P2X7 receptor as the regulator of T-cell function in intestinal barrier disruption

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Abstract

The intestinal mucosa is a highly compartmentalized structure that forms a direct barrier between the host intestine and the environment, and its dysfunction could result in a serious disease. As T cells, which are important components of the mucosal immune system, interact with gut microbiota and maintain intestinal homeostasis, they may be involved in the process of intestinal barrier dysfunction. P2X7 receptor (P2X7R), a member of the P2X receptors family, mediates the effects of extracellular adenosine triphosphate and is expressed by most innate or adaptive immune cells, including T cells. Current evidence has demonstrated that P2X7R is involved in inflammation and mediates the survival and differentiation of T lymphocytes, indicating its potential role in the regulation of T cell function. In this review, we summarize the available research about the regulatory role and mechanism of P2X7R on the intestinal mucosa-derived T cells in the setting of intestinal barrier dysfunction.

Key Words: Intestinal barrier dysfunction; P2X7 receptor; T lymphocyte

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INTRODUCTION

The intestinal tract is one of the largest interfaces in the human body that directly contacts the external environment[1]. The intestine, a highly specialized and complex organ, plays an important role in absorbing useful substances and presenting potentially harmful substances[2]. The intestinal barrier also maintains the homeostasis of the inner environment and develops the intestinal immune system[3]. The intestinal barrier is composed of several parts, including the microbiological barrier, the chemical barrier, the physical barrier and the immune barrier[4]. Dysfunction of the intestinal barrier increases intestinal permeability and is related to the pathophysiology of several serious diseases[5]. The intestinal tract is exposed to various commensal bacteria, dietary antigens and pathogens that are related to immune tolerance and defense, showing the importance of the immune system in the intestine[6]. The immune barrier mainly includes the lamina propria lymphocytes, dendritic cells (DCs), mast cells, macrophages and lymphocytes — mainly CD8+T cells — located among epithelial cells[7]. Considering the involvement of T cells in the oral tolerance and immune defense against pathogens in the intestine, it is not surprising that they have an essential role in the pathology of intestinal barrier dysfunction[8,9].

The purinergic signaling pathway is highly conserved and plays a critical role in immune regulatory response[10]. This signaling pathway is mainly mediated by adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NAD+). Purinergic receptors are a group of transmembrane proteins widely expressed in immune cells[11]. According to their different structural properties, these receptors can be divided into the following three families: P2X receptor, P2Y receptor and P1 receptor[12]. Among them, P2X receptors, a class of ligand-gated, cationic-selective channels, are mainly activated by extracellular ATP (eATP)[13]. P2X7 receptors (P2X7R) have a low affinity for ATP and need to be triggered by high concentrations of ATP[14]. When the concentration of ATP is low, P2X7R can act as ion channels for Na+, K+ or Ca2+. However, P2X7R can form nonselective and large-conductance pores in settings with high concentrations of ATP, thereby inducing cell apoptosis[14]. Under normal conditions, the cell membrane is impermeable to ATP and other related substances, and the maintenance of low eATP concentration is achieved by the strong degrading activity of ATPases[15,16]. The leakage of intracellular ATP due to the destruction of cell membrane could result in significant elevation of eATP concentration, thereby inducing the activation of the immune system[17-19]. Indeed, an ultrahigh concentration of eATP can be observed at the inflammatory sites[20]. In the process of acute inflammation, ATP activates P2X7R on the Treg cells, inhibiting their activity and viability[21]. P2X receptor channels on effector T cells are stimulated by eATP, facilitating the activation of nuclear factor of activated T cells and the production of IL-2, which could increase the activation of effector T cells[22,23]. The receptor can also be activated by NAD+ released from damaged cells or activated T cells[24,25]. This NAD+-dependent process is associated with ecto-ADP-ribosyltransferase ARTC2.2, which is activated by NAD+ and induces the ADP-ribosylation of P2X7. In the presence of low micromolar concentrations of extracellular NAD+, this process finally leads to cell death because of the activated P2X7R, a phenomenon known as NAD+-induced cell death (NICD)[26,27]. In contrast, NAD+ may be degraded into hydrolysate in the case of high levels of ATP, which would block the NAD+-dependent process[28,29] (Figure 1). Intestinal barrier dysfunction is usually accompanied by inflammation and the death of epithelial cells, which may lead to an elevated concentration of eATP and the intestinal immune response[30]. Meanwhile, available studies have demonstrated that P2X7R can be an important regulatory factor in the activation and differentiation of T cells[31], suggesting that P2X7R may play a key role in intestinal barrier disruption by regulating T cells.

