7R blockade could stimulate the proliferation of intestinal epithelial cells [109], which suggested that P2X7R activation may aggravate inflammation of IBD through decreasing the level of TGF-β to block the repairmen of intestinal epithele.

As we know, the expression levels of P2X7R differ dramatically depending on the different tissues, among which colonic mast cells (MCs) highly express the P2X7R. Activation of MCs meditated by P2X7R could exacerbate intestinal inflammation via inducing inflammatory cytokines, chemokines and leukotrienes to recruit neutrophils, suggesting a potential new mechanism of IBD that is independent of inflammasome pathway [30]. Kurashima et al. [30] found significantly increased numbers of P2X7R positive MCs in colons of both CD patients and TNBS induced model. They also showed that treatment of P2X7R-specific antibody blocked mast cell activation and subsequent intestinal inflammation.

Additionally, IBD always accompanies with long-term gut dysfunction associated with the alterations to enteric neurons, as well as enteric nervous system, whose abnormalities in development could contribute to IBD [110,111]. Gulbransen et al. [111] reported that P2X7R-pannexin-1 meditated inflammation-induced neuron cell death and colonic motor dysfunction via in vivo models of experimental colitis, which indicated that P2X7R in enteric neurons are crucially involved in gut dysfunction of IBD.

However, some studies demonstrated that the expression of P2X7R was significantly down-regulated in intestinal epithelial cells of CD patients [30,112]. This may be regarded as the acute protective response in IBD based on the fact that P2X7R blockade could stimulate the proliferation of intestinal epithelial cells via enhanced production of TGF-β. Of note, over-proliferation of intestinal epithelial cells could also partly explain why P2X7R acts a critical risk factor for CAC. Conversely, Miller et al. [113] reported that P2X7R inhibit inflammation in protozoan parasite Toxoplasma induced ileitis, which is exactly opposite to that P2X7R promotes inflammation in classical models including DSS and TNBS induced model. In addition, another clinical evaluation on safety and efficacy of a P2X7R inhibitor did not get expected anti-inflammatory effect [114]. These all suggested that P2X7R could not be regarded as a simple promoting-inflammatory receptor and it may meditate some other different pathogenesis in different inflammation of IBD.

3.4. Multiple sclerosis (MS)

Multiple sclerosis (MS) is an autoimmune inflammatory disease of central nervous system (CNS), presenting with immune cell infiltration, glia activation, loss of oligodendrocytes and axonal depletion, resulting in extensive demyelination and neurodegeneration [115]. With unknown etiology, it has become evident that P2X7R exerts a pivotal role in pathogenesis of MS based on its widespread involvement in inflammation [116].

The diverse expression of P2X7R in different cell types related to MS is so fascinating. The autopsy of brain tissues by Narcisse et al. [117] detected a high expression of P2X7R on reactive astrocytes. Similarly, in brain samples from secondary progressive MS patients, Amadio et al. [118] also found incremental P2X7R on astrocytes in the parenchyma of frontal cortex. However, in spite of the occurrence of inflammation, Amadio et al. demonstrated that P2X7R was inhibited on peripheral monocytes during the acute phase, even absolutely absent from microglia/macrophages or oligodendrocytes during the secondary progressive phase. Furthermore, P2X7R was decreased in human monocytes after pro-inflammatory stimulation in vitro. In fact, this could be explained by the fact that down-regulation of P2X7R may increase their survival and invasion into the CNS tissue to further lead to the neuroinflammation [118]. Additionally, elevated P2X7R expression was found in normal appearing axon tracts in MS patients, indicating that disordered level of P2X7R likely to precede the emergence of clinical symptom and may be an early risk factor for the development of the

