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Review

Purinergic P2X7R expressed on regulatory T cells potentially links molecular mimicry to autoimmune responses

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Abstract: The immune system is meant to protect against invading microbes. Although this system is effective against many microbes, some can use molecular mimicry to turn the immune system against the host and activate autoimmune responses. The resulting autoimmunity has significant implications for public health and healthcare costs. It is well known that regulatory T cells (Tregs) are crucial for self-tolerance and that their function is impaired after exposure to self-antigens or antigens with molecular mimicry, leading to the activation of autoimmune responses. How molecular mimicry disrupts Tregs in this manner remains under debate. This review contributes to the field of the pathogenesis of autoimmunity by proposing that purinergic signaling in the lymph nodes, with extracellular ATP, ADP, and adenosine as ligands, plays a pivotal role in this process. Repeated or high-dose microbial infection causes the release of large amounts of extracellular ATP sufficient to reach the threshold of extracellular ATP levels for activating P2X7 purinergic receptors (P2X7Rs) on dendritic cells and Tregs. This hampers the ability of Tregs to suppress autoimmune responses. Crucially, P2X7Rs are activated at very high extracellular ATP levels, thus only after repeated or high-dose infection with microbes. Arguably, in contrast to the rapid elimination of microbes with foreign antigens, the clearance of invading microbes that employ molecular mimicry requires the activation of P2X7Rs at the expense of self-tolerance. Because all processes required to activate autoimmune responses occur in secondary lymphoid organs, this article hypothesizes that, contrary to current convention, microbes do not need to enter organs to initiate autoimmunity. However, some types of microbes can prevent P2X7R-induced Treg disruption by converting extracellular ATP to adenosine, mitigating autoimmune responses resulting in chronic diseases with less severe inflammation. The

proposed hypothesized mechanism has potential implications for the understanding and treatment of autoimmune disorders.

Keywords: P2X7R; purinergic signaling; extracellular ATP; Tregs; Bregs; self-tolerance; molecular mimicry; autoimmune responses

1. Introduction

Autoimmune disorders have a major impact on the daily lives of patients and their families, as well as on public health. With their rapidly increasing prevalence, autoimmune disorders also contribute to rising healthcare costs [1]. Therefore, understanding the mechanism by which autoimmunity develops is essential and urgently needed [1]. Currently, the development of autoimmunity is attributed to a complex interaction of multiple genetic and environmental risk factors, including microbial infections [1]. In this review, I will discuss the link between microbes that mimic human antigens and autoimmunity.

The immune system should be the best ally of the host. It successfully protects against many microbes when they attempt to invade the body and proliferate in host cells. For example, Newcastle disease virus (NDV) can be a ruthless killer in birds [2] but only causes transient inflammation of the local mucosa at its entry site and flu-like symptoms in humans (avian pseudopest) [3,4]. However, numerous microbes can manipulate the immune system by mimicking host antigens (molecular mimicry). These microbes cause the best ally of the host to turn against itself [5–8]. It is no surprise that these microbes are strongly related to autoimmune disorders [9].

Recently, in the context of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, autoantibodies (antibodies specific for self-antigens) associated with viral infections have attracted increasing attention. However, interactions between autoantibodies and microbial infections have long been known to occur. The first hypothesis that there was an autoimmune response in the form of autoantibodies in patients with syphilis dates back to 1909 [10]. Later, in 1934, researchers found brain-specific antibodies (autoantibodies) in rabbits. These autoantibodies were induced by injections of a fresh rabbit brain emulsion and an emulsion of brain tissue infected with a vaccine virus [11]. A few years later, in 1945, autoantibodies directed against infected liver and normal liver tissue were observed in rhesus monkeys vaccinated against yellow fever [12]. Additionally, autoantibodies specific for the human heart were found in the majority of patients with streptococcal rheumatic fever in 1945 [13].

Since then, advances in immunology have shown that autoreactive T cells play a key role in autoimmune responses [14,15]. The basic concept is that the immune system manages precursors of autoreactive T cells in the thymus (thymocytes) by eliminating the clones with the strongest responses (thymic clonal deletion) or by directing them to become regulatory T cells (Tregs) that can control the remaining autoreactive T cells [16]. However, it has become clear that molecular mimicry can disrupt the control of autoreactive T cells. Microbes that employ molecular mimicry harbor antigens with sufficient similarity to the host's antigens to be recognized as self-antigens.

There is ample evidence from research in humans and animals and *in vitro* studies to support the role of molecular mimicry in the development of autoimmune disorders [5,17–20]. However, the

precise mechanism by which molecular mimicry can cause the immune system to lose its ability to promote self-tolerance has not yet been fully clarified and is therefore still debated [1,6,9,21]. This review attempts to contribute to the understanding of the mechanism of autoimmune responses by proposing a link between microbial molecular mimicry and autoimmune responses. This approach is based on the relatively newly understood immunobiological effects of purinergic signaling (see the graphical abstract in Figure 1).

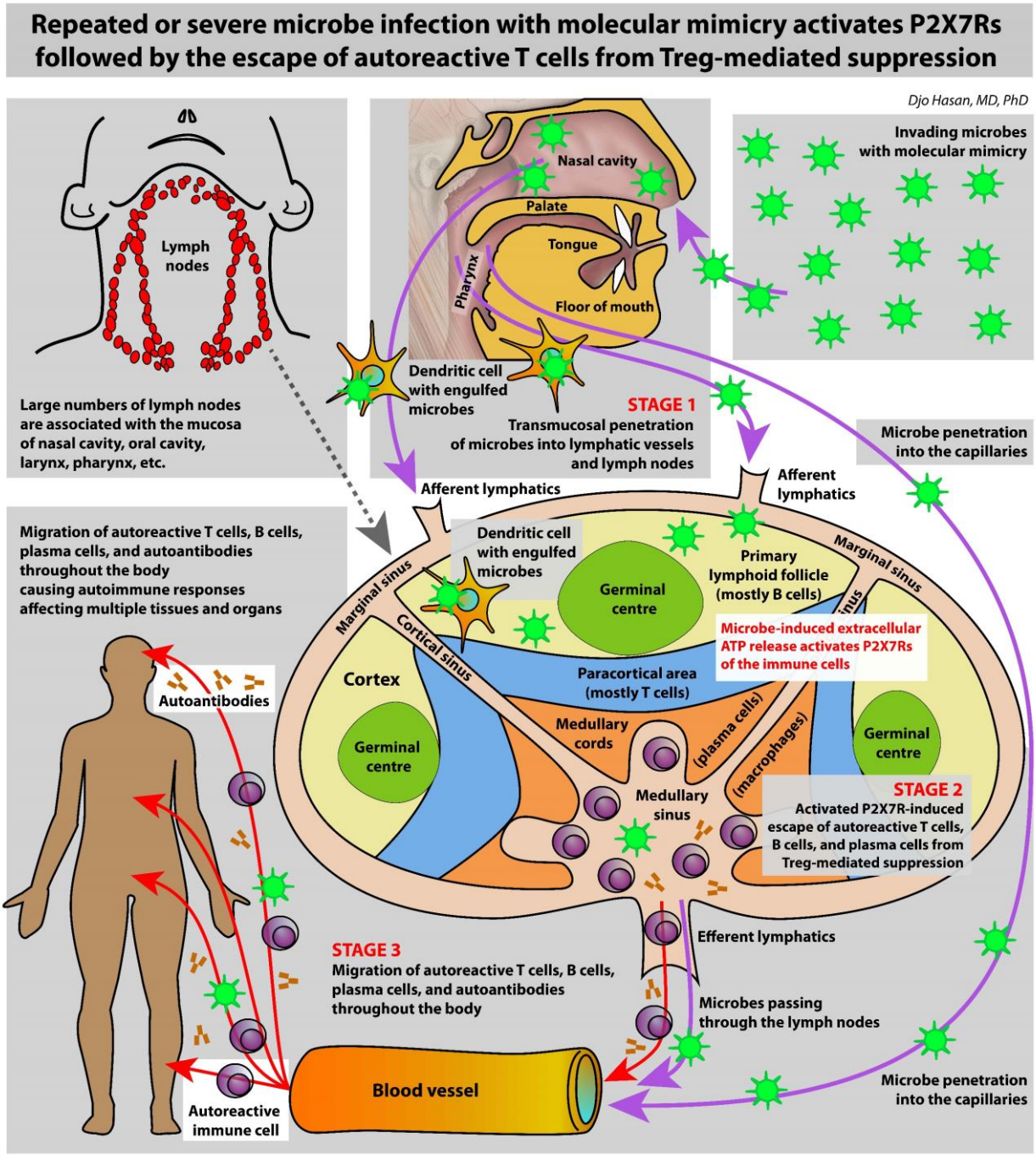

Figure 1. Graphical abstract showing how the purinergic receptor P2X7R putatively links molecular mimicry with autoimmune responses. Tregs are known to maintain self-tolerance by controlling autoreactive lymphocytes, and activation of their P2X7Rs impairs the number

and, more importantly, the suppressive function of Tregs. This occurs only at high extracellular ATP levels resulting from repeated or high-dose infection with these microbes and allows autoreactive T cells and B cells to escape Treg suppression and activate autoimmune responses with autoantibody production. Subsequently, these autoreactive immune cells migrate via systemic circulation and cause tissue damage in the body, depending on the self-antigens they mimic. Therefore, the defense against invading microbes that are sufficiently similar to human antigens to be recognized as self-antigens by the human immune system (molecular mimicry) requires activation of P2X7Rs on immune cells at the expense of self-tolerance. Source: The figure was extensively modified from Hasan D et al. (2022) [22] under the Creative Commons Attribution License CC BY 4.0, with permission.

2. Control of autoimmune responses by Tregs

In 1955, Jerne postulated that immunoglobulins could react with any antigen except for host antigens (self-antigens) because these antibodies are supposed to be eliminated (via clonal selection) [23]. Building on this hypothesis, Burnet hypothesized in 1957, using the concept of clonal selection, that it is not autoreactive antibodies but rather autoreactive lymphocytes that are eliminated [24,25].