Therefore, in this review, we summarized the recent advances regarding the intestinal barrier, the role of P2X7R and T-cells in the pathophysiology of intestinal barrier disruption, and the role of T cell-derived P2X7R in the pathophysiology of intestinal barrier dysfunction.
Figure 1 The activation of the P2X7 receptor and NLRP3 inflammasome. The P2X7 receptor is activated by extracellular ATP and NAD$^+$ and serves as an ion channel. The activated P2X7 receptor induces the decreasing of intracellular K$^+$, which initiates NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation. The activated process of pro-interleukin (IL)-1$\beta$ and pro-IL-18 are triggered by the active caspase-1 that results from the formation of NLRP3 inflammasome. Mature inflammatory cytokines are released into extracellular space from cells, which finally results in the cell death. ADPR: ADP-ribose; ARTC2.2: ADP-ribosyltransferase 2.2; ASC: Apoptosis-associated speck-like protein containing a CARD; NLRP3: NOD-like receptor family pyrin domain containing 3; IL-18: Interleukin-18; IL-1$\beta$: Interleukin-1$\beta$.

derived P2X7R in the pathophysiology of intestinal barrier dysfunction.

THE OVERVIEW OF THE INTESTINAL BARRIER

The intestinal barrier, one of the most important biological barriers in the body, is composed of various extracellular and cellular components. It works as a semipermeable membrane that allows nutrients to pass through while limiting the transport of pathogens and noxious substances. This dual function is regulated by the interaction among the four components of the intestinal barrier (the microbiological barrier, the chemical barrier, the physical barrier and the immunological barrier)[2].

There are over 10$^{14}$ microorganisms and about 10000 bacterial species in the human intestine[32]. The microbiological barrier is formed by symbiotic microorganisms in the outermost position of the mucus layer, which effectively prevents harmful substances from entering intestinal epithelial cells[31,33,34]. The chemical barrier, also known as the inner mucus layer, is composed of macromolecules, including proteins, enzymes, peptides and immunoglobulins[35,36]. Mucin2 secreted by goblet cells is the main mucus protein and it serves as a protective barrier[37]. In intestinal crypts, pluripotent stem cells can differentiate into five different cell types, including enterocytes, goblet cells, Paneth cells, enteroendocrine cells and microfold cells[38]. The physical barrier beneath the mucus layer is composed of intestinal epithelial cells which are critical to the physical features of the intestinal barrier[30].

Beneath the intestinal epithelium, the immunological barrier consists of various immune cells, including T lymphocytes, B lymphocytes, dendritic cells, macrophages and plasma cells. This barrier is involved in innate and adaptive immune responses via antigen presentation and the secretion of inflammatory mediators and antibodies[39,40]. In addition to immune cells, substances secreted from these cells are also important in the construction of the intestinal immunological barrier. Secretory IgA, another constituent of the immunological barrier, is mainly found at the intestinal mucosal surface, and it provides antipathogen protection by interacting with bacteria[41].

There are several interactions among different components of the intestinal barrier. The physical barrier and the inner mucus layer separate the microbiological barrier and the intestinal immunological barrier, preventing unnecessary conflict and maintaining intestinal homeostasis[42]. The intestinal microbiota induces the functional maturation of innate and adaptive immunity, and instructs immune response through microbiota-derived metabolites and components (such as lipopolysaccharides and...
peptidoglycans)[43,44]. The metabolites maintain intestinal homeostasis and regulate inflammation through immune responses, while the components of the microbiota direct immune responses by activating the intestinal TLR pathway[45-47]. For example, the expression of IL17, an inflammatory cytokine produced by γδ T cells, can be inhibited by propionate, a metabolite of intestinal bacteria[48]. Conversely, intestinal immune cells precisely regulate the microbial community both directly and indirectly, thus establishing a sustainable balance between the immune cells and intestinal microbiota [49-51].

The intestinal barrier should be considered a highly dynamic and complex structure that responds to internal and external stimuli[52,53]. Dysfunction of the intestinal barrier often occurs when the damage of the intestinal mucosa is severe and the components of the intestinal barrier change[54]. Under pathological conditions such as stress[55] and ischemia or hypoxia[56], the intestinal barrier is destroyed and the permeability of the intestine increases, thereby inducing bacterial translocation, electrolyte disorders and inflammatory response[57] (Figure 2). With the increasing permeability of the intestine, locally produced ATP is released into the intestinal microenvironment, followed by the activation of immune cells via ATP receptors, including P2X7 purinoreceptor. When the intestinal immune system is activated, the inflammatory effects may not be regulated, which may lead to the irreversible destruction of the intestinal barrier[58]. More recently, it has been reported that increased ATP concentrations promote T-cell responses by enhancing the expression of the CD86 costimulatory molecule on antigen-presenting cells, an effect mediated through P2X7 purinergic receptor. Thus, the immune system may be the key player in barrier dysfunction and T cells may be involved in adaptive immune responses.