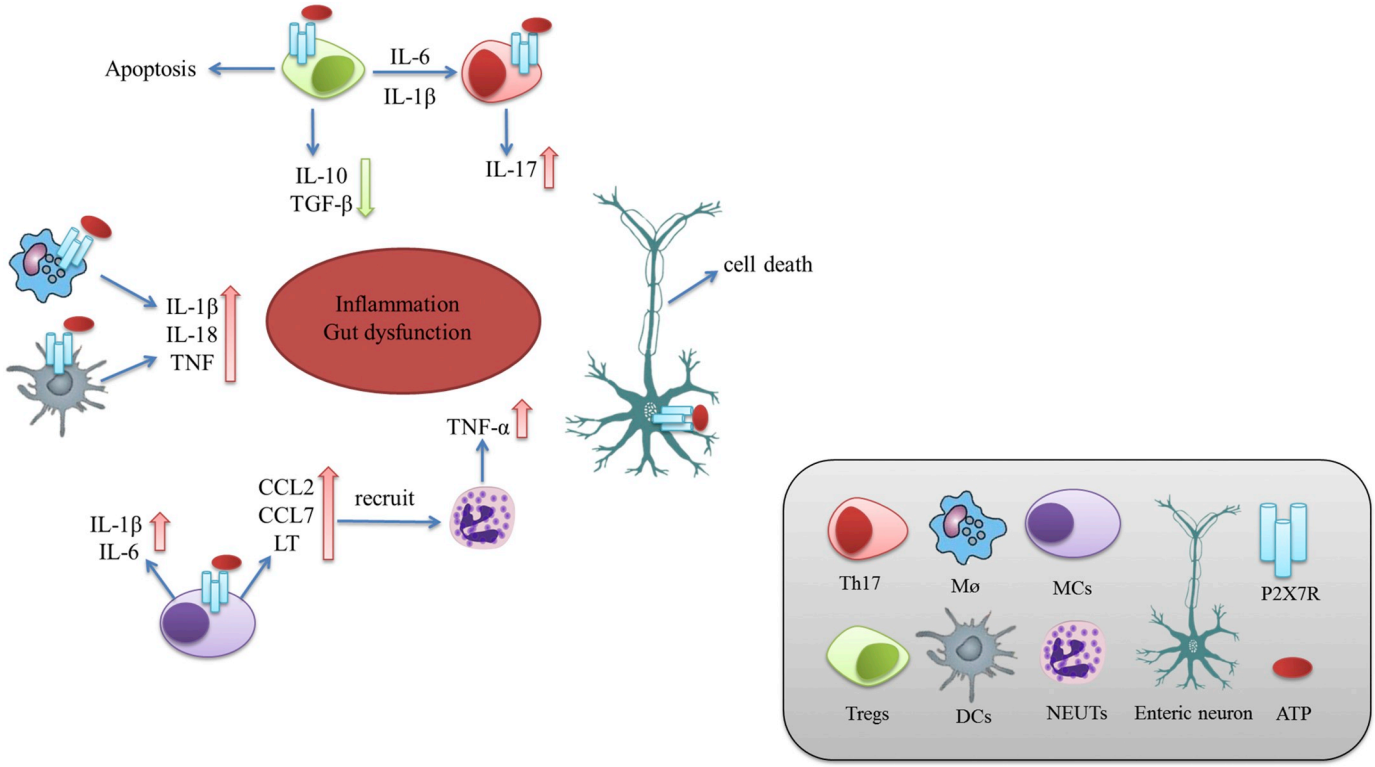

Fig. 2. ATP-P2X7 receptor signals meditated responses in IBD.
(1) In macrophages or dendritic cells, ATP-P2X7R signals lead to the release of IL-1β and IL-18, as well as TNF through mediating inflammasome and NFκB pathways. (2) ATP-P2X7R signals promote the release of IL-17 in Th17 cells whereas induce apoptosis and decrease the secretion of IL-10 and TGF-β in Tregs. IL-1β and IL-6, especially IL-6, could meditate the conversion from Treg cells to Th17 cells. (3) Extracellular ATP induces P2X7R activation in mast cells to exacerbate intestinal inflammation via inducing the release of inflammatory cytokines (IL-1β, IL-6,), chemokines (CCL2, CCL7, etc.) and leukotrienes (LT) to recruit neutrophils, which could produce massive TNF-α. (4) ATP- P2X7R- pannexin-1 meditates inflammation-induced neuron cell death contributing to gut dysfunction of IBD.
ATP: adenosine triphosphate; IBD: inflammatory bowel disease; TNF: tumor necrosis factor; NF-κB: nuclear factor kappa B; Th17: T helper 17; TGF-β: transforming growth factor-β; Tregs: regulatory T cells; Mø: macrophage; DCs: dendritic cells; MCs: mast cells; NEUTs: neutrophils.

disease [119].

Several studies have supported that ATP-P2X7R signaling is a crucial factor for the pathology of MS. As a rat model of MS, experimental autoimmune encephalomyelitis (EAE) is the most commonly used to explore the molecular mechanisms accountable for the inflammation and advanced demyelination features [120]. Matute et al. has demonstrated that enhanced ATP signaling via P2X7R could trigger oligodendrocyte excitotoxicity and lead to lesions that resembled the major characteristics of MS including oligodendrocyte loss, demyelination and axonal damage. Importantly, treatment with P2X7R antagonists to EAE rats substantially reduced demyelination and ameliorated the related neurological symptoms effectively [119].

Interestingly, the levels of P2X7R in different cell types are distinct depending on stages of the disease. Overexpression of P2X7R connecting to astrocytic pool of cells was detected at very early asymptomatic phase of EAE, suggesting that P2X7R might involve in the initiation and development of MS via certain pathway [121]. A potential mechanism is that P2X7R-induced cytokine release by glia likely lead to the inflammatory milieu establishment at early stage of the disease [2]. However, the increased expression of P2X7R relating to neurons was observed in the acute phase and peak of neurological symptoms, contributing to progressive inflammation in EAE [121]. Moreover, despite in the recovery phase of EAE, overexpression of P2X7R was still present and reported to be related to the glial fraction [122]. Notably, glial fibrillary acidic protein (GFAP), a marker of astrocyte activation, whose enhanced immunoreactivity in brain sections did not decline to control values in the recovery phase, similarly to P2X7R expression as mentioned above, indicating a role for P2X7R in sustaining the activation of astrocyte [122].

The gene variants of P2X7R may also act a key role in the pathogenesis of MS. A Spanish case-control study reported that the frequency of a gain-of-function P2X7R SNP (rs17525809) in MS patients was significantly higher compared to normal control [123]. Additionally, a meta-analysis of Australasian and European cohorts suggested that the Arg307Gln, which is encoded by a loss-of-function P2X7R SNP (rs28360457), conferred a protection against MS. The protective effect on the risk of MS may arise from dominant impaired pore formation and negative downstream pro-inflammatory responses [124].

3.5. Other autoimmune diseases

Besides above diseases, the P2X7R is also reported to be implicated in the complicated and elusive pathogenesis of several other autoimmune disorders, such as SS, psoriasis and SSc.

Sjögren's syndrome (SS) is a systemic autoimmune disease featured with salivary and lacrimal glands infiltrated by lymphocytes and monocytes leading to acini damage and exocrine secretion failure, predominantly in women [71,125]. Xie et al. [126] and Yu et al. [127] found that the expression of P2X7R on PBMCs in patients with primary SS (pSS) was substantially higher than normal controls. Meanwhile, significantly higher P2X7R expression in salivary glands from pSS individuals was showed by Baldini et al. [128]. Moreover, they also indicated an involvement of the P2X7R-inflammasome-caspase-1-IL-18 axis in the development of pSS pathology [128]. Several results from animal experiments further elucidated the role of P2X7R in SS. In wild-type mice, in vivo administration of P2X7R agonist 3'-O-(4-benzoyl) benzoyl-ATP (BzATP) to ligated submandibular gland (SMG) excretory ducts enhanced immune cell infiltration and triggered salivary

epithelial cells apoptosis, whereas P2X7R$^{-/-}$ mice was absent from the phenomenon [129]. Importantly, treatment of the P2X7R antagonist A438079 to CD28$^{-/-}$, IFNγ$^{-/-}$, NOD.H-2^{h4} mouse model of salivary gland exocrinopathy in vivo could reduce salivary gland inflammation and promote saliva secretion, representing a promising therapeutic strategy [125]. Of note, in vitro studies using SMG cell aggregates from wild-type and P2X7R$^{-/-}$ mice suggested that activation of ATP/BzATP-P2X7R could stimulate the cleavage and release of α-fodrin, which is thought to serve as an auto-antigen in the development of SS, indicating a possible pathogenic mechanism [129].

Psoriasis is one of the most common chronic inflammatory human skin diseases, presenting with over-proliferation of keratinocytes and infiltration of leukocytes contributing to epidermal hyperplasia (acanthosis) and plaque- or pustular-like skin lesions [130,131]. Killeen et al. have shown increased presence of P2X7R in lesional and non-lesional psoriatic skin compared to healthy tissues. Furthermore, analysis of the P2X7R at the mRNA level indicated that non-lesional psoriatic samples displayed significantly higher P2X7R mRNA than that in lesional samples and healthy controls [72]. Meanwhile, the miR-150, which induces instability of P2X7R mRNA, was also reported to decrease in non-lesional tissues [72,132]. These findings prompted that non-lesional psoriatic tissues may be ready for the conversion to its lesion state via up-regulating the expression of P2X7R. Indeed, following treatment with a P2X7R agonist in non-lesional tissue, the psoriatic responses was initiated. Importantly, based on a series of data, the study also revealed that ATP-P2X7R-miR21 pathway leading to the expression of vascular endothelial growth factor (VEGF) and IL-6 may serve as a potential pathogenic mechanism for the initiation and development of psoriasis lesions [72]. However, another study indicated that P2X7R is not essential for the development of imiquimod (IMQ)-induced psoriasis-like inflammation, nevertheless, this result could not exclude a possible role for P2X7R in the development of human psoriasis or other animal models of this disease [130].

As for systemic sclerosis (SSc), it is a connective tissue disease (CTD) characterized by small vessel alterations and fibroblasts dysfunction, resulting in severe deposition of collagen and extracellular matrix (ECM), tissue fibrosis and even organ failure [133]. Compared to normal subjects, P2X7R surface expression was increased with enhanced Ca2+ influx in SSc dermal fibroblasts. In LPS-primed fibroblasts from SSc patients, activation of P2X7R could promote collagen production, α-smooth muscle actin (αSMA) expression, cell migration and connective tissue growth factor (CTGF) release to lead to pro-fibrotic effects. Additionally, the study has also shown that inhibition of extracellular signal-regulated kinases-1/2 (ERK-1/2) prevented P2X7R-induced collagen production and CTGF release, indicating a novel cytokine-independent pathway in P2X7R- induced fibrosis [73].