2.1. Control of autoreactive T cells: Clonal deletion and Treg suppression

Tregs are known to maintain self-tolerance by controlling autoreactive lymphocytes. They are essential for the prevention of autoimmune disorders [26,27]. Currently, the mechanisms of self-tolerance and activation of autoimmune responses are known to be complex [16], as illustrated in Figure 2. Although autoreactive thymocytes (T cell precursors) with high autoreactive T cell receptor (TCR)-peptide-MHC affinity or peptide-MHC density [the major histocompatibility complex (MHC) in mammals corresponds to human leukocyte antigen (HLA) in humans] are clonally deleted in the thymus, autoreactive thymocytes with intermediate autoreactive TCR-peptide-MHC affinity or peptide-MHC density are diverted to Tregs [16] (Figure 2B). However, a substantial proportion of autoreactive thymocytes escape from clonal deletion in the thymic cortex and medulla by dodging thymic negative selection due to their dual αβ TCR expression [28–31]. Tregs suppress these autoreactive T cells to prevent the activation of autoimmune responses (Figure 2C) [16,32–35]. Similar to autoreactive T cells, a proportion of autoreactive B cells also escape deletion in the bone marrow [36,37]. This is probably due to altered BCR/TLR signaling through coreceptor B cell–activating factor receptor (BAFFR) and/or coreceptor CD40 because of the presence of a single-nucleotide polymorphism (C1858T; R620W) in protein tyrosine phosphatase nonreceptor type 22 ($PTPN22^{R620W}$) [36,37]. These autoreactive B cells give rise to plasma cells that produce autoantibodies [38,39]. Fortunately, Treg suppression is not limited to autoreactive T cells. Additionally, autoreactive B cells and the production of autoantibodies—a sensitive indicator of the activation of autoimmune responses [40,41]—are controlled by Tregs and by follicular regulatory T cells (Tfrs) [42,43].

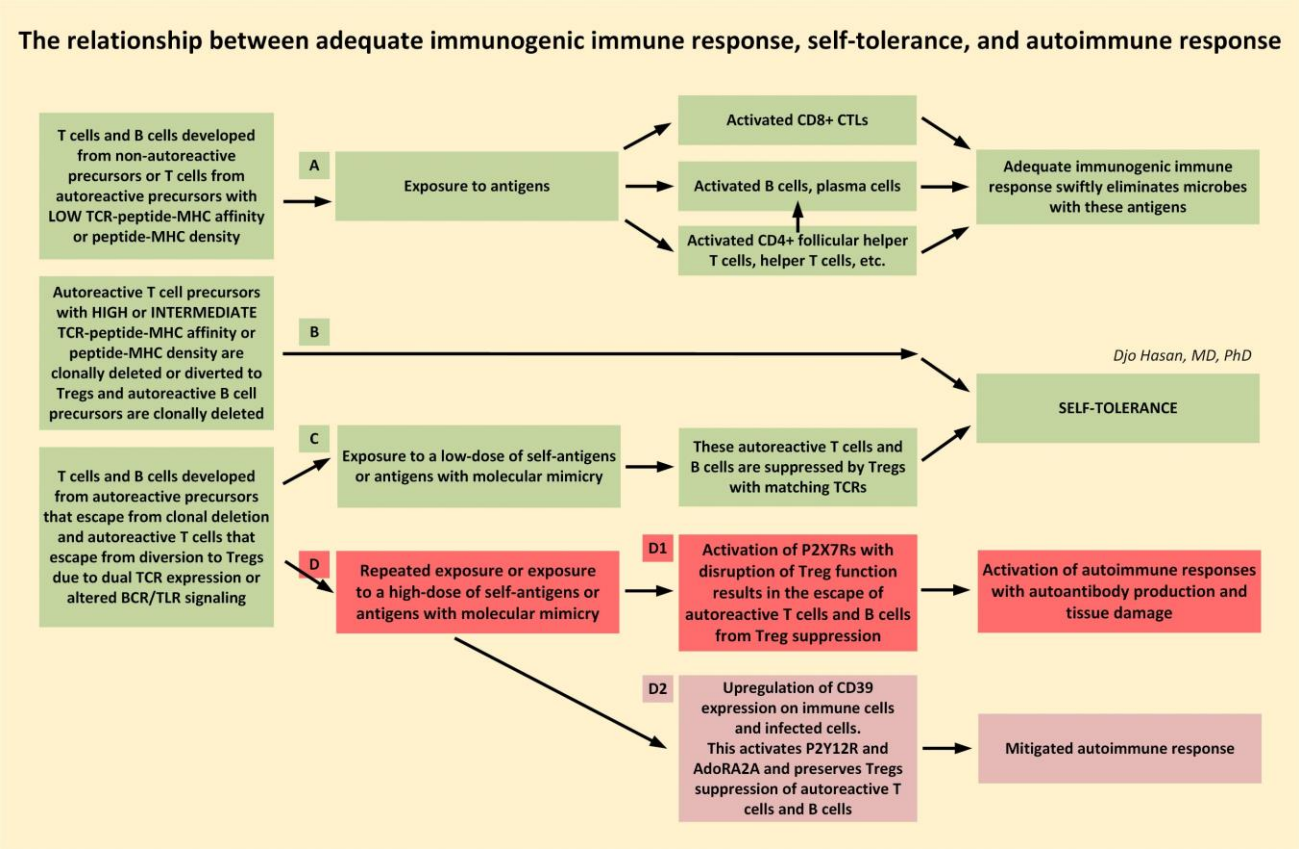

Figure 2. Graphical representation of the putative relationships among adequate immunogenic immune response, self-tolerance, and autoimmune response. A) T cells and B cells develop from nonautoreactive precursors or precursors with low autoreactive TCR-peptide-MHC affinity or low peptide-MHC density following the classic pathway of epitope presentation by antigen-presenting cells (especially DCs), leading to T cell and B cell activation. This allows the immune system to rapidly eliminate invading microbes. B) Autoreactive T cell precursors with high TCR-peptide-MHC affinity or high peptide-MHC density are clonally deleted or diverted to Tregs in the thymus. In addition, autoreactive B cell precursors are clonally deleted in the bone marrow. C) However, due to dual TCR expression or altered BCR/TLR signaling, a proportion of these autoreactive T cell and B cell precursors escape from clonal deletion, and a proportion of autoreactive T cell precursors fail to be diverted to Tregs. The damaging activities of these cells are constantly suppressed by Tregs. D1) However, this protection mechanism is not as robust as protection by means of thymic clonal deletion; certain circumstances (repeated exposure or exposure to a high load of antigens) can lead to the activation of the purinergic P2X7Rs of Tregs and DCs, followed by the disruption of Treg suppressive function. This enables autoreactive T cells to escape Treg suppression—a powerful trigger for the activation of autoimmune responses of the adaptive immune system. D2) Some microbes have a special trick up their sleeves: They encode proteins that upregulate the expression of the ectoenzyme CD39 in infected cells, including immune cells. This decreases the levels of extracellular ATP by converting ATP to ADP and adenosine, activating P2Y12Rs and AdoRA2As in Tregs and conserving their ability to mitigate autoimmune responses. Green

text boxes indicate a state in which autoimmune responses are not activated; red text boxes indicate a state in which autoimmune responses are activated; and pink text boxes indicate a state in which activated autoimmune responses are mitigated. DCs: dendritic cells; P2X7R: purinergic P2X7 receptor; P2Y12R: purinergic P2Y12 receptor; AdoRA2A: adenosine receptor A2A; TCR: T cell receptor; Tregs: regulatory T cells; MHC: major histocompatibility complex; CD39: ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD 1).

2.2. The importance of memory Tregs

Self-antigen-specific Tregs are consistently induced in the thymus [16] and in secondary lymphoid organs [44,45]. Notably, T cells need continuous TCR signaling to remain viable. When TCR signaling decreases because antigen levels decrease, such as during the contraction phase after an immune response, the cells undergo apoptosis. This also applies to Tregs. Self-antigens are structural parts of our body. It is obvious that the ability of Tregs to promote self-tolerance and protect against autoreactive T cells must have existed from the beginning of life. Because memory Tregs can escape from apoptosis during the contraction phase of an immune response, they do not need continuous TCR signaling to survive and do not proliferate. Thus, memory Tregs can persist for decades in infected peripheral sites or secondary lymphoid organs, ensuring durable maintenance of self-tolerance [46–49]. It is therefore essential that a significant proportion of Tregs are memory Tregs.

2.3. Autoreactivity of Treg TCRs

It makes sense that to specifically suppress autoreactive T cells, Treg TCRs must be able to recognize epitopes of self-antigens and hence must be autoreactive [50,51]. At first glance, reports of Tregs specific to microbes (such as *Mycobacterium vaccae* [52], *Leishmania major* [53,54], *Candida albicans* [55], *Bordetella pertussis* [56], and *Helicobacter hepaticus* [57]) and to alloantigens [58,59] seem to challenge the self-reactive nature of Tregs. However, at a closer look, it appears that all these microbes [60–67] and alloantigens [68–70] harbor pentamer peptides that have a sufficient degree of similarity to human antigens to be recognized as self-antigens by the human immune system (molecular mimicry) [71]. This also applies to a report that used a naïve T cell hybridoma and a Treg hybridoma from transgenic mice with a very limited TCR repertoire (a single Ea52–68 peptide) and analyzed hundreds of TCRs derived from Tregs. That report concluded that there is evidence opposing the tendency of Tregs to self-react [72]. However, this finding is under scrutiny and is disputed because the reported self-reactivity of the T cell hybridoma and Treg hybridoma may be below the threshold of detection [73]. Therefore, it is still reasonable to believe that Tregs are truly autoreactive.

2.4. Treg tools for maintaining self-tolerance

Tregs have several tools at their disposal to complete the important task of suppressing autoreactive T cells [74]. Tregs can secrete anti-inflammatory cytokines (IL-10, IL-35, and TGF-β) that inhibit autoreactive effector T cell function. Tregs can use cytotoxic serine proteases in their cytoplasmic granules to destroy autoreactive T cells (leading to apoptosis) by "drilling" a hole through the cell membrane using the enzyme perforin and delivering deadly content. In addition, Tregs can cause metabolic disruption by depriving autoreactive T cells of IL-2 and by hydrolyzing extracellular

ATP to adenosine to suppress autoreactive T cell function. Tregs can also target DCs through the binding of their cytotoxic T lymphocyte–associated protein 4 (CTLA-4) to the CD80/CD86 receptor on DCs. This induces the production of immunosuppressive indoleamine 2,3-dioxygenase (IDO) by DCs. Finally, Tregs can inhibit the maturation and function of DCs through the interaction of immunosuppressive LAG-3 molecules on Tregs with membrane-bound MHC class II molecules on DCs [74]. It is clear that Treg tools are sufficiently powerful to destroy autoreactive T cells and effectively control the activation of autoimmune responses.