THE ROLE OF T CELLS IN THE INTEGRITY OF THE INTESTINAL BARRIER

T lymphocytes, which are adaptive immune cells, respond to specific antigens and remain the bacterial diversity by complex mechanisms in the homeostatic condition[2]. In the intestine, invariant NKT (iNKT) cells could either enhance or inhibit the immune response, and they might directly or indirectly regulate the microbiota in the intestine[59-62]. CD8+ T cells are the main intraepithelial lymphocytes that monitor and respond to pathogens[63]. CD4+ T cells and T-helper (Th) cells are mainly located in the intestinal lamina propria, and Th1 and Th17 cells can be found in the intestine[64]. Activated intestinal effector T cells could mount immune responses and influence the gut microbiota, and the excess of these cells might induce advanced inflammatory responses and acute or chronic inflammatory diseases[65-67]. In the intestinal adaptive immune response, dendritic cells ingest antigens and activate T cells, and Thy1 cells are induced to differentiate into three different types of Th cells[68]. When lymphocytes respond to different stimuli, they can be divided into different groups based on their cytokine profile, such as Th1, Th2, or Treg cells, which are regulated by P2X7 purinergic receptor, mechanistically[69]. Activated T cells can modulate immune responses by secreting inflammatory cytokines or by interacting with other cells. The function of Th1 cells is to activate and proliferate cytotoxic T cells, thereby inducing the damage of infected intestinal epithelial cells[70]. Th2 cells can release inflammatory cytokines (IL-4, IL-5, and IL-13) and activate B cells to attack the infected cells[71-73]. Transforming growth factor β is capable of suppressing immunoglobulins M and G and promoting their switch to immunoglobulin A. This cytokine is secreted by T cells in Peyer's patches, suggesting the role of T cells in oral tolerance[74].

When intestinal permeability is damaged, antigens can pass through the intestinal epithelial cells and be taken up by macrophages or dendritic cells. Then, the antigens are presented to T cells in the lamina propria by these antigen-presenting cells, which stimulates T cells and induces their proliferation[75,76]. Some antigens may be taken up by intestinal epithelial cells via endocytosis and then be presented to T cells after intracellular processing. This process is based on the classical and nonclassical histocompatibility molecules[77,78]. T cells use both their receptor and a costimulatory signal to recognize antigens[79].

Intestinal barrier disruption is usually accompanied by intestinal inflammation and pathogen invasion. T cells, the key components of adaptive immunity, can effectively limit the invading bacteria and regulate the inflammatory response together with the innate immune system and cytokines[80]. For example, the T helper cell type (Th)1 immune response is necessary in antipathogen protection and is involved in intestinal inflammation[81,82]. In humans, Th17 cells mainly reside in the intestine, where their polarization occurs. Because of the plasticity of Th17 cells, polarized cells have antipathogenic functions and maintain the intestinal epithelial integrity under normal physiological conditions, but they may turn into proinflammatory cells when exposed to IL-23[83]. Th17 cells can mediate inflammation by secreting a proinflammatory cytokine, IL-17A[70]. Peripheral Th17 cells are produced and migrate to the intestine in the case of oral inflammation, which may cause intestinal inflammation[84]. In addition to suppressing the proliferation of Th cells, Treg cells can protect against bacteria and dietary antigens and can produce anti-inflammatory cytokines to exert their anti-inflammatory function, thereby maintaining the homeostasis of the intestinal epithelium[85-87]. With the development of intestinal inflammation, the balance between Th17 cells and Treg cells may be broken up, biasing the function of Th17 cells[88]. In a recent study, it has been found that tissue-resident memory T cells are important in the development of intestinal inflammation, but the role of these cells in this process is not...
T-cell function in intestinal barrier disruption

Figure 2 Intestinal barrier components and the intestinal barrier dysfunction. The normal intestinal barrier is formed by many layers which includes cytokines, bacteria, cells and secretory IgA. The intestinal barrier dysfunction results in the increasing of the intestinal permeability, which subsequently causes the inflammatory response and bacteria translocation.

In summary, T cells are very likely to become effective regulatory targets in the intestinal barrier, and T cell-associated therapy may be used in clinical settings in the future.