4. P2X7R as a potential therapeutic target for autoimmune disease

Based on its crucial roles in pathogenesis of inflammation cascade and autoimmunity, P2X7R may serve as a promising therapeutic target for autoimmune diseases. Understanding the molecular mechanisms of P2X7R in autoimmune diseases, together with research to develop more specific P2X7R inhibitor, may provide a novel therapeutic option.

Experimental blockade of P2X7R in animal models has gained auspicious results for several autoimmune diseases. A study was performed by application of P2X7R antagonist brilliant blue G (BBG) or specific small interfering RNA (siRNA) silencing P2X7R to MLR/*lpr* mice. At the macroscopic level, the lifespan of the treated mice was substantially prolonged and the severity of nephritis was ameliorated. At the microscopic level, blockade or absence of P2X7R activation strongly reduced renal immune complex deposition and the Th17:Treg cells ratio. At the molecular level, the inhibition or absence of P2X7R significantly decreased the NLRP3/ASC/caspase 1 assembly, serum levels of IL-1β and IL-17, as well as the circulating anti-double-stranded DNA (anti-dsDNA) antibodies [77]. Due to the limitation that the disorder in MLR/*lpr* mice is primarily induced by Fas deficiency, further experiment was carried out in NZM2328 mice, a new mouse model of SLE, in which the disease resembles immune complex-mediated glomerulonephritis [134]. The results manifested a significant reduction of IL-1β and a twice-confirmation of the effectiveness of BBG treatment, which suggested that development of pharmacologic inhibitors blocking the P2X7R pathway may provide a novel therapeutic strategy for human SLE with general applicability [77].

Several other studies also evaluated the potential of targeting P2X7R in treatment of RA. Using animal models, the incidence and severity of arthritis including joint lesions and collagen degradation production induced by antibody + LPS in wild-type mice were markedly reduced in P2X7R-deficient mice [135]. Similarly, inhibition of P2X7R to SCW-induced model also ameliorated the inflammation and erosive progression of arthritis [91]. In cellular experiments, P2X7R knockdown via a siRNA in an immortalized RA synovial cell line (MH7A) obviously reduced the secretion of IL-1β and IL-6 [92]. Blockade of P2X7R to two cytokine-independent pathway in RA including P2X7R-TG2 and P2X7R-cathepsin pathway has manifested expected effects: inhibition of P2X7R blocked acute release of a large quantity of TG2 by macrophages with no apparent effects on the level of cellular surface-related enzyme [50], meanwhile, the ATP-induced cathepsin release from macrophages was abolished by P2X7R antagonists (AZ10573295 and AZ11648720) and absent from P2X7R$^{-/-}$ mouse [97]. Additionally, administration of P2X7R inhibitor oATP into inflamed paws of CFA-induced mouse model remarkably relieved the inflammatory pain [102]. However, some clinical evaluations have not achieved the expected efficacy of P2X7R antagonist to the treatment of RA and therein Keystone et al. even showed that P2X7R appeared not to be a therapeutically useful target [136,137]. This may be due to the wide variation of P2X7R gene resulting in the significantly high polymorphism in human population. Therefore, taking P2X7R genotype into consideration is requisite when evaluating the efficacy of P2X7R antagonists.

Besides positive effects of P2X7R blockade in SLE and RA, pharmacological blockade of P2X7R also effectively attenuated intestinal inflammation of TNBS and DSS induced mouse mode, as well as CAC mouse model [107–109]. Importantly, P2X7R-KO mice failed to develop colitis while induced by TNBS or DSS [106]. Of note, despite the lack in anti-inflammatory potential of P2X7R inhibitor in a clinical evaluation, the results of the study indicated a great value of P2X7R antagonism for the relief of chronic abdominal pain [114].

Collectively, these evidences suggest that P2X7R may serve as a potential therapeutic target for autoimmune diseases.

5. Conclusion

The advanced researches have amplified our understanding of the pivotal role of P2X7R in inflammation and autoimmune diseases, as well as its intrinsic molecular mechanisms. Although there is much to be explored, accumulating evidences from in vitro and in vivo model in conjunction with development of P2X7R pharmacology and increased structural insights together support targeting P2X7R as a potential method for the treatment of autoimmune diseases [138,139]. However, several main unresolved aspects in mechanisms and therapeutic value of P2X7R should be noted. One of these is the difference of P2X7R between human and animal models. Firstly, P2X7R of mice could be also activated by NAD^+, leading to similar downstream cascade responses as compared to that induced by ATP, which may contributed to ligand-associated signaling difference of P2X7R. Next, the affinity of ATP to P2X7R may differ dramatically among diverse species [140]. Meanwhile, significantly high polymorphism of P2X7R in human population may also result in functional distinction. There is another crucial resistance against the therapeutic value of P2X7R. Due to its extensive distribution in human body, the inhibitor relieving symptoms via regulating P2X7R in inflammatory tissues may also result in some

other side effects, which could be called as “Off-target” phenomenon. Therefore, on the one hand, further studies are seriously in need, especially in human systems to explicate the role of P2X7R in autoimmune diseases and evaluate the actual efficacy and safety of existing potential P2X7R inhibitor. On the other hand, to provide more details for new drug development and reduce the side effects, or even absolutely avoid the “Off-target” phenomenon, the different expression of P2X7R in different tissues or status, as well as other responses and physical or pathogenic effects that may be triggered by P2X7R signaling, should be also comprehensively explored. Undoubtedly, a further understanding of biological function and regulation of P2X7R will certainly be beneficial in the development of future therapeutics of autoimmune diseases.

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Declaration of Competing Interest

The authors report no conflicts of interest.