2.5. Regulatory B cells (Bregs)

In addition to Tregs, Bregs also exist. Bregs differentiate from B cells and/or from immature B cells [75,76], and some authors have reported that regulatory Tfh cells in patients with hepatitis B infection [77] and Tfrs in ARDS [78] induce the differentiation of Bregs. Tfrs are controlled by Tregs [42,75]; thus, the loss of Tregs affects the number and function of Bregs. Bregs contribute to immune suppression by producing soluble anti-inflammatory cytokines (IL-10, TGF-β, IL-35, and adenosine) [75,79–82]. Bregs express several immunosuppressive surface molecules, such as CD1d, programmed cell death protein ligand 1 (PD-L1) [83], Fas ligand (FasL or CD95L) [84], and even T cell immunoglobulin and mucin domain 1 (TIM-1), in selected populations of Bregs [85]. Additionally, Bregs can induce the expansion of Tregs and the inhibition of Th17 cells [86–88]. Bregs can also release cytotoxic serine proteases [granzyme B (GrB)] after cell-to-cell contact and perforin-mediated plasma membrane perforation. The anti-inflammatory mechanism of these GrB^+ Bregs involves inhibiting the proliferation of $CD4^+$ T cells [89,90] and the activation of Th1 and Th17 cells [91].

Thus, Tregs and Bregs play crucial roles in maintaining self-tolerance. Because Tregs and Bregs produce and release the anti-inflammatory cytokines IL-10, IL-35, TGF-β, and adenosine, the proinflammatory activity of innate immune cells [neutrophils, mast cells, macrophages, natural killer (NK) cells, etc.] is also suppressed near Tregs and Bregs [92–94].

2.6. Treg-mediated protection against autoimmunity is not perfect

A key idea in self-tolerance research is that the protective effect of Tregs is not as robust as that of thymic clonal deletion. Although moderate antigen loads increase the number and suppressive function of Tregs [33], specific circumstances (such as repeated self-antigen exposure or high self-antigen loads) can lead to the escape of autoreactive T cells from normal suppression by Tregs [32–35]. This occurs via impairment of the suppressive function of Tregs rather than via reduced Treg numbers [32,34,35] (Figure 2D1), which inevitably leads to the activation of autoimmune responses. Conveniently, this activation results in the expression of autoantibodies [40,41], which can be measured in clinical settings, as illustrated in a recent report on patients with moderate and severe traumatic brain injury (TBI) [95]. It is reasonable to assume that in these patients, high systemic levels of free self-antigens from damaged brain tissue are sufficient to hamper Treg suppressive function. That paper described the upregulation of IgM and IgG autoantibodies in the first week, and this change persisted for several years in the majority of patients. These autoantibodies were specific to self-antigens in brain tissue, such as myelin-associated glycopeptide (MAG), myelin basic protein (MBP), paraneoplastic Ma antigen 2 (PNMA2), tight junction protein 1 (TJP1), claudin 5 (CLDN5), zinc finger protein 397 (ZNF397), and selectin E (SELE). Additionally, autoantibodies to thyroid-specific thyroid

stimulating hormone receptor (TSHR) [95] and autoantibodies to ubiquitous self-antigens, such as collagen type V alpha 2 chain (COL5A2), gamma-aminobutyric acid type A receptor subunit beta3 (GABRB3), and angiotensin I-converting enzyme (ACE), were observed. Autoantibodies in TBI patients have also been reported by other authors [96–98], and some authors have suggested that the presence of autoantibodies is associated with worse outcomes and may predict late post-TBI neurodegeneration [95,97,98]. A remarkable paper described the association of the presence of autoantibodies in the pituitary and hypothalamus with inflammation and persistent male hypogonadotropic hypogonadism after TBI [99]. Moreover, autoantibodies have been reported after spinal cord injury [100–102], and these autoantibodies are correlated with elevated serum proinflammatory cytokine levels [103,104].

Overall, extensive (traumatic) tissue damage can induce autoimmune responses with increased autoantibody levels, presumably due to a high load of free self-antigens. Some microbes have reportedly developed the ability to mimic human self-antigens [71]. This provides them with immune camouflage when they enter the human body. In addition, high systemic levels of these antigens may also interfere with Treg suppressive function and activate autoimmune responses.

3. Microbes that exhibit molecular mimicry can regulate Tregs and activate autoimmune responses

Microbes have developed a clever method to evade recognition by our adaptive immune system. Although many microbial antigens do not exhibit molecular mimicry, some antigens may exhibit such mimicry [71]. Available data suggest that invading microbes (such as viruses, bacteria, and fungi) that possess antigenic cross-reactivity with human self-antigens and human autoreactive TCRs and BCRs have the potential to disrupt the control of autoreactivity. A paper published in 2001 reported an interesting experiment in mice infected with herpes simplex virus type 1 strain KOS (HSV-1 KOS) [105]. The cause of corneal damage [herpes stromal keratitis (HSK)] after HSV-1 KOS infection was identified as the UL6 peptide of the virus. This protein exhibits molecular mimicry with mouse corneal self-antigens. The researchers generated a replication-competent HSV-1 KOS mutant with a single amino acid substitution in the UL6 peptide ($UL6^{S309L}$). Although wild-type (WT) HSV-1 KOS infection induced HSK at a specific dose, mutant HSV-1 KOS infection induced HSK only at a 1000-fold greater dose. These high doses are not typically observed in nature. On day 5, when the virus was still present, the histopathology of the damaged cornea in mice infected with mutant and WT HSV-1 KOS was comparable. By day 10, when the virus was no longer present, the corneal pathology in mice infected with the mutant virus was clearly reduced, and the pathology resolved on day 15 in these mice. In contrast, the corneal pathology in mice infected with the WT virus became progressively worse, presumably due to the activation of autoimmune responses [105]. In addition, researchers have developed transgenic mice that generate monoclonal $CD4^+$ T cells that exclusively recognize UL-6 (C1-6 mice) and mice that generate $CD4^+$ T cells that exclusively recognize ovalbumin (OVA mice). WT HSV-1 KOS infection caused HSK in C1-6 mice but not in OVA mice. Thus, molecular mimicry appears to play a crucial role in the development of microbe-induced HSK [105].

3.1. Putative relationships between adequate immunogenic immune response, self-tolerance, and autoimmune response

If invading microbes harbor non-self-antigens (foreign antigens), the microbes are swiftly eliminated, and inflammation is limited (Figure 2A). Even if an invading microbe exhibits molecular mimicry, it is unlikely that all of its antigens are similar to human antigens (these antigens that differ from human antigens are regarded as foreign). A mixture of foreign antigens and antigens with molecular mimicry is more likely. Hence, even at low infection doses, these foreign antigens may induce a proinflammatory response that clears the pathogen and infected cells (Figure 2A). Presumably, this occurs without disturbing Tregs because, at low levels of antigens with molecular mimicry, autoreactive T cells remain under Treg suppression (Figure 2C). This is a clever mechanism that stops low-dose infection by microbes with molecular mimicry from evading human adaptive immune surveillance.

In contrast, repeated or high-dose infection with microbes harboring antigens that exhibit molecular mimicry simulates repeated exposure to self-antigens or exposure to a high load of self-antigens. In this case, the suppressive function of Treg is decreased, activating autoimmune responses [32–35] characterized by the production of autoantibodies [41,43,75,106–109] (Figures 1 and 2D1). Hence, microbes harboring antigens with molecular mimicry cannot be eliminated easily. Autoreactive T cells must escape Treg suppression before they can attack the invading pathogen. I propose that this type of microbe can only be eliminated at the expense of self-tolerance.

Remarkably, this hypothesis corresponds with an extraordinary but long-forgotten finding that was reported in 1945 [110–113]. In rabbits, 7–14 days after a single injection of rabbit kidney emulsion plus *Staphylococcus*, a low incidence of proteinuria, casts and red cells in the urine, and serum autoantibodies to kidney tissue were observed. However, after repeated injections of the emulsion, the incidence of urinary changes corresponding to nephritis increased dramatically, reaching 100%.

Molecular mimicry of vaccine antigens has also been reported [114,115], and the recent pandemic provides an example of this concept in medical practice. Reportedly, in 22 healthy individuals who received at least two SARS-CoV-2 mRNA–based vaccines, the number of SARS-CoV-2 spike-specific Tregs in the peripheral blood mononuclear cell population increased. In addition, these individuals developed SARS-CoV-2 spike-specific Treg memory cells [116]. Indeed, secondary infection can quickly activate memory Tregs and cause a rapid Treg response to prevent tissue damage caused by autoimmune responses [46,47]. This observation is consistent with the finding that in many patients, autoreactivity (in the form of autoantibodies) was not observed after administration of the SARS-CoV-2 mRNA vaccine [117]. However, in other patients, autoantibody formation after SARS-CoV-2 vaccination (including mRNA-based vaccines) was observed [118–121]. In a few patients, this was accompanied by severe autoimmune symptoms such as thrombotic thrombocytopenia [119,122] or pericarditis [123–125]. In addition, in patients with severe COVID-19, both increased Treg numbers [126–129] and reduced Treg numbers [130–134], including reduced SARS-CoV-2-reactive Treg numbers [135], have been reported.

Thus, vaccination with antigens or infection with microbes that exhibit molecular mimicry may prevent autoimmune responses in some patients but induce autoimmune responses in other patients. The available data suggest that autoimmune responses can be induced by repeated or high-dose microbe infection, by a high-dose of vaccine antigens or by vaccination shortly after microbial infection.

4. Purinergic signaling

Microbes harboring molecular mimics can evade immunosurveillance at low antigen loads and can activate autoimmune responses after repeated exposure to antigens or at high antigen loads [9,17–21,136,137]. However, the underlying mechanism is unclear. Recent advances in the study of purinergic signaling in the context of immunobiology have made it clear that purinergic receptors on immune cells play a pivotal role in the activation of autoimmune responses [138,139]. This may partially explain the mechanism of microbe-induced autoimmune responses.