THE ROLE OF P2X7R IN THE INTESTINAL BARRIER DYSFUNCTION

Among the members of P2X receptor family, P2X7R (encoded by p2rx7) is the largest (with 595 amino acids in humans). It has special structural and signaling features because of its long intracellular carboxy-terminal, which helps prevent receptor desensitization[90,91]. The monomeric structure of P2X7R has two intracellular domains (C-terminal and N-terminal) and an extracellular ATP-binding domain that separates two transmembrane domains[92]. There were over 1500 single nucleotide polymorphisms (SNPs) reported in NCBI database, and most of them were missense, intronic or nonsynonymous[93]. In highly polymorphic human P2RX7, SNPs play a critical role in the biological process and function of P2X7R. About 10 loss of function SNPs and 3 gain of function SNPs have been identified[12]. For example, the activity of human P2X7R was reduced when Ala replaced Glu[94]. When Asn replaced Ile-568, the expression of P2X7R was decreased to approximately 50% of normal, and P2X7R became nonfunctional[95]. The mutation of R307Q located in the ATP-binding pocket impaired the binding of ATP to P2X7R[96]. Genetic variants in P2X7R may be involved in the inflammatory response[97,98]. P2X7R function related SNPs played a regulatory role in inflammatory diseases[32]. Unlike other P2X receptors, the complete activation of P2X7R requires a higher concentration of ATP (range from about 0.1 to 2.5 mmol/L)[99]. When activated by ATP, P2X7R not only mediates the uptake of cations and macromolecules, but also leads to the activation of intracellular signaling pathways[100-102]. It has been demonstrated that the formation of macropores requires pannexin-1 channels, and pannexin-1 antagonists can decrease the formation of these pores[103]. However, recent data have suggested that the formation of macropores may be intrinsic to P2X7R without accessory molecules[104-106]. Moreover, P2X7R is associated with the activation of the signaling pathway and transcription factors, including MAP kinases, the cyclic AMP response element[107,108]. P2X7R is widely expressed in immune cells, which suggests its importance in the regulation of both the innate
and adaptive immunity, especially in the regulation of inflammation[109,110]. ATP is the most important energy molecule and a common extracellular signaling nucleotide that participates in the regulation of cellular proliferation, differentiation and death[111-113]. In a healthy body, eATP is maintained in a low concentration thanks to ATPases in extracellular spaces. ATP can leak from damaged or distressed cells, and can also be released by nonlytic regulated mechanisms, which increase the concentration of eATP[114-117]. It has been proven that the concentration of eATP is higher in different inflammatory conditions than in normal conditions[118,119].

The intestinal barrier dysfunction induces the inflammatory response and epithelial cell death[120,121]. In the acute-inflammatory tissue, high amounts of IL-6 are released, thereby inducing the synthesis and release of ATP from Treg cells exposed to IL-6[122]. The concentration of eATP may increase after intestinal barrier dysfunction, which may activate P2X7R. T follicular helper cells enhance germinal center reactions by deleting P2X7, resisting ATP-mediated immune cell death[123]. When the concentration of eATP produced by the intestinal microbiota is high, commensal-specific IgA responses initiated by intestinal lymphoid tissues are inhibited, which influences the composition of intestinal microbiota[124,125]. Moreover, Perruzza et al[126] showed that the blockade of P2X7R could decrease proinflammatory cytokines and protect the intestinal barrier function by inhibiting the activation of macrophages. Nucleotide-binding domain, leucine-rich-repeat receptor, pyrin domain-containing NLR family pyrin domain containing 3 (NLRP3) is a multiprotein complex that participates in the occurrence and development of many inflammatory diseases[127]. The inhibition of NLRP3 can reduce intestinal inflammation and enhance the barrier function[128]. Both NLRP3 and P2X7R are expressed in different immune cells, including T cells, B cells and monocytes[99]. Several signaling pathways induced by activated P2X7R may lead to a decrease in intracellular K+, an increase in Ca²⁺ and the production of reactive oxygen species, which are key steps in NLRP3 activation[129-132] (Figure 1).