References

[1] Verkhratsky A, Burnstock G. Biology of purinergic signalling: its ancient evolutionary roots, its omnipresence and its multiple functional significance. Bioessays 2014;36:697–705. https://doi.org/10.1002/bies.201400024.
[2] Savio LEB, de Andrade Mello P, da Silva CG, Coutinho-Silva R. The P2X7 receptor in inflammatory diseases: angel or demon? Front Pharmacol 2018;9:52https://doi.org/10.3389/fphar.2018.00052.
[3] Di Virgilio F, Giuliani AL. Purinergic signalling in autoimmunity: a role for the P2X7R in systemic lupus erythematosus? Biom J 2016;39:326–38. https://doi.org/10.1016/j.bj.2016.08.006.
[4] Morandini AC, Savio LE, Coutinho-Silva R. The role of P2X7 receptor in infectious inflammatory diseases and the influence of ectonucleotidases. Biom J 2014;37:169–77. https://doi.org/10.4103/2319-4170.127803.
[5] Dubyak GR. P2X7 receptor regulation of non-classical secretion from immune effector cells. Cell Microbiol 2012;14:1697–706. https://doi.org/10.1111/cmi.12001.
[6] Shen HH, Yang YX, Meng X, Luo XY, Li XM, Shuai ZW, et al. NLRP3: a promising therapeutic target for autoimmune diseases. Autoimmun Rev 2018;17:694–702. https://doi.org/10.1016/j.autrev.2018.01.020.
[7] Kumar H, Kawai T, Akira S. Pathogen recognition by the innate immune system. Int Rev Immunol 2011;30:16–34. https://doi.org/10.3109/08830185.2010.529976.
[8] Bours MJ, Swennen EL, Di Virgilio F, Cronstein BN, Dagnelie PC. Adenosine 5′-triphosphate and adenosine as endogenous signaling molecules in immunity and inflammation. Pharmacol Ther 2006;112:358–404. https://doi.org/10.1016/j.pharmthera.2005.04.013.
[9] Oppenheim JJ, Yang D. Alarmins: chemotactic activators of immune responses. Curr Opin Immunol 2005;17:359–65. https://doi.org/10.1016/j.coi.2005.06.002.
[10] Di Virgilio F. Liaisons dangereuses: P2X(7) and the inflammasome. Trends Pharmacol Sci 2007;28:465–72. https://doi.org/10.1016/j.tips.2007.07.002.
[11] Franceschini A, Capece M, Chiozzi P, Falzoni S, Sanz JM, Sarti AC, et al. The P2X7 receptor directly interacts with the NLRP3 inflammasome scaffold protein. FASEB J 2015;29:2450–61. https://doi.org/10.1096/fj.14-268714.
[12] Yi YS. Role of inflammasomes in inflammatory autoimmune rheumatic diseases. Korean J Physiol Pharmacol 2018;22:1–15. https://doi.org/10.4196/kjpp.2018.22.1.1.
[13] Arulkumaran N, Unwin RJ, Tam FW. A potential therapeutic role for P2X7 receptor (P2X7R) antagonists in the treatment of inflammatory diseases. Expert Opin Investig Drugs 2011;20:897–915. https://doi.org/10.1517/13543784.2011.578068.
[14] Mehta N, Kaur M, Singh M, Chand S, Vyas B, Silakari P, et al. Purinergic receptor P2X(7): a novel target for anti-inflammatory therapy. Bioorg Med Chem 2014;22:54–88. https://doi.org/10.1016/j.bmc.2013.10.054.
[15] Burnstock G. Purinergic signalling: therapeutic developments. Front Pharmacol 2017;8:661https://doi.org/10.3389/fphar.2017.00661.
[16] Baudelet D, Lipka E, Millet R, Ghinet A. Involvement of the P2X7 purinergic receptor in inflammation: an update of antagonists series since 2009 and their promising therapeutic potential. Curr Med Chem 2015;22:713–29.
[17] Burnstock G. Pathophysiology and therapeutic potential of purinergic signaling. Pharmacol Rev 2006;58:58–86. https://doi.org/10.1124/pr.58.1.5.
[18] Buell GN, Talabot F, Gos A, Lorenz J, Lai E, Morris MA, et al. Gene structure and chromosomal localization of the human P2X7 receptor. Receptors Channels 1998;5:347–54.
[19] Liu X, Ma W, Surprenant A, Jiang LH. Identification of the amino acid residues in the extracellular domain of rat P2X(7) receptor involved in functional inhibition by acidic pH. Br J Pharmacol 2009;156:135–42. https://doi.org/10.1111/j.1476-5381.2008.00002.x.
[20] Coddou C, Yan Z, Obsil T, Huidobro-Toro JP, Stojilkovic SS. Activation and regulation of purinergic P2X receptor channels. Pharmacol Rev 2011;63:641–83. https://doi.org/10.1124/pr.110.003129.
[21] Clyne JD, Wang LF, Hume RI. Mutational analysis of the conserved cysteines of the rat P2X2 purinoceptor. J Neurosci 2002;22:3873–80. (doi:20026390).
[22] Dahl G. ATP release through pannexon channels. Philos Trans R Soc Lond B Biol Sci 2015;370. https://doi.org/10.1098/rstb.2014.0191.
[23] Cantiello HF. Electrodiffusional ATP movement through CFTR and other ABC transporters. Pflugers Arch 2001;443(Suppl. 1):S22–7. https://doi.org/10.1007/s004240100639.
[24] Cohen HB, Briggs KT, Marino JP, Ravid K, Robson SC, Mosser DM. TLR stimulation initiates a CD39-based autoregulatory mechanism that limits macrophage inflammatory responses. Blood 2013;122:1935–45. https://doi.org/10.1182/blood-2013-04-496216.
[25] Wang Y, Martins I, Ma Y, Kepp O, Galluzzi L, Kroemer G. Autophagy-dependent ATP release from dying cells via lysosomal exocytosis. Autophagy. 2013;9:1624–5. https://doi.org/10.4161/auto.25873.
[26] Pellegatti P, Falzoni S, Pinton P, Rizzuto R, Di Virgilio F. A novel recombinant plasma membrane-targeted luciferase reveals a new pathway for ATP secretion. Mol Biol Cell 2005;16:3659–65. https://doi.org/10.1091/mbc.e05-03-0222.
[27] Burnstock G, Knight GE. Cellular distribution and functions of P2 receptor subtypes in different systems. Int Rev Cytol 2004;240:31–304. https://doi.org/10.1016/s0074-7696(04)40002-3.
[28] Surprenant A, North RA. Signaling at purinergic P2X receptors. Annu Rev Physiol 2009;71:333–59. https://doi.org/10.1146/annurev.physiol.70.113006.100630.
[29] Schenk U, Frascoli M, Proietti M, Geffers R, Traggiai E, Buer J, et al. ATP inhibits the generation and function of regulatory T cells through the activation of purinergic P2X receptors. Sci Signal 2011;4:ra12. https://doi.org/10.1126/scisignal.2001270.
[30] Kurashima Y, Amiya T, Nochi T, Fujisawa K, Haraguchi T, Iba H, et al. Extracellular ATP mediates mast cell-dependent intestinal inflammation through P2X7 purinoceptors. Nat Commun 2012;3:1034https://doi.org/10.1038/ncomms2023.
[31] Montreekachon P, Chotjumlong P, Bolscher JG, Nazmi K, Reutrakul V, Krisanaprakornkit S. Involvement of P2X(7) purinergic receptor and MEK1/2 in interleukin-8 up-regulation by LL-37 in human gingival fibroblasts. J Periodontal Res 2011;46:327–37. https://doi.org/10.1111/j.1600-0765.2011.01346.x.
[32] Souza CO, Santoro GF, Figliuolo VR, Nanini HF, de Souza HS, Castelo-Branco MT, et al. Extracellular ATP induces cell death in human intestinal epithelial cells. Biochim Biophys Acta 2012;1820:1867–78. https://doi.org/10.1016/j.bbagen.2012.08.013.
[33] Janks L, Sharma CVR, Egan TM. A central role for P2X7 receptors in human microglia. J Neuroinflammation 2018;15:325https://doi.org/10.1186/s12974-018-1353-8.
[34] Novak I. Purinergic receptors in the endocrine and exocrine pancreas. Purinergic Signal 2008;4:237–53. https://doi.org/10.1007/s11302-007-9087-6.
[35] Jiang LH, Kim M, Spelta V, Bo X, Surprenant A, North RA. Subunit arrangement in P2X receptors. J Neurosci 2003;23:8903–10.
[36] Pelegrin P, Surprenant A. The P2X(7) receptor-pannexin connection to dye uptake and IL-1beta release. Purinergic Signal 2009;5:129–37. https://doi.org/10.1007/s11302-009-9141-7.
[37] Pelegrin P. Many ways to dilate the P2X7 receptor pore. Br J Pharmacol 2011;163:908–11. https://doi.org/10.1111/j.1476-5381.2011.01325.x.
[38] Baroja-Mazo A, Barbera-Cremades M, Pelegrin P. The participation of plasma membrane hemichannels to purinergic signaling. Biochim Biophys Acta 2013;1828:79–93. https://doi.org/10.1016/j.bbamem.2012.01.002.
[39] Kubick C, Schmalzing G, Markwardt F. The effect of anions on the human P2X7 receptor. Biochim Biophys Acta 2011;1808:2913–22. https://doi.org/10.1016/j.bbamem.2011.08.017.
[40] Burnstock G, Boeynaems JM. Purinergic signalling and immune cells. Purinergic Signal 2014;10:529–64. https://doi.org/10.1007/s11302-014-9427-2.
[41] Munoz-Planillo R, Kuffa P, Martinez-Colon G, Smith BL, Rajendiran TM, Nunez G. K(+) efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. Immunity. 2013;38:1142–53. https://doi.org/10.1016/j.immuni.2013.05.016.
[42] Murakami T, Ockinger J, Yu J, Byles V, McColl A, Hofer AM, et al. Critical role for calcium mobilization in activation of the NLRP3 inflammasome. Proc Natl Acad Sci U S A 2012;109:11282–7. https://doi.org/10.1073/pnas.1117765109.
[43] Lee GS, Subramanian N, Kim AI, Aksentijevich I, Goldbach-Mansky R, Sacks DB, et al. The calcium-sensing receptor regulates the NLRP3 inflammasome through Ca2+ and cAMP. Nature. 2012;492:123–7. https://doi.org/10.1038/nature11588.
[44] Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC, et al. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol 2011;12:222–30. https://doi.org/10.1038/ni.1980.
[45] Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity. 2012;36:401–14. https://doi.org/10.1016/j.immuni.2012.01.009.
[46] Cruz CM, Rinna A, Forman HJ, Ventura AL, Persechini PM, Ojcius DM. ATP