4.1. Introduction to purinergic signaling

Adenosine and nucleotide molecules were discovered between 1929 and 1936 [140,141]. In 1939, researchers attributed the ability to transport intracellular energy to ATP [142–145]. In 1948 and 1959, it was discovered that extracellular ATP functions differently from intracellular ATP, namely through intercellular signaling (communication between cells) [146,147], which was later termed purinergic signaling. Geoffrey Burnstock was the first to describe purinergic co-transmission in neurons in 1972 [148]. Almost 20 years passed before the relevance of purinergic signaling became widely accepted [149,150]. The ever-so-important P2X7R (initially named P2Z receptor) was identified and cloned by researchers in Geneva, Switzerland [151], and was first reported by researchers at the University of Ferrara, Italy, in 1995 [152].

Purinergic signaling is indispensable for intercellular signaling in mammals [150,153,154]. A total of four adenosine receptors (AdoRs), seven P2X purinergic receptors (P2XRs), and eight P2Y purinergic receptors (P2YRs) have been identified [155–159] (Table 1). These receptors are expressed in almost every cell in the body. The effect of the activation of purinergic receptors depends, among other factors, on the type of receptor activated and the type of cell where the receptor is located [154]. For example, P2X7Rs play a key role in the physiological functions of several organs, such as electrical signaling in the central and peripheral nervous systems [160,161], surfactant release in the lungs [162–164], mucin production in the airways [165], and insulin release in pancreatic islet beta cells [166,167]. This paper focuses on the effect of the activation of purinergic signaling in immune cells, particularly the effect of the activation of P2X7Rs in the immune system.

4.2. Purinergic signaling in immunity

Purinergic signaling, which involves all related ligands (ATP, ADP, UTP, adenosine, etc.) and all related receptors except P2X6Rs, is crucial for the regulation of inflammation [22,168–172]. Some receptors are involved in proinflammatory responses, some are involved in anti-inflammatory effects, and others may be involved in both responses [22,168–172]. For example, the activation of AdoRs by adenosine may promote an immune response in some cells; however, in general, it suppresses the activation of immune responses (Table 2, rows 1–3). In contrast, P2X7Rs are not involved in anti-inflammatory responses, and they stand out from other purinergic receptors [22,152,171,172].

Table 1. Purinergic receptors and their ligands. ATP: adenosine triphosphate; ADP: adenosine diphosphate; UTP: uridine triphosphate; UDP: uridine diphosphate; AdoR: adenosine receptor; P2XRs and P2YRs: purinergic nucleotide receptors.

Purinergic receptors and their ligands [155–159]	
Natural ligands	Receptors
Adenosine	AdoRA1, AdoRA2A, AdoRA2B, and AdoR3
ATP	P2X1R, P2X2R, P2X3R, P2X4R, P2X5R, P2X7R, and P2Y11R
ADP	P2Y12R
ADP and ATP (ADP > ATP)	P2Y1R and P2Y13R
UDP, UTP, and ATP (UDP > UTP >> ATP)	P2Y6R
UDP	P2Y14R
UTP and ATP (UTP > ATP)	P2Y2R and P2Y4R
ATP	P2X6R molecules are mostly retained in the endoplasmic reticulum. They do not exit the endoplasmic reticulum as a homopolymer but do so as a heteropolymer (with P2X2R and/or P2X4R) or after enhanced glycosylation-induced improved trafficking of P2X6R homopolymers. After exiting the endoplasmic reticulum and becoming inserted into the cell membrane, P2X6R can be activated by extracellular ATP.

Table 2. Examples of the effects of extracellular adenosine, ATP, and ADP on selected immune cells through three purinergic receptors. CGS-21680: Specific AdoRA2A agonist; NECA: 5'-N-ethylcarboxamide adenosine, an agonist of AdoRA2A, AdoRA1, and AdoRA3; oATP: periodate-oxidized ATP (P2X7R antagonist); Treg: regulatory T cell; DCs: dendritic cells; AdoR: adenosine receptor; IFN-β: interferon beta; FoxP3: Forkhead box P3; CTL: cytotoxic T lymphocyte; Th: T helper cell; Th17: IL-17-secreting T helper cell; CTLA-4: cytotoxic T lymphocyte-associated protein 4 (CD152); CD39: nucleoside triphosphate diphosphohydrolase 1 (NTPD1); CD73: 5'-nucleotidase (5'-NT); TCR: T cell receptor; ART2-P2X7 pathway: extracellular NAD^+-induced ATP-independent p2X7R activation involving ADP-ribosyltransferase 2; STAT-1: signal transducer and activator of transcription 1; GVHD: graft-versus-host disease; WT: wildtype. Source: Modified table from Hasan D et al. (2022) [22] and Hasan D et al. (2017) [162] under the Creative Commons Attribution License CC BY 4.0, with permission.

Examples of the effects of extracellular adenosine, ATP, and ADP on select immune cells through the activation of three purinergic receptors (AdoRA2A, P2X7R, and P2Y12R)					
Row number	Receptor	Ligand [149]	Immune cell type or experimental model	Results of receptor signaling	Reference number
1	AdorA2A	CGS-21680	Mouse naïve T cells	Promotes differentiation toward $CD4^+FoxP3^+Lag3^+$ Tregs, inhibits Th1 and Th17 differentiation, inhibits IL-6 secretion, and increases TGF-β secretion.	[173]
2		CGS-21680 and NECA	Mouse $CD4^+CD25^+FoxP3^+$ Tregs	Increases the number of Tregs and increases CTLA-4 receptor expression. Upregulates expression of the ectoenzymes CD39 and CD73, accelerating adenosine generation from extracellular ATP.	[174]
3		Adenosine	Human $CD4^+CD25^+CD127low/-$Tregs and $CD8^+$ T cells	Tregs from gastric cancer patients hydrolyze ATP to generate adenosine. Adenosine synthesized by Tregs promotes apoptosis and suppresses the proliferation of $CD8^+$ T cells. Tregs reduce $CD8^+$ T cell activity by promoting cAMP synthesis. Tregs inhibit the immune function of $CD8^+$ T cells through the AdoRA2A pathway.	[175]
4	P2X7R	Inactivated state in the absence of ATP	Macrophages and P2X7R-transfected HEK-293 cells	P2X7 is a scavenger receptor for apoptotic cells in the absence of its ligand ATP.	[176,177]
5	P2X7R	ATP-release channel	Alveolar epithelial type I cells (AT I cells), murine osteoclast cells, murine neuroblastoma cells, astrocytic cell line, murine astrocytes, and B16 melanoma cells	Release ATP after mechanical deformation (AT I cells), spontaneously (osteoblast cells), after activation (neuroblastoma cells, astrocytic cell line), and after γ irradiation (melanoma cells).	[178–183]
6			Mouse 3T3 fibroblasts	P2X7R-mediated ATP secretion is accompanied by depletion of cytosolic ATP.	[184]

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Examples of the effects of extracellular adenosine, ATP, and ADP on select immune cells through the activation of three purinergic receptors (AdoRA2A, P2X7R, and P2Y12R)

Row number	Receptor	Ligand [149]	Immune cell type or experimental model	Results of receptor signaling	Reference number
7			Bone marrow–derived DCs from WT mice and Panx1−/− C57BL/6 mice	Upon stimulation of the P2X7 receptor by ATP, Panx-1 contributes to rapid DC motility by increasing the permeability of the plasma membrane, which results in supplementary ATP release.	[185]
8			Murine macrophages and RAW 264.7 macrophages	Infection with *Leishmania donovani* substantially increases extracellular release of ATP.	[186]
9			A549 alveolar epithelial cells	Infection with human rhinovirus RV-16 increases basal extracellular ATP release and ATP release after a second stimulation by hypotonic and isotonic solutions.	[187]
10			Mouse influenza model	Influenza infection increases plasma ATP levels 3-fold and pulmonary ATP levels 5-fold.	[188]
11			RAW 264.7 macrophages and L929 fibroblasts	Infection with vesicular stomatitis virus (VSV) increases extracellular ATP in a time-dependent manner.	[189]
12	P2X7R	ATP, low tonic basal activation	HEK 293 and HELA cells	Increases mitochondrial calcium level, membrane potential, and cellular ATP levels, and promotes serum-independent growth. This process requires an intact pore-forming function.	[190]
13			*In vitro* scratch wound assay with HaCat cells (human skin keratinocytes)	Medium hyaluronan fragment (MMW-HA, between 100 and 300 kD) increases expression of the tight junction protein ZO-1 and induces a low activation of the P2X7 receptor, resulting in improved closure of the wound. This is accompanied by pore formation, as shown with Yo-Pro-1 cellular uptake. The P2X7R antagonist brilliant blue G (BBG) completely inhibits this process.	[191]
14			HEK293 and NIH3T3 cells	Increases the $Ca2^{+}$ content of the endoplasmic reticulum, activates NFATc1, and protects from apoptosis.	[192]
15			PC3 cells LNCaP, Kelly, RPMI-8226, DU145, and SK-MEL-5 cells	Drives the expression of nfP2X7, a key mediator of cell survival.	[193]
16			Human osteoclast-like cells	Promotes an increase in extracellular adenosine concentrations.	[194]

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Examples of the effects of extracellular adenosine, ATP, and ADP on select immune cells through the activation of three purinergic receptors (AdoRA2A, P2X7R, and P2Y12R)