activates a reactive oxygen species-dependent oxidative stress response and secretion of proinflammatory cytokines in macrophages. J Biol Chem 2007;282:2871–9. https://doi.org/10.1074/jbc.M608083200.
[47] Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. Nature. 2011;469:221–5. https://doi.org/10.1038/nature09663.
[48] Ferrari D, Pizzirani C, Adinolfi E, Lemoli RM, Curti A, Idzko M, et al. The P2X7 receptor: a key player in IL-1 processing and release. J Immunol 2006;176:3877–83.
[49] Aeschlimann D, Knauper V. P2X7 receptor-mediated TG2 externalization: a link to inflammatory arthritis? Amino Acids 2017;49:453–60. https://doi.org/10.1007/s00726-016-2319-8.
[50] Adamczyk M, Griffiths R, Dewitt S, Knauper V, Aeschlimann D. P2X7 receptor activation regulates rapid unconventional export of transglutaminase-2. J Cell Sci 2015;128:4615–28. https://doi.org/10.1242/jcs.175968.
[51] Liu Y, Xiao Y, Li Z. P2X7 receptor positively regulates MyD88-dependent NF-kappaB activation. Cytokine 2011;55:229–36. https://doi.org/10.1016/j.cyto.2011.05.003.
[52] Bradford MD, Soltoff SP. P2X7 receptors activate protein kinase D and p42/p44 mitogen-activated protein kinase (MAPK) downstream of protein kinase C. Biochem J 2002;366:745–55. https://doi.org/10.1042/bj20020358.
[53] Dubyak GR. Purinergic signaling at immunological synapses. J Auton Nerv Syst 2000;81:64–8.
[54] Yip L, Woehrle T, Corriden R, Hirsh M, Chen Y, Inoue Y, et al. Autocrine regulation of T-cell activation by ATP release and P2X7 receptors. FASEB J 2009;23:1685–93. https://doi.org/10.1096/fj.08-126458.
[55] Hogan PG, Chen L, Nardone J, Rao A. Transcriptional regulation by calcium, calcineurin, and NFAT. Genes Dev 2003;17:2205–32. https://doi.org/10.1101/gad.1102703.
[56] Cekic C, Linden J. Purinergic regulation of the immune system. Nat Rev Immunol 2016;16:177–92. https://doi.org/10.1038/nri.2016.4.
[57] Cascao R, Vidal B, Raquel H, Neves-Costa A, Figueiredo N, Gupta V, et al. Effective treatment of rat adjuvant-induced arthritis by celastrol. Autoimmun Rev 2012;11:856–62. https://doi.org/10.1016/j.autrev.2012.02.022.
[58] Omenetti S, Pizarro TT. The Treg/Th17 Axis: a dynamic balance regulated by the gut microbiome. Front Immunol 2015;6:639. https://doi.org/10.3389/fimmu.2015.00639.
[59] Ben-Sasson SZ, Hu-Li J, Quiel J, Cauchetaux S, Ratner M, Shapira I, et al. IL-1 acts directly on CD4 T cells to enhance their antigen-driven expansion and differentiation. Proc Natl Acad Sci U S A 2009;106:7119–24. https://doi.org/10.1073/pnas.0902745106.
[60] Palomo J, Dietrich D, Martin P, Palmer G, Gabay C. The interleukin (IL)-1 cytokine family—balance between agonists and antagonists in inflammatory diseases. Cytokine. 2015;76:25–37. https://doi.org/10.1016/j.cyto.2015.06.017.
[61] Fasching P, Stradner M, Graninger W, Dejaco C, Fessler J. Therapeutic potential of targeting the Th17/Treg Axis in autoimmune disorders. Molecules. 2017;22. https://doi.org/10.3390/molecules22010134.
[62] Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, et al. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. Nat Immunol 2005;6:1133–41. https://doi.org/10.1038/ni1261.
[63] Rose NR. Prediction and prevention of autoimmune disease in the 21st century: a review and preview. Am J Epidemiol 2016;183:403–6. https://doi.org/10.1093/aje/kwv292.
[64] Leishman AJ, Sims GP, Sleeman M, Braddock M. Emerging small molecule and biological therapeutic approaches for the treatment of autoimmunity. Expert Opin Investig Drugs 2011;20:23–39. https://doi.org/10.1517/13543784.2011.540569.
[65] Cope AP, Feldmann M. Emerging approaches for the therapy of autoimmune and chronic inflammatory disease. Curr Opin Immunol 2004;16:780–6. https://doi.org/10.1016/j.coi.2004.09.005.
[66] Schneider M. Target therapy in SLE. Autoimmun Rev 2019;18:21–4. https://doi.org/10.1016/j.autrev.2018.07.007.
[67] Yang CA, Chiang BL. Inflammasomes and human autoimmunity: a comprehensive review. J Autoimmun 2015;61:1–8. https://doi.org/10.1016/j.jaut.2015.05.001.
[68] Zeng D, Yao P, Zhao H. P2X7, a critical regulator and potential target for bone and joint diseases. J Cell Physiol 2019;234:2095–103. https://doi.org/10.1002/jcp.27544.
[69] Meng SP, Ma B. P2X7 receptor and inflammatory bowel disease. Sheng Li Xue Bao 2016;68:343–51.
[70] Domercq M, Zabala A, Matute C. Purinergic receptors in multiple sclerosis pathogenesis. Brain Res Bull 2018. https://doi.org/10.1016/j.brainresbull.2018.11.018.
[71] Lester S, Stokes L, Skarratt KK, Gu BJ, Sivils KL, Lessard CJ, et al. Epistasis with HLA DR3 implicates the P2X7 receptor in the pathogenesis of primary Sjogren's syndrome. Arthritis Res Ther 2013;15:R71. https://doi.org/10.1186/ar4248.
[72] Killeen ME, Ferris L, Kupetsky EA, Falo Jr. L, Mathers AR. Signaling through purinergic receptors for ATP induces human cutaneous innate and adaptive Th17 responses: implications in the pathogenesis of psoriasis. J Immunol 2013;190:4324–36. https://doi.org/10.4049/jimmunol.1202045.
[73] Gentile D, Lazzerini PE, Gamberucci A, Natale M, Selvi E, Vanni F, et al. Searching novel therapeutic targets for scleroderma: P2X7-receptor is up-regulated and promotes a Fibrogenic phenotype in systemic sclerosis fibroblasts. Front Pharmacol 2017;8:638https://doi.org/10.3389/fphar.2017.00638.
[74] Nath SK, Quintero-Del-Rio AI, Kilpatrick J, Feo L, Ballesteros M, Harley JB. Linkage at 12q24 with systemic lupus erythematosus (SLE) is established and confirmed in Hispanic and European American families. Am J Hum Genet 2004;74:73–82. https://doi.org/10.1086/380913.
[75] Portales-Cervantes L, Nino-Moreno P, Doniz-Padilla L, Baranda-Candido L, Garcia-Hernandez M, Salgado-Bustamante M, et al. Expression and function of the P2X(7) purinergic receptor in patients with systemic lupus erythematosus and rheumatoid arthritis. Hum Immunol 2010;71:818–25. https://doi.org/10.1016/j.humimm.2010.05.008.