Row number	Receptor	Ligand [149]	Immune cell type or experimental model	Results of receptor signaling	Reference number
17			HEK293 cells	Initiates anaerobic glycolysis independent of the oxygen content. Upregulates glucose transporter Glut1 (thus enhancing intracellular glycogen stores). Upregulates glycolytic enzymes (PFK, G3PDH, PKM2), phosphorylated Akt/PKB, and hypoxia-inducible factor 1a (HIF-1a) expression. Impedes the Krebs cycle independent of oxygen concentrations by promoting pyruvate dehydrogenase kinase 1 (PDHK1) and inhibiting pyruvate dehydrogenase (PDH, conversion of pyruvate to acetyl-CoA).	[195]
18	P2X7R	ATP ≥ 100 μM	C57BL/6 mice	P2X7 activation inhibits the suppressive potential and stability of Tregs and promotes the conversion of Tregs to Th17 cells in vivo. In contrast, P2X7R inhibition promotes the conversion of $CD4^+$ T cells into Tregs after stimulation of their T cell receptors (TCRs).	[196]
19			C57BL/6 wild type and P2X7 knockout mice	P2X7 knockout mice show an increase in the number of CD90/CD45RBlow $FoxP3^+$ Tregs in the colon lamina propria, with prevention of Treg death in mesenteric lymph nodes, and these Tregs produce more IL-10. Colitis is prevented or reduced in P2X7 knockout mice. Treg cells lacking the P2X7 receptor have higher levels of integrin CD103. ATP activation of P2X7R triggers Treg death.	[197]
20			C57BL/6 mice, renal ischemia–reperfusion injury	P2X7R antagonist oATP prior to renal ischemia increases renal Foxp3DCD4D Treg infiltration and reduces IL-6 and CCL2 levels. oATP treatment following injury improves renal function, decreases the infiltration of innate and adaptive effector cells, increases the renal infiltration of $Foxp3^+CD4^+$ Tregs, increases tubular cell proliferation, and reduces renal fibrosis.	[198]
21			C57BL/6 mice	P2X7R activation reduces the frequency of Tregs, and P2X7R inhibition increases the expansion of Tregs.	[198]
22			$CD4^+CD25^+FoxP3^+$ Tregs	Facilitates NAD^+-induced Treg depletion through the ART2-P2X7 pathway.	[199]

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Examples of the effects of extracellular adenosine, ATP, and ADP on select immune cells through the activation of three purinergic receptors (AdoRA2A, P2X7R, and P2Y12R)

Row number	Receptor	Ligand [149]	Immune cell type or experimental model	Results of receptor signaling	Reference number
23			Humanized mice model GVHD, HaCat cell, Jurkat cells (E6-1 clone), and mouse DCs	Increases CD80, CD 86, STAT-1, and P2X7R expression; IFN-β release; and T cell expansion. Reduces Treg numbers.	[200]
24			Humanized mice model GVHD	Anti-hP2X7 monoclonal antibodies increase human Treg and human NK cell numbers on Day 21 and reduce clinical and histological GVHD in the liver and lung compared to the control treatment at the disease endpoint.	[201]
25			LGMDR3 (Limb-girdle muscular dystrophy R3) mice with α-sarcoglycan gene (SGCA) knockout	P2X7 antagonist A438079 improves mouse motor function and decreases serum creatine kinase levels, reduces the percentage of central nuclei, reduces fiber size variability, and reduces the extent of local fibrosis and inflammation significantly. Flow cytometric characterization of muscle inflammatory infiltrates revealed significantly decreased numbers of innate immune cells and increased numbers of Tregs.	[202]
26			Mouse $CD4^+CD25^+FoxP3^+$ Tregs	P2X7R activation facilitates NAD^+-induced Treg depletion through the ART2-P2X7 pathway.	[199]
27			BALB/c mice GVHD model, DCs	Activation of P2X7Rs increases CD80, CD 86, STAT-1, and P2X7R expression, IFN-β release, and effector T cell expansion. Reduces Treg numbers. P2X7R blockade in GVHD improves survival.	[200]
28			Mouse, human, murine B cells	Induces shedding of IgE receptor (CD23) and CXCL16. Soluble CD23 sustains growth of B cell precursors, promotes B cell and T cell differentiation, and drives cytokine release from monocytes. CXCL16 is a chemoattractant for lymphocytes.	[203,204]
29			Jurkat cells (E6-1 clone) Naïve T cells	TCR stimulation triggers rapid release of ATP and upregulates P2X7 gene expression. Autocrine ATP stimulation through the P2X7R is required for TCR-mediated calcium influx, NFAT activation, and IL-2 production.	[205]
30			Wild-type and Panx-1 knockout C57BL/6 mice, bone marrow–derived DCs	ATP promotes the rapid migration of DCs through the activity of pannexin 1 channels and P2X7 receptors.	[185]

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Examples of the effects of extracellular adenosine, ATP, and ADP on select immune cells through the activation of three purinergic receptors (AdoRA2A, P2X7R, and P2Y12R)

Row number	Receptor	Ligand [149]	Immune cell type or experimental model	Results of receptor signaling	Reference number
31			Mouse and P2X7 knockout mice, $CD11c^+CD103^+$ DCs	Mediates rapid infection-induced recruitment of $CD11c^+CD103^+$ DC subsets into the epithelial layer of the gut.	[206]
32			DCs cultured from murine bone marrow precursor cells	Induces autocrine-mediated (pannexin-1 channels) rapid migration of DCs through reorganization of the actin cytoskeleton.	[185]
33			Human monocytes	Induces MMP-9 and TIMP-1 release.	[207]
34			Wild-type and P2X7 knockout C57BL/6 mice, M1 macrophages	Induces release of 74 proinflammatory proteins detected by an antibody array and 33 inflammatory proteins detected by LC–MS/MS.	[208]
35			Wild-type and P2X7 knockout C57BL/6 mice M2 macrophages	Induces release of 21 anti-inflammatory proteins detected by LC–MS/MS.	[208]
36			CLP-induced sepsis in mice, macrophages	Enhances intracellular bacterial killing.	[209]
37			Macrophages and P2X7R-transfected HEK-293 cells	Mediates rapid uptake of beads and bacteria in the absence of serum after ATP activation.	
38			Human mast cells	Induces degranulation.	[210]
39			Wild-type and P2X7 knockout C57BL/6 mice, naïve NKTs	Facilitates NAD^+-induced inhibitory signaling through the ART2-P2X7 pathway, resulting in nonfunctional NKTs.	[211]
40			Wild-type and P2X7 knockout C57BL/6 mice, activated NKTs	Facilitates NAD^+-induced stimulatory signaling through the ART2-P2X7 pathway, resulting in functional NKTs with increased IFN-γ and IL-4 release.	[211]
41			Human peripheral neutrophils	Human CAP18/LL-37 suppresses neutrophil apoptosis through the activation of formyl-peptide receptor-like 1 and P2X7R.	[212]
42	P2X7R	ATP > 1 mM, prolonged vigorous activation	Macrophages, HeLa cells, 1321N1 astrocytes, and HEK293 cells	Induces Panx-1-mediated large pore formation and interleukin-1 beta release.	[213]
43			Human neutrophils and HL-60 cells	Mediates large pore formation and superoxide generation.	[214]

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Examples of the effects of extracellular adenosine, ATP, and ADP on select immune cells through the activation of three purinergic receptors (AdoRA2A, P2X7R, and P2Y12R)

Row number	Receptor	Ligand [149]	Immune cell type or experimental model	Results of receptor signaling	Reference number
44			Female C57BL/6 (B6) and BALB/c mice, ART2 knockout BALB/c mice, P2X7 knockout C57BL/6 mice, mature peripheral T cells	High-dose ATP promotes apoptosis, cell death, and CD62L shedding (homing receptor for central T cells) independent of the NAD^+-induced ART2-P2X7 pathway.	[215–217]
45			J774 cells and HEK cells expressing the P2X7 receptor	Promotes the formation of pores permeable to very large ions, leading to cytolysis	[151]
46	P2Y12R	ADP > ATP	Murine model of sepsis, cecal ligation, and puncture (CLP). Cocultures of human platelets and T cells with or without anti-CD3/CD28	Blockade of the P2Y12 signaling pathway restrains Treg proliferation in vivo and *in vitro*.	[218,219]

4.3. The role of P2X7Rs in the immune system

In general, P2X7Rs have several functions, and they are all present in immune cells. First, P2X7Rs expressed on the surface of monocytes and macrophages act as scavenger receptors for apoptotic cells by effectively enhancing their engulfment (Table 2, row 4). P2X7Rs are indispensable for cytoskeletal rearrangement [220] and membrane blebbing [221] during the process of phagocytosis [222]. Second, P2X7Rs act as ATP release channels after mechanical deformation, after irradiation, after activation, after stimulation with isotonic or hypotonic solutions, after stimulation by microbe-infected cells, or spontaneously, often in conjunction with pannexin 1 channels (Panx-1s) (Table 2, rows 5–11). Third, P2X7Rs act as promotors of cell proliferation—referred to as low tonic basal activation—in cells with high expression of P2X7Rs, such as cells involved in wound closure or cancer (Table 2, rows 12–17). Fourth, P2X7Rs act as intrinsic cation channels that transduce transmembrane signals, inciting a proinflammatory response in innate and adaptive immune cells [149,223] (Table 2, rows 18–41). Finally, P2X7Rs act as promoters of cell death by promoting the formation of macropore channels (Table 2, rows 42–45).

4.4. A crucial element in the activation of autoimmune responses: The threshold for extracellular ATP-induced activation of P2X7Rs is much greater than that of other purinergic receptors

Extracellular levels of purinergic signaling ligands are very low under resting conditions (Figure 3A). After release, extracellular ATP molecules are hydrolyzed by membrane-bound ectonucleotidases or extracellular soluble nucleotidases (CD39, CD73, tissue nonspecific alkaline phosphatase, etc.),

generating extracellular ADP, AMP, adenosine, inosine, and other metabolites and returning their extracellular levels to those observed under resting conditions (Figures 3A and 4) [168–170]. This process, referred to as resensitization, is essential for purinergicreceptors to recover from desensitization following receptor activation, during which the receptors are unresponsive to stimuli. To a certain extent, desensitization occurs after every activation, and time is required to return to a state of complete resensitization after ligand clearance [224–229]. The resensitization time is dependent on, among other factors, the extent of activation. Specifically, the higher the activation level is, the longer the time required for complete resensitization to occur [227,229] (orange boxes at the bottom of the graph in Figure 3).