[76] Le Gall SM, Legrand J, Benbijja M, Safya H, Benihoud K, Kanellopoulos JM, et al. Loss of P2X7 receptor plasma membrane expression and function in pathogenic B220+ double-negative T lymphocytes of autoimmune MRL/lpr mice. PLoS One 2012;7:e52161https://doi.org/10.1371/journal.pone.0052161.
[77] Zhao J, Wang H, Dai C, Wang H, Zhang H, Huang Y, et al. P2X7 blockade attenuates murine lupus nephritis by inhibiting activation of the NLRP3/ASC/caspase 1 pathway. Arthritis Rheum 2013;65:3176–85. https://doi.org/10.1002/art.38174.
[78] Kahlenberg JM, Yalavarthi S, Zhao W, Hodgin JB, Reed TJ, Tsuji NM, et al. An essential role of caspase 1 in the induction of murine lupus and its associated vascular damage. Arthritis Rheumatol 2014;66:152–62. https://doi.org/10.1002/art.38225.
[79] Turner CM, Tam FW, Lai PC, Tarzi RM, Burnstock G, Pusey CD, et al. Increased expression of the pro-apoptotic ATP-sensitive P2X7 receptor in experimental and human glomerulonephritis. Nephrol Dial Transplant 2007;22:386–95. https://doi.org/10.1093/ndt/gfl589.
[80] Taylor SR, Turner CM, Elliott JI, McDaid J, Hewitt R, Smith J, et al. P2X7 deficiency attenuates renal injury in experimental glomerulonephritis. J Am Soc Nephrol 2009;20:1275–81. https://doi.org/10.1681/asn.2008060559.
[81] Kahlenberg JM, Carmona-Rivera C, Smith CK, Kaplan MJ. Neutrophil extracellular trap-associated protein activation of the NLRP3 inflammasome is enhanced in lupus macrophages. J Immunol 2013;190:1217–26. https://doi.org/10.4049/jimmunol.1202388.
[82] Chen GM, Feng CC, Ye QL, Tao JH, Li R, Peng H, et al. Association of P2X7R gene polymorphisms with systemic lupus erythematosus in a Chinese population. Mutagenesis. 2013;28:351–5. https://doi.org/10.1093/mutage/get007.
[83] Forchap SL, Anandacoomarasamy A, Wicks J, Di Virgilio F, Baricordi OR, Rubini M, et al. P2X7 gene polymorphisms do not appear to be a susceptibility gene locus in sporadic cases of systemic lupus erythematosus. Tissue Antigens 2008;72:487–90. https://doi.org/10.1111/j.1399-0039.2008.01136.x.
[84] Bidere N, Su HC, Lenardo MJ. Genetic disorders of programmed cell death in the immune system. Annu Rev Immunol 2006;24:321–52. https://doi.org/10.1146/annurev.immunol.24.021605.090513.
[85] Faliti CE, Gualtierotti R, Rottoli E, Gerosa M, Perruzza L, Romagnani A, et al. P2X7 receptor restrains pathogenic Tfh cell generation in systemic lupus erythematosus. J Exp Med 2019;216:317–36. https://doi.org/10.1084/jem.20171976.
[86] Fan ZD, Zhang YY, Guo YH, Huang N, Ma HH, Huang H, et al. Involvement of P2X7 receptor signaling on regulating the differentiation of Th17 cells and type II collagen-induced arthritis in mice. Sci Rep 2016;6:35804https://doi.org/10.1038/srep35804.
[87] Baroja-Mazo A, Pelegrin P. Modulating P2X7 receptor Signaling during rheumatoid arthritis: new therapeutic approaches for bisphosphonates. J Osteoporos 2012;2012:408242https://doi.org/10.1155/2012/408242.
[88] Al-Shukaili A, Al-Kaabi J, Hassan B, Al-Araimi T, Al-Tobi M, Al-Kindi M, et al. P2X7 receptor gene polymorphism analysis in rheumatoid arthritis. Int J Immunogenet 2011;38:389–96. https://doi.org/10.1111/j.1744-313X.2011.01019.x.
[89] Portales-Cervantes L, Nino-Moreno P, Salgado-Bustamante M, Garcia-Hernandez MH, Baranda-Candido L, Reynaga-Hernandez E, et al. The His155Tyr (489C > T) single nucleotide polymorphism of P2RX7 gene confers an enhanced function of P2X7 receptor in immune cells from patients with rheumatoid arthritis. Cell Immunol 2012;276:168–75. https://doi.org/10.1016/j.cellimm.2012.05.005.
[90] Al-Shukaili A, Al-Kaabi J, Hassan B. A comparative study of interleukin-1beta production and p2x7 expression after ATP stimulation by peripheral blood mononuclear cells isolated from rheumatoid arthritis patients and normal healthy controls. Inflammation. 2008;31:84–90. https://doi.org/10.1007/s10753-007-9052-0.
[91] McInnes IB, Cruwys S, Bowers K, Braddock M. Targeting the P2X7 receptor in rheumatoid arthritis: biological rationale for P2X7 antagonism. Clin Exp Rheumatol 2014;32:878–82.
[92] Chen Y, Su B, Shang M. Diagnostic value of P2X7 receptor and its role in inflammatory reaction in rheumatoid arthritis. Nan Fang Yi Ke Da Xue Xue Bao vol. 38. 2018. p. 1453–8. https://doi.org/10.12122/j.issn.1673-4254.2018.12.09.
[93] Caporali F, Capecchi PL, Gamberucci A, Lazzerini PE, Pompella G, Natale M, et al. Human rheumatoid synoviocytes express functional P2X7 receptors. J Mol Med (Berl) 2008;86:937–49. https://doi.org/10.1007/s00109-008-0365-8.
[94] Ferraccioli G, Zizzo G. The potential role of Th17 in mediating the transition from acute to chronic autoimmune inflammation: rheumatoid arthritis as a model. Discov Med 2011;11:413–24.
[95] Paulissen SM, van Hamburg JP, Dankers W, Lubberts E. The role and modulation of CCR6+ Th17 cell populations in rheumatoid arthritis. Cytokine. 2015;74:43–53. https://doi.org/10.1016/j.cyto.2015.02.002.
[96] Brand DD, Latham KA, Rosloniec EF. Collagen-induced arthritis. Nat Protoc 2007;2:1269–75. https://doi.org/10.1038/nprot.2007.173.
[97] Lopez-Castejon G, Theaker J, Pelegrin P, Clifton AD, Braddock M, Surprenant A. P2X(7) receptor-mediated release of cathepsins from macrophages is a cytokine-independent mechanism potentially involved in joint diseases. J Immunol 2010;185:2611–9. https://doi.org/10.4049/jimmunol.1000436.
[98] Dzhambazov B, Lindh I, Engstrom A, Holmdahl R. Tissue transglutaminase enhances collagen type II-induced arthritis and modifies the immunodominant T-cell epitope CII260-270. Eur J Immunol 2009;39:2412–23. https://doi.org/10.1002/

eji.200939438.
[99] Wang D, Bromme D. Drug delivery strategies for cathepsin inhibitors in joint diseases. Expert Opin Drug Deliv 2005;2:1015–28. https://doi.org/10.1517/17425247.2.6.1015.
[100] Kokubun M, Imafuku Y, Okada M, Ohguchi Y, Ashikawa T, Yamada T, et al. Serum amyloid a (SAA) concentration varies among rheumatoid arthritis patients estimated by SAA/CRP ratio. Clin Chim Acta 2005;360:97–102. https://doi.org/10.1016/j.cccn.2005.04.006.
[101] Christenson K, Bjorkman L, Tangemo C, Bylund J. Serum amyloid a inhibits apoptosis of human neutrophils via a P2X7-sensitive pathway independent of formyl peptide receptor-like 1. J Leukoc Biol 2008;83:139–48. https://doi.org/10.1189/jlb.0507276.
[102] Dell'Antonio G, Quattrini A, Cin ED, Fulgenzi A, Ferrero ME. Relief of inflammatory pain in rats by local use of the selective P2X7 ATP receptor inhibitor, oxidized ATP. Arthritis Rheum 2002;46:3378–85. https://doi.org/10.1002/art.10678.
[103] Loddo I, Romano C. Inflammatory bowel disease: genetics, epigenetics, and pathogenesis. Front Immunol 2015;6:551https://doi.org/10.3389/fimmu.2015.00551.
[104] Liu Y, Zhao J, Zhao Y, Zong S, Tian Y, Chen S, et al. Therapeutic effects of lentinan on inflammatory bowel disease and colitis-associated cancer. J Cell Mol Med 2019;23:750–60. https://doi.org/10.1111/jcmm.13897.
[105] Haas SL, Ruether A, Singer MV, Schreiber S, Bocker U. Functional P2X7 receptor polymorphisms (His155Tyr, Arg307Gln, Glu496Ala) in patients with Crohn's disease. Scand J Immunol 2007;65:166–70. https://doi.org/10.1111/j.1365-3083.2006.01876.x.
[106] Neves AR, Castelo-Branco MT, Figliuolo VR, Bernardazzi C, Buongusto F, Yoshimoto A, et al. Overexpression of ATP-activated P2X7 receptors in the intestinal mucosa is implicated in the pathogenesis of Crohn's disease. Inflamm Bowel Dis 2014;20:444–57. https://doi.org/10.1097/01.Mib.0000441201.10454.06.
[107] Wan P, Liu X, Xiong Y, Ren Y, Chen J, Lu N, et al. Extracellular ATP mediates inflammatory responses in colitis via P2 x 7 receptor signaling. Sci Rep 2016;6:19108https://doi.org/10.1038/srep19108.
[108] Marques CC, Castelo-Branco MT, Pacheco RG, Buongusto F, do Rosario Jr. A, Schanaider A, et al. Prophylactic systemic P2X7 receptor blockade prevents experimental colitis. Biochim Biophys Acta 2014;1842:65–78. https://doi.org/10.1016/j.bbadis.2013.10.012.
[109] Hofman P, Cherfils-Vicini J, Bazin M, Ilie M, Juhel T, Hebuterne X, et al. Genetic and pharmacological inactivation of the purinergic P2RX7 receptor dampens inflammation but increases tumor incidence in a mouse model of colitis-associated cancer. Cancer Res 2015;75:835–45. https://doi.org/10.1158/0008-5472.Can-14-1778.
[110] Margolis KG, Stevanovic K, Karamooz N, Li ZS, Ahuja A, D'Autreaux F, et al. Enteric neuronal density contributes to the severity of intestinal inflammation. Gastroenterology. 2011;141:588–98. 98.e1-2 https://doi.org/10.1053/j.gastro.2011.04.047.
[111] Gulbransen BD, Bashashati M, Hirota SA, Gui X, Roberts JA, MacDonald JA, et al. Activation of neuronal P2X7 receptor-pannexin-1 mediates death of enteric neurons during colitis. Nat Med 2012;18:600–4. https://doi.org/10.1038/nm.2679.
[112] Cesaro A, Brest P, Hofman V, Hebuterne X, Wildman S, Ferrua B, et al. Amplification loop of the inflammatory process is induced by P2X7R activation in intestinal epithelial cells in response to neutrophil transepithelial migration. Am J Physiol Gastrointest Liver Physiol 2010;299:G32–42. https://doi.org/10.1152/ajpgi.00282.2009.
[113] Miller CM, Zakrzewski AM, Robinson DP, Fuller SJ, Walker RA, Ikin RJ, et al. Lack of a functioning P2X7 receptor leads to increased susceptibility to Toxoplasmic ileitis. PLoS One. 2015;10:e0129048https://doi.org/10.1371/journal.pone.0129048.
[114] Eser A, Colombel JF, Rutgeerts P, Vermeire S, Vogelsang H, Braddock M, et al. Safety and efficacy of an Oral inhibitor of the Purinergic receptor P2X7 in adult patients with moderately to severely active Crohn's disease: a randomized placebo-controlled, double-blind, phase IIa study. Inflamm Bowel Dis 2015;21:2247–53. https://doi.org/10.1097/mib.0000000000000514.
[115] Garg N, Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. Brain Behav 2015;5:e00362https://doi.org/10.1002/brb3.362.
[116] Sperlagh B, Illes P. P2X7 receptor: an emerging target in central nervous system diseases. Trends Pharmacol Sci 2014;35:537–47. https://doi.org/10.1016/j.tips.2014.08.002.
[117] Narcisse L, Scemes E, Zhao Y, Lee SC, Brosnan CF. The cytokine IL-1beta transiently enhances P2X7 receptor expression and function in human astrocytes. Glia. 2005;49:245–58. https://doi.org/10.1002/glia.20110.
[118] Amadio S, Parisi C, Piras E, Fabbrizio P, Apolloni S, Montilli C, et al. Modulation of P2X7 receptor during inflammation in multiple sclerosis. Front Immunol 2017;8:1529https://doi.org/10.3389/fimmu.2017.01529.
[119] Matute C, Torre I, Perez-Cerda F, Perez-Samartin A, Alberdi E, Etxebarria E, et al. P2X(7) receptor blockade prevents ATP excitotoxicity in oligodendrocytes and ameliorates experimental autoimmune encephalomyelitis. J Neurosci 2007;27:9525–33. https://doi.org/10.1523/jneurosci.0579-07.2007.