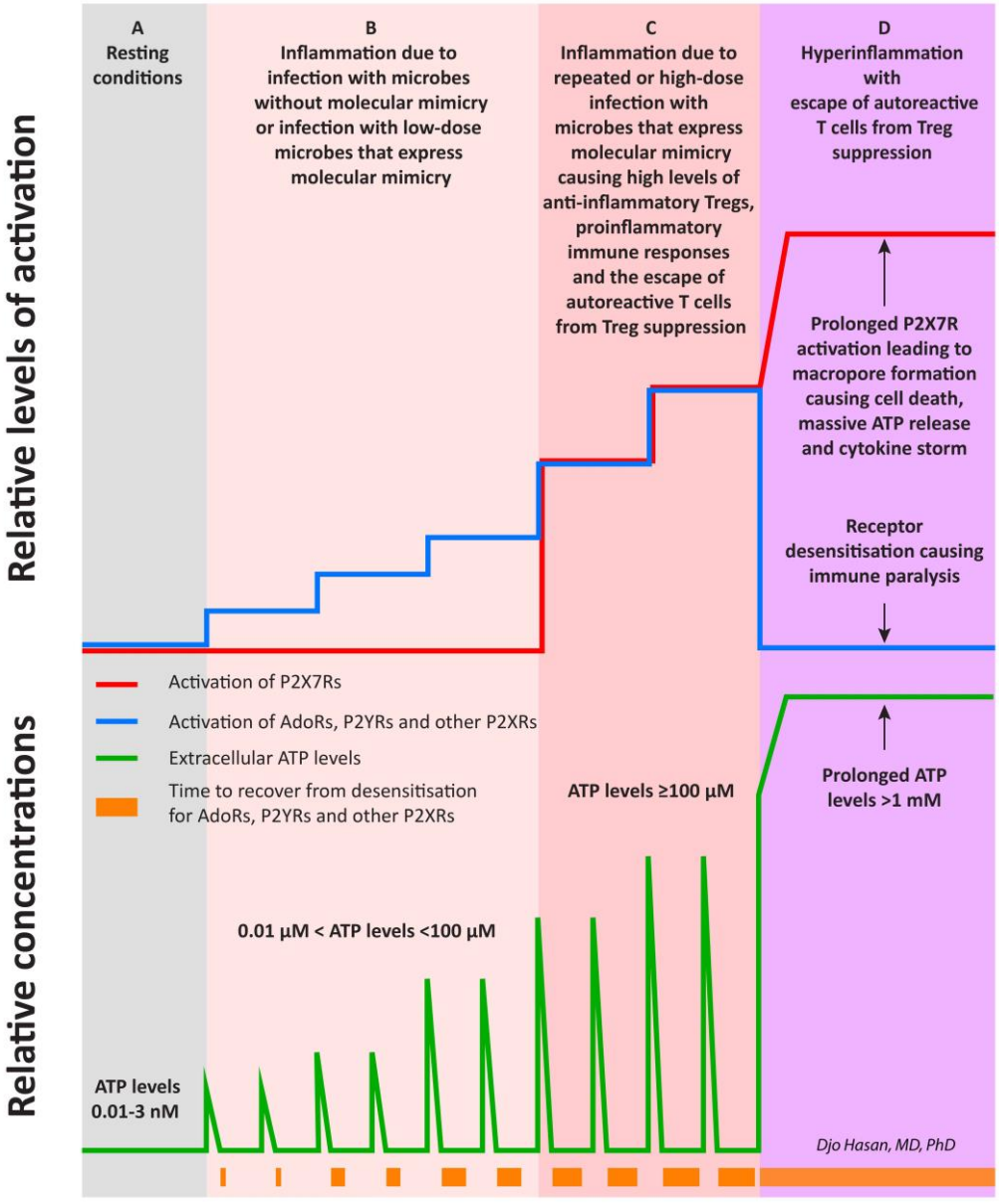

Figure 3. Schematic representation of the activation of purinergic receptors on immune cells. A) Basal levels of purinergic receptors under resting conditions. B) Microbial infection drives the controlled cellular release of ATP molecules. Increased extracellular nucleotides and adenosine produced by extracellular hydrolyzing nucleotidases activate

P2XRs, P2YRs, and adenosine receptors (AdoRs). This results in the activation of the proinflammatory response without P2X7R activation. C) In the case of repeated infection or infection with a high-dose of microbes that exhibit molecular mimicry, ATP release increases, and extracellular ATP levels reach or exceed 100 μM, activating P2X7Rs. On the one hand, this causes an increase in the activation of AdoRA2As and P2Y12Rs, increasing the number of anti-inflammatory Tregs. On the other hand, the increased activation of other P2XRs, P2YRs, and AdoRs fuels a proinflammatory immune response, and P2X7R activation disrupts Treg function, allowing autoreactive T cells and B cells to escape Treg suppression. D) As inflammation progresses, prolonged and high levels of extracellular ATP (with concomitant high levels of ADP and adenosine due to extracellular hydrolysis of ATP) induce all purinergic receptors, except for P2X7Rs, to enter a state of desensitization without recovery, causing paralysis of the immune response against invading microbes. This also induces macropore formation, leading to cell death (except for CTLs, which are resistant to extracellular ATP-induced cytolysis), with massive release of ATP, inducing a state of hyperinflammation. The green line represents the extracellular ATP levels. The ascending part of the line represents increasing ATP levels due to the extracellular release of ATP, and the descending part of the line reflects decreasing ATP levels resulting from the clearance of ATP by extracellular or membrane-bound ATP-hydrolyzing ectonucleotidases and soluble extracellular nucleotidases. The blue line represents the activation of purinergic receptors other than P2X7Rs, and the red line represents the activation of P2X7Rs. The orange boxes at the bottom of the graph represent the recovery time of the receptors from a state of desensitization to a state of complete resensitization. Increasing the intensity and duration of receptor activation increases the recovery time. Prolonged high ATP levels prevent recovery from the desensitized state. ATP: adenosine triphosphate; AdoR: adenosine receptor; P2XRs and P2YRs: purinergic nucleotide receptors; CTLs: cytotoxic T cells. Source: Modified figure from Hasan D et al. (2022) [22] under the Creative Commons Attribution License CC BY 4.0, with permission.

Microbial infection is linked to purinergic signaling, as it increases extracellular ATP release through P2X7R combined with Panx-1 as an ATP release channel [186–189]. In experimental virus-infected cells, extracellular ATP concentrations and activation of P2X7Rs increase with increasing exposure time and microbe concentration [189]. Extracellular ATP hydrolysis (Figure 4) causes extracellular ADP, AMP, and adenosine levels to increase. The subsequent activation of P2Rs (P2XRs and P2YRs) and AdoRs initiates the proinflammatory immune response to counter-invading microbes (Figure 3B). However, the levels of extracellular ligands required to activate P2Rs (other than P2X7Rs) and AdoRs are quite modest [228,230,231]. The activation of P2X7R, an intrinsic cation channel that activates a proinflammatory response, is initiated at extracellular ATP levels that are at least 10-fold or greater than the ligand concentrations observed to activate other P2Rs [223,226,230]. The EC_{50} (the effective concentration 50, defined as the level required for the ligand to reach effective receptor activation halfway between maximal and baseline receptor activation) of AdoRs for adenosine ranges from 1 nM to 1.4 μM [228,232], and the EC_{50} of P2Rs for ATP, ADP, or UTP ranges from 0.01 μM to 10 μM [155–159,230–232]. In contrast, the activation of P2X7R is initiated at 10-fold or greater levels of extracellular ATP (≥100 μM, with an EC_{50} > 1 mM) [223,226,230] (Figures 3B and C). Thus,

the P2X7R-induced proinflammatory response occurs only after a certain dose of microbes is exceeded, as occurs in repeated or severe infection (Figures 3C and D).