[120] Tsunoda I, Fujinami RS. Two models for multiple sclerosis: experimental allergic encephalomyelitis and Theiler's murine encephalomyelitis virus. J Neuropathol Exp Neurol 1996;55:673–86.
[121] Grygorowicz T, Struzynska L, Sulkowski G, Chalimoniuk M, Sulejczak D. Temporal expression of P2X7 purinergic receptor during the course of experimental autoimmune encephalomyelitis. Neurochem Int 2010;57:823–9. https://doi.org/10.1016/j.neuint.2010.08.021.
[122] Grygorowicz T, Sulejczak D, Struzynska L. Expression of purinergic P2X7 receptor in rat brain during the symptomatic phase of experimental autoimmune encephalomyelitis and after recovery of neurological deficits. Acta Neurobiol Exp (Wars) 2011;71:65–73.
[123] Oyanguren-Desez O, Rodriguez-Antiguedad A, Villoslada P, Domercq M, Alberdi E, Matute C. Gain-of-function of P2X7 receptor gene variants in multiple sclerosis. Cell Calcium 2011;50:468–72. https://doi.org/10.1016/j.ceca.2011.08.002.
[124] Gu BJ, Field J, Dutertre S, Ou A, Kilpatrick TJ, Lechner-Scott J, et al. A rare P2X7 variant Arg307Gln with absent pore formation function protects against neuroinflammation in multiple sclerosis. Hum Mol Genet 2015;24:5644–54. https://doi.org/10.1093/hmg/ddv278.
[125] Khalafalla MG, Woods LT, Camden JM, Khan AA, Limesand KH, Petris MJ, et al. P2X7 receptor antagonism prevents IL-1beta release from salivary epithelial cells and reduces inflammation in a mouse model of autoimmune exocrinopathy. J Biol Chem 2017;292:16626–37. https://doi.org/10.1074/jbc.M117.790741.
[126] Xie B, Chen Y, Zhang S, Wu X, Zhang Z, Peng Y, et al. The expression of P2X7 receptors on peripheral blood mononuclear cells in patients with primary Sjogren's syndrome and its correlation with anxiety and depression. Clin Exp Rheumatol 2014;32:354–60.
[127] Yu J, Chen Y, Li M, Gao Q, Peng Y, Gong Q, et al. Paeoniflorin down-regulates ATP-induced inflammatory cytokine production and P2X7R expression on peripheral blood mononuclear cells from patients with primary Sjogren's syndrome. Int Immunopharmacol 2015;28:115–20. https://doi.org/10.1016/j.intimp.2015.05.023.
[128] Baldini C, Rossi C, Ferro F, Santini E, Seccia V, Donati V, et al. The P2X7 receptor-inflammasome complex has a role in modulating the inflammatory response in primary Sjogren's syndrome. J Intern Med 2013;274:480–9. https://doi.org/10.1111/joim.12115.
[129] Woods LT, Camden JM, Batek JM, Petris MJ, Erb L, Weisman GA. P2X7 receptor activation induces inflammatory responses in salivary gland epithelium. Am J Physiol Cell Physiol 2012;303:C790–801. https://doi.org/10.1152/ajpcell.00072.2012.
[130] Geraghty NJ, Mansfield KJ, Fuller SJ, Watson D, Sluyter R. The P2X7 receptor is not essential for development of imiquimod-induced psoriasis-like inflammation in mice. Purinergic Signal 2017;13:405–15. https://doi.org/10.1007/s11302-017-9569-0.
[131] Sticherling M. Psoriasis and autoimmunity. Autoimmun Rev 2016;15:1167–70. https://doi.org/10.1016/j.autrev.2016.09.004.
[132] Zhou L, Qi X, Potashkin JA, Abdul-Karim FW, Gorodeski GI. MicroRNAs miR-186 and miR-150 down-regulate expression of the pro-apoptotic purinergic P2X7 receptor by activation of instability sites at the 3′-untranslated region of the gene that decrease steady-state levels of the transcript. J Biol Chem 2008;283:28274–86. https://doi.org/10.1074/jbc.M802663200.
[133] Denton CP, Khanna D. Systemic sclerosis. Lancet. 2017;390:1685–99. https://doi.org/10.1016/s0140-6736(17)30933-9.
[134] Waters ST, Fu SM, Gaskin F, Deshmukh US, Sung SS, Kannapell CC, et al. NZM2328: a new mouse model of systemic lupus erythematosus with unique genetic susceptibility loci. Clin Immunol 2001;100:372–83. https://doi.org/10.1006/clim.2001.5079.
[135] Labasi JM, Petrushova N, Donovan C, McCurdy S, Lira P, Payette MM, et al. Absence of the P2X7 receptor alters leukocyte function and attenuates an inflammatory response. J Immunol 2002;168:6436–45.
[136] Keystone EC, Wang MM, Layton M, Hollis S, McInnes IB. Clinical evaluation of the efficacy of the P2X7 purinergic receptor antagonist AZD9056 on the signs and symptoms of rheumatoid arthritis in patients with active disease despite treatment with methotrexate or sulphasalazine. Ann Rheum Dis 2012;71:1630–5. https://doi.org/10.1136/annrheumdis-2011-143578.
[137] Stock TC, Bloom BJ, Wei N, Ishaq S, Park W, Wang X, et al. Efficacy and safety of CE-224,535, an antagonist of P2X7 receptor, in treatment of patients with rheumatoid arthritis inadequately controlled by methotrexate. J Rheumatol 2012;39:720–7. https://doi.org/10.3899/jrheum.110874.
[138] Kasuya G, Yamaura T, Ma XB, Nakamura R, Takemoto M, Nagumo H, et al. Structural insights into the competitive inhibition of the ATP-gated P2X receptor channel. Nat Commun 2017;8:876https://doi.org/10.1038/s41467-017-00887-9.
[139] Donnelly-Roberts DL, Jarvis MF. Discovery of P2X7 receptor-selective antagonists offers new insights into P2X7 receptor function and indicates a role in chronic pain states. Br J Pharmacol 2007;151:571–9. https://doi.org/10.1038/sj.bjp.0707265.
[140] Bartlett R, Stokes L, Sluyter R. The P2X7 receptor channel: recent developments and the use of P2X7 antagonists in models of disease. Pharmacol Rev 2014;66:638–75. https://doi.org/10.1124/pr.113.008003.