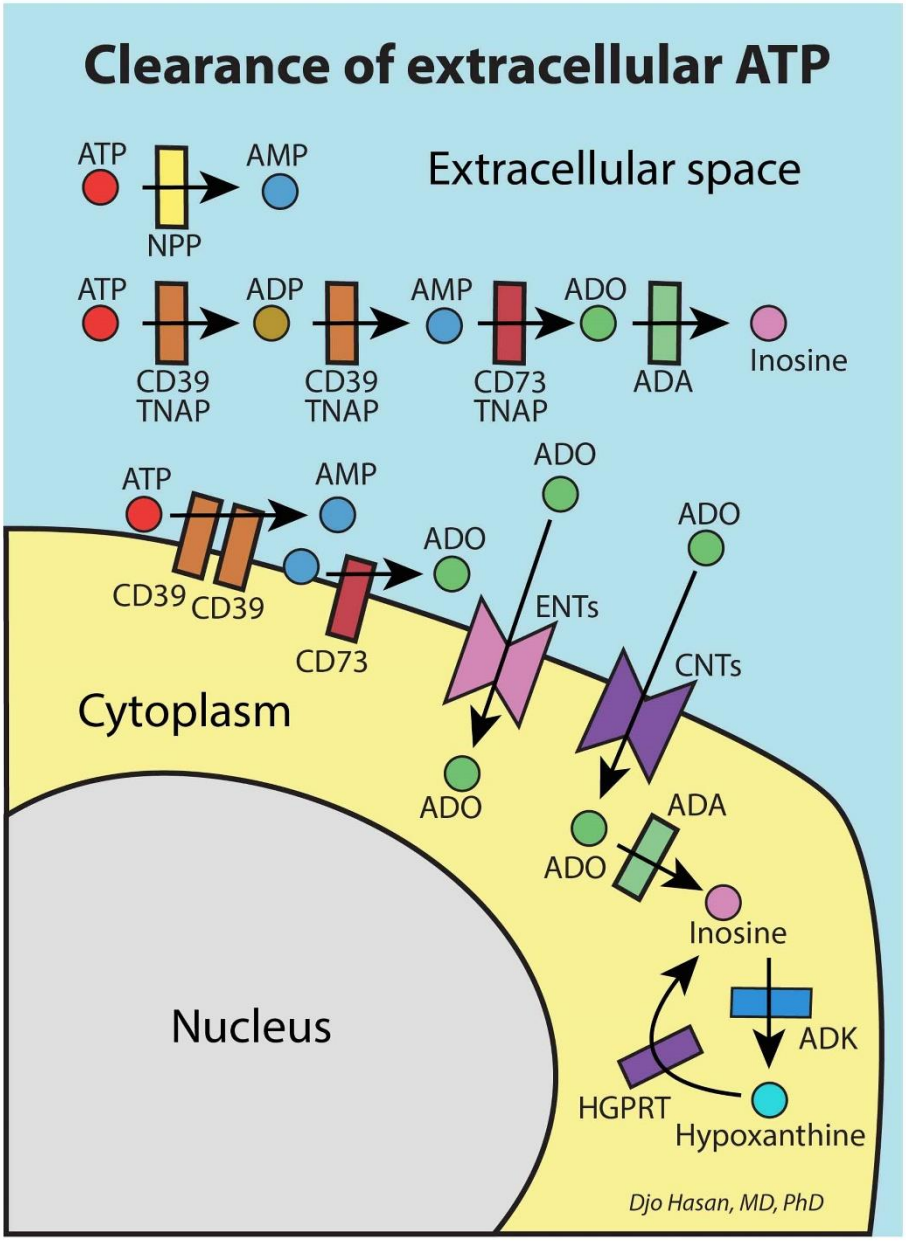

Figure 4. Extracellular ATP, ADP, AMP, and adenosine clearance by ATP-hydrolyzing ectonucleotidases (membrane-bound enzymes) and soluble extracellular nucleotidases. To prevent the accumulation of adenosine and nucleotide molecules from the extracellular space, ATP is converted to adenosine in several steps by ectoenzymes or soluble extracellular enzymes. These enzymes include NPP, CD39, CD73, TNAP, and ADA. Some adenosine molecules are then converted to inosine by the soluble extracellular enzyme ADA. The remaining extracellular adenosine molecules enter cells through specific channels (ENTs and CNTs). Inside the cells, adenosine and inosine are converted to inosine and hypoxanthine by ADA and ADK, respectively. This process is essential for receptors to recover from desensitization following receptor activation (resensitization).

CD39: ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD 1); CD73: ecto-5'-nucleotidase (5'-NT); NPP: nucleotide pyrophosphatase/phosphodiesterase; TNAP: tissue-nonspecific alkaline phosphatase; ADA: adenosine deaminase; ADK: adenosine kinase; HGPRT: hypoxanthine-guanine phosphoribosyltransferase; ATP: adenosine triphosphate; ADP: adenosine diphosphate; AMP: adenosine monophosphate; ADO: adenosine; ENTs: equilibrative nucleoside transporters; CNTs: concentrative nucleoside transporters. Source: Figure from Hasan D et al. (2022) [22] under Creative Commons Attribution License CC BY 4.0, with permission.

As summarized in Table 2 (rows 1–3 and 46), activation of AdoRA2A or P2Y12R may increase the number and suppressive function of Tregs. P2X7Rs are highly expressed in Tregs and dendritic cells (DCs) [196,197,199,200]. In contrast to the activation of AdoRA2A and P2Y12R, activation of P2X7Rs causes changes in T cell balance, promoting effector T cell expansion and Treg contraction [196,197,199,200]. Crucially, the disruption of Tregs occurs exclusively after the activation of P2X7Rs on DCs, Tregs, and other immune cells and not via the activation of any other purinergic receptor [22,162]. The mechanisms by which P2X7R activation affects Tregs and DCs are presented in Table 2, rows 18–27 and 30–32, respectively. As shown in Figure 3C, P2X7Rs are activated only after high levels of extracellular ATP are reached. Activated P2X7Rs disrupt Treg suppressive function, allowing autoreactive T cells to be activated and attack invading microbes exhibiting molecular mimicry at the expense of self-tolerance. This is highlighted by the finding that although P2X7R is not required to control lung tuberculosis after aerosol infection with a low dose (~50 CFU) of *M. tuberculosis* (Erdman strain) in P2X7 knockout mice [233], P2X7R blockade can significantly reduce lung inflammation in WT mice intratracheally infected with a high-dose (~100 CFU) of the *M. bovis* MP287/03 strain in a model of severe lung tuberculosis [234].

Thus, available data suggest that the activation of purinergic receptors on immune cells activates inflammation at moderate extracellular levels of their ligands. However, the activation of P2X7Rs on immune cells, which interferes with Treg suppression of autoreactive T cells, occurs at much higher extracellular ATP levels.

4.5. Evidence of the relationship between P2X7R and autoantibody production

Immunization with type II collagen (CII) in mice induces arthritis with IgG autoantibodies specific to CII. Intraperitoneal treatment with the P2X7R antagonist oxidized ATP (oATP) significantly decreases CII-specific IgG autoantibody levels and improves clinical outcomes [235]. Other researchers reported that immunization with a plasmid containing the M_2 receptor (M_2AChR) cDNA sequence induces dilated cardiomyopathy with autoantibodies to M_2AChR in P2X7 knockout and WT mice. The autoantibody levels in P2X7 knockout mice are significantly lower than those in WT mice [236]. Additionally, in Sjogren's syndrome, the expression and activation of the P2X7R inflammasome axis in human salivary glands and human circulating lymphomonocytes are greater in autoantibody-positive patients than in autoantibody-negative patients [237,238].

4.6. Immune responses, autoimmune responses, and hyperinflammation with a cytokine storm

Infections caused by microbes that contain foreign antigens (antigens without molecular mimicry) that can be eliminated rapidly are associated with modest increases in extracellular adenosine and nucleotide levels. In these infections, all of the purinergic receptors required for an adequate immune response, except P2X7Rs, are activated (Figure 3B). However, infections caused by microbes that exhibit molecular mimicry (these microbes also harbor foreign antigens) will initially increase Treg numbers and activation [33], delaying the (auto) immune response against their antigens. When the immune response against foreign antigens is not sufficiently effective, microbes proliferate extensively. I believe that this causes an increase in ATP release and extracellular ATP levels above the threshold that allows P2X7Rs to become activated in addition to P2XRs, P2YRs, and AdoRs, hampering the ability of Tregs to suppress autoreactive T cells and B cells (Figure 3C). A faster autoimmune response is expected after repeated doses or under high-dose infection (associated with greater ATP release) with microbes that exhibit molecular mimicry. If the proinflammatory process is not resolved and severe inflammation occurs, extracellular ATP levels further increase, causing prolonged vigorous activation of P2X7Rs. This inevitably leads to macropore formation and cytolysis, with concomitant uncontrolled ATP release (Table 2, rows 42–45) [151,172,213,214]. All immune cells are affected by cytolysis, except for cytotoxic T cells (CTLs), which include autoreactive CTLs, because CTLs are resistant to extracellular ATP-induced cytolysis [239], possibly due to the very high expression and activity of ATP-hydrolyzing nucleotidases on the CTL membrane [240]. This results in a state known as hyperinflammation, with maximally activated autoreactive CTLs and abundant cytokine production (cytokine storm, Figure 3D) [22,241,242]. Hyperinflammation is a potentially life-threatening condition. However, even hyperinflammation may resolve spontaneously. At the macropore-formation stage, P2X7R-dependent release of matrix metalloproteinase 2 (MMP-2) occurs, which can control runaway P2X7Rs by proteolytic degradation of P2X7Rs [243,244].

4.7. Purinergic receptors are subject to desensitization at high extracellular ligand concentrations, but P2X7Rs are exempt from receptor desensitization

As mentioned above, one intriguing phenomenon certainly deserves more attention: desensitization. At very high extracellular adenosine and nucleotide concentrations, purinergic receptors are likely to become unresponsive to stimulation by their ligands. An even more fascinating finding is that all purinergic receptors except for P2X7Rs are subject to desensitization [223,226,230] (Figure 3D). At very high extracellular adenosine and nucleotide concentrations, all immune responses except for autoimmune responses are paralyzed. Thus, there is simultaneous immunosuppression (against foreign antigens) and strong activation of autoimmune responses. During severe microbial infection, ATP is released beyond the capacity of extracellular hydrolyzing nucleotidases to clear it (as depicted in Figure 4), after which extracellular ATP accumulates [245] alongside elevated extracellular levels of adenosine and other nucleotides. This results in hyperinflammation, with highly activated P2X7Rs, disruption of many immune cells (except CTLs), cytokine storm, and desensitization of other purinergic receptors, which interferes with normal immune responses to microbes [22]. Hence, during hyperinflammation, the host is more susceptible to invading microbes [22,163] (Figure 3D). I hypothesize that the desensitization of purinergic receptors on immune cells may be the underlying mechanism of secondary immune paralysis in severe diseases. For example, sepsis-induced

immunosuppression [246,247] is also known as compensatory anti-inflammatory response syndrome (CARS) in critically ill patients [248,249].

4.8. Two examples of the involvement of purinergic signaling in autoimmune responses: Increased versus decreased blood Treg levels in COVID-19 patients

Recently, a study reported that the blood levels of Tregs, Bregs, and autoantibodies to type I IFNs in COVID-19 patients requiring high-flow oxygen therapy or noninvasive ventilation are significantly greater than those in nonhospitalized COVID-19 patients and healthy controls. The increased Treg and Breg levels are even greater in those positive for autoantibodies to type I IFNs [129]. This phenomenon can be interpreted as the simultaneous activation of proinflammatory immune responses, autoimmune responses, and tolerogenic responses. It is quite challenging to explain this phenomenon from the perspective of immunobiology. However, when purinergic signaling is involved, we can deduce that ATP, ADP, and adenosine levels are sufficiently high to activate all purinergic receptors, including P2X7Rs, and can still achieve adequate resensitization. In this scenario, there is simultaneous activation of anti-inflammatory responses (by activated AdoRA2As and P2Y12Rs) that increase Treg numbers and activation of proinflammatory responses (against foreign antigens) fueled by the activation of other P2XRs, P2YRs, and AdoRs. In addition, the activation of P2X7Rs in immune cells hampers Treg suppressive function, leading to the escape of autoreactive T cells and B cells from Treg suppression (Figure 3C), which initiates, among other processes, the production of autoantibodies despite the increased numbers of Tregs. Thus, Treg numbers and autoantibody levels are expected to increase with increasing extracellular ATP, ADP, and adenosine levels.

In contrast, other researchers reported exactly the opposite results. In one study, healthy controls were not included, and autoantibody levels were not determined. The lack of autoantibody levels makes it difficult to assess whether Treg suppressive function is affected. The blood Treg numbers in patients who did not require oxygen therapy (those with mild disease) were slightly but still significantly greater than those of patients who required oxygen via a nasal cannula or oxygen mask (those with moderate disease). However, blood Treg numbers in patients requiring noninvasive or invasive mechanical ventilation (those with severe disease) were far lower than those in patients with moderate or mild disease [134]. Hypothetically, from the perspective of purinergic signaling, we can deduce that the activation of purinergic receptors in patients with mild and moderate disease in this cohort corresponds to the mechanism presented in Figure 3C. In patients with severe disease who are undergoing mechanical ventilation, it corresponds to a state of hyperinflammation where Treg numbers are affected by ATP-induced macropore formation and cytolysis, as depicted in Figure 3D.

4.9. Autoimmune disorders often have common symptoms involving the disruption of multiple tissues or organs

On the one hand, in the case of disruption of Tregs with TCRs matching ubiquitous antigens, we would expect that symptoms would be generalized. On the other hand, in the case of tissue-restricted antigens (TRAs), symptoms are expected to be confined to certain tissues or organs. However, in reality, this is often not true; autoimmune disorders share many common symptoms, such as headache [250,251], pruritus [252], sleep disturbances [253], fatigue [253,254], pain [255], chronic pain [256], and neuropsychiatric symptoms [257].

There are two explanations for the common symptoms of autoimmune disorders. First, P2X7Rs are expressed on all Tregs [196,197,199,200]; therefore, activation of these receptors disrupts the suppressive function of Tregs in general, irrespective of whether their TCRs are specific to microbes that mimic self-antigens. This leads to autoimmune responses against self-antigens in multiple tissues or organs. This phenomenon may be the basis of the well-known "bystander T cell activation" phenomenon in which T cells that are not specific to disease-related antigens damage host cells without proper antigen recognition [258–262]. Second, according to bioinformatics analysis, microbes tend to exhibit molecular mimicry with multiple human antigens rather than a single antigen [263,264]. An interesting article reported that after severe COVID-19, the generated antibodies include autoantibodies, specific antibodies to the SARS-CoV-2 spike protein receptor-binding domain, and other nonspecific antibodies. Remarkably, the profile of autoreactive antibodies in critically ill patients with COVID-19 was very comparable to that in patients with acute respiratory distress syndrome (ARDS) following bacterial pneumonia in the ICU with similar self-antigen targets, such as antinuclear antibodies (ANAs) and anti-carbamylated protein responses (anti-CarPs). Researchers have even observed an overlap with autoantibodies found in patients with systemic lupus erythematosus (SLE) [265].

Thus, undermining the suppressive function of Tregs can easily promote the escape of autoreactive T cells and B cells specific to multiple antigens. This clearly affects multiple tissues or organs with concomitant production of autoantibodies to more than one antigen [106]. However, critically, not all microbial infections lead to immediate and severe autoimmune responses; some microbes are able to efficiently suppress autoimmune responses.

4.10. Some microbes that exhibit molecular mimicry have a clever strategy to mitigate autoimmune responses

Although the activation of AdoRs by adenosine may promote an immune response in some immune cells, in general, AdoR activation reduces the number and inhibits the functions of DCs, T cells, B cells, antibody-producing plasma cells, macrophages, neutrophils, and NK cells [266]. In addition, activation of AdoRA2A increases the number and promotes the suppressive function of Tregs (Table 2, rows 1–3). Microbes, after invading the body, can reduce the extracellular concentration of ATP by converting ATP to adenosine to such an extent that the activation of P2X7Rs in immune cells may not occur. The "advantage" for microbes is that the resulting increase in extracellular adenosine levels restores the number and suppressive function of Tregs, mitigating autoimmune responses; however, for the host, this occurs at the expense of defense against these microbes (Table 2, rows 1–3 and Figure 2D2). It is therefore not a coincidence that, in patients infected with certain viruses that exhibit molecular mimicry, such as Epstein–Barr virus (EBV), human immunodeficiency virus (HIV), and hepatitis C virus (HCV) [5], the expression of the ATP-hydrolyzing enzyme CD39 (Figure 4) is upregulated in infected cells, Tregs, and other immune cells [267–270]. Subsequently, activation of AdoRA2A by adenosine increases Treg number and suppressive function. This mitigates autoimmune responses, resulting in a chronic condition with much less severe inflammation, such as chronic EBV infection [271], chronic HIV infection [272], and chronic HCV infection [273].

In severe infection with EBV, HIV, or HCV, a further complication develops. Presumably, ATP release [178,180,185] combined with upregulated CD39 expression reduce extracellular ATP concentrations, preventing P2X7R activation and converting extracellular ATP to adenosine. Because

ATP release does not depend on extracellular ATP-induced P2X7R activity but rather is driven by microbial infection [186–189], in severe infection, high ATP release combined with upregulated ATP-hydrolyzing nucleoside activities strongly decrease ATP levels and further increase high extracellular adenosine levels [162,163]. This potentially increases the risk of organ fibrosis [274,275], and organ fibrosis has been reported in patients with chronic EBV [276], HIV [277], and HCV [278,279] infection.

In short, I propose that by employing this strategy, microbes can survive and proliferate in the body for quite a long time, causing chronic inflammatory disease and increasing the risk of fibrosis without triggering severe autoimmune responses.

4.11. A P2X7R antagonist must reach adequate inhibitory concentrations in secondary lymphoid organs to ameliorate autoimmune symptoms

Blocking P2X7Rs on DCs and Tregs is an obvious next step in treating autoimmune disorders. However, to ameliorate the symptoms of autoimmune responses, P2X7R antagonists must reach adequate effective concentrations in secondary lymphoid organs, where DC-activated T cells and Tregs are induced. P2X7R activation is indispensable in many organs (the central and peripheral nervous system [160,161], the lung [162–164], the airways [165], the pancreas [166,167], etc.). Consequently, traditional approaches involving oral or intravenous administration of P2X7R antagonists cannot safely achieve adequate concentrations without disrupting essential organ functions. Indeed, despite effective ex vivo antagonism of P2X7Rs in immune cells, clinical trials have failed to demonstrate the efficacy of the P2X7R antagonists CE-224,535 (Pfizer) [280] and AZD-9056 (AstraZeneca) [281] in the treatment of rheumatoid arthritis and major depressive disorder under JNJ-54175446 (Johnson and Johnson) [282]. Apparently, the safe serum levels of these antagonists are not high enough to produce effective P2X7R inhibition of Tregs in secondary lymphoid organs. This is referred to as the very narrow therapeutic index (NTI, a narrow window between effective doses and doses causing adverse toxic effects), which is a common and difficult to overcome problem in drug development [283]. In contrast, oral AZD9056 significantly improved the Crohn's Disease Activity Index (CDAI) in patients with Crohn's disease [284]. I propose that this success can theoretically be ascribed to the effect of high local concentrations of AZD9056 in tertiary lymphoid organs in the gut, where the drug enters the mucosa, enabling effective antagonism of P2X7Rs on local immune cells involved in the pathogenesis of Crohn's disease [285].

5. Conclusions

In this review, I discuss the regulation of autoimmunity in relation to self-antigens and antigens of microbes with molecular mimicry. Under certain conditions, microbes with molecular mimicry are able to activate autoimmune responses. In addition, I have explained the mechanism of the activation of autoimmune responses by microbes with molecular mimicry using the knowledge of purinergic signaling. I found that P2X7Rs on immune cells, especially on Tregs and DCs, play a critical role by affecting the suppressive function of Tregs followed by the activation of autoimmune responses. Previously, it was thought that microbes had to reach target organs and enter cells to damage organs. However, since the activation of autoimmune responses occurs almost exclusively in the secondary lymphoid organs, it appears that it is sufficient for microbes with molecular mimicry to reach the lymph

nodes to initiate autoimmune responses. The resulting autoreactive T cells that escape Treg suppression migrate via systemic circulation and cause organ damage throughout the body. As a result, depending on the mimicked self-antigens, one or more organs are affected. Consequently, the elimination of microbes with molecular mimicry occurs at the expense of self-tolerance (Figure 1).

I have also proposed that some types of microbes that express molecular mimicry, by exploiting the purinergic conversion of extracellular ATP to the anti-inflammatory adenosine, may mitigate autoimmune responses at the expense of the ability to clear microbes. This may be the basis for the development of microbe-induced chronic diseases.

As mentioned in the Introduction section of this review, autoimmune disorders resulting from the activation of autoimmune responses have a major impact on people's daily lives and public health. In addition, their rapidly increasing prevalence contributes to rising healthcare costs. Therefore, effective treatments are urgently needed. However, the development of effective treatments for autoimmune disorders is challenging due to their NTIs. This review provides an indication for targeting secondary lymphoid organs (such as local lymph nodes) with a P2X7R antagonist. I believe it is not necessary to target all lymph nodes. The drug dose required to effectively inhibit the P2X7Rs of immune cells in a small volume of local lymph nodes is relatively low. When the drug reaches systemic circulation, it is highly diluted to very low concentrations. This prevents systemic P2X7R inhibition and other adverse effects. As suggested previously [22], I hypothesize that targeting local lymph nodes with a P2X7R antagonist can increase the production and suppressive function of Tregs. These Tregs migrate through the systemic circulation to suppress autoreactive T cells and B cells throughout the body.

In my opinion, this review differs from reviews in the field of microbe-induced autoimmunity because of the involvement of purinergic signaling. This allows me to elucidate biological processes that would otherwise be nearly impossible to explain. In addition, this approach provides an opportunity to explore new avenues in the field of microbe-induced autoimmunity.

Use of AI tools declaration

The author declares that he did not use Artificial Intelligence (AI) tools in the preparation of this article.

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Conflicts of interest

The author (Djo Hasan) declares that he has filed patent applications concerning P2X7R antagonists.

Ethics approval and consent to participate

Not applicable for this review article.

Author contributions

Conception, design and data handling: Djo Hasan
Acquisition, analysis or interpretation of data for the manuscript: Djo Hasan
Drafting and revising the manuscript: Djo Hasan
Critically revising the manuscript for intellectual content: Djo Hasan
Final approval of the version to be published: Djo Hasan
Agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Djo Hasan.

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Consent for publication

I am the only author of this manuscript, and I have approved the manuscript for publication.

Availability of data and materials

Any dataset generated during and/or analyzed during the current study is available from the author upon reasonable request.

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