THE ROLE OF T CELL-DERIVED P2X7R IN THE INTESTINAL BARRIER DYSFUNCTION

It has been reported that activated P2X7R can affect several of the biological processes of T cells, including activation, differentiation and death[133]. After recognizing antigens, T cells rapidly release ATP through pannexin channels due to the T cell receptor signaling and co-stimulatory molecules[134,135]. Because of the highly expressed P2X7 in iNKT cells, they were susceptible to P2X7-mediated cell death and regulated by vitamin A, finally influencing the intestinal homeostasis[136]. ATP released from T cells can activate P2X receptor which increases the expression of the p2rx7 gene[14,135]. Yip et al[135] found that the silencing of P2X7R blocked Ca²⁺ influx and inhibited T cell activation in human CD4⁺ T cells. These findings suggest that activated P2X7R is essential for the activation of T cells. L-selectin (CD62L) is related to the migration of T cells[137,138]. Low expression of L-selectin is necessary for activated or differentiated T cells to egress from the lymph node[139]. P2X7R activated by ATP can trigger CD62L shedding in human naïve T cells[140]. In a lymph node, activated P2X7R also affects the motility of T cells by inducing their calcium waves[141]. When intracellular ATP and NAD⁺ nucleotides are released from cells, they can trigger the activation of P2X7R and induce apoptosis or necrosis[142]. In the case of low micromolar concentration of extracellular NAD⁺, ADP ribosylation of P2X7R induces cell death because of persistent P2X7R activation[27]. Under the condition of activated P2X7R, there are two independent ways to induce T cell death: one of them depends on the phosphorylation of ERK1/2, and the other is associated with the nonselective pore[143,144]. In addition, CD62L shedding triggered by the activated P2X7R may induce cell death by apoptosis[145,146]. Compared with native T cells, activated T cells are less sensitive to NICD induced by P2X7R[147]. The expression of P2X7R is different in different populations of T cells. For example, Tregs and follicular helper T cells exhibit high expression of the P2X7 receptor, suggesting that they are more susceptible to cell death than other populations of T cells[148,149]. eATP and P2X7R influence the differentiation of T cells and play a significant role in the metabolism, generation, and memory function of CD8⁺ T cells[150]. It has been shown that the AMP-activated protein kinase signaling pathway may promote constant efflux of intracellular ATP in memory CD8⁺ T cells, and is involved in the differentiation and maintenance of memory T cells induced by P2X7R[151,152]. In an inflammatory environment, activated P2X7R drives the differentiation from T cells to Th17 cells[153], and the receptor reduces the differentiation of Tr1 cells with a high expression of IL-10 without Foxp3[21,155]. Activated P2X7R can also regulate the plasticity of Th17 cells and induce Th17 cells to differentiate[156]. In addition to acting directly on T cells, P2X7R can regulate the differentiation of T cells by affecting the physiological functions of dendritic cells[157,158]. Although ATP may not only reduce the DCs-induced Th1 cell differentiation but can also influence the interaction of DCs with T cells, there is little research on the role of P2X7R during this process[159,160]. Moreover, activated P2X7R regulates the cytokine secretion and polarization of Th17 cells by influencing dendritic cells[161,162] (Figure 3). Myeloid derived suppressor cells were considered as the regulator of immunosuppression via affecting the amounts, functions, or phenotypes of T cells, and the ATP/P2X7R signaling axis may be involved in this process[163].
**DISCUSSION**

The intestinal barrier dysfunction is a complex and severe pathological condition, which induces the inflammatory response and bacterial invasion. Sepsis is a serious systemic inflammatory disease with high morbidity and mortality in the intensive care unit because it can cause multiple organ failure in patients[164]. Given that the progression and pathogenesis of sepsis have been attributed to intestinal barrier dysfunction, further research on the immune and inflammatory factors of the intestinal barrier dysfunction is necessary[165,166].

According to the above description, T cells are involved in oral tolerance and immune response to antigens in the intestine, and they are the most common lymphocytes that reside in the intestine[167]. Moreover, infiltration by inflammatory T cells is a significant pathological characteristic of intestinal inflammation[168]. Thus, an appropriate number and population of T cells may mitigate the damage of intestinal barrier dysfunction.

P2X7R is widely expressed in T cells and serves as a regulatory factor of their biological processes. Heiss et al[169] found that intestinal CD8+ T cells express a high concentration of P2X7R and are highly sensitive to extracellular nucleotides, indicating that P2X7R can regulate intestinal T cell responses. Inflammatory effector T cells can be depleted and intestinal inflammation can be relieved after treatment with NAD+[170]. P2X7R has been shown to be the trigger for the activation of NLRP3, indicating that this receptor regulates the release of inflammatory cytokines (IL-1β, IL-1β) and the initiation of an inflammatory response[171-174]. Therefore, P2X7R may influence inflammation via T cells which is indirect. The selectively P2X7 antagonist was proven to significantly inhibit the innate immune cells and upregulate the immunosuppressive-associated T cells, indicating that this antagonist may be a kind of potential treatment[175]. The effect of P2X7-blockade drug has also been demonstrated in the mouse models with advanced tuberculosis[176]. In addition to the above intracellular signaling pathways (MAPK pathway), previous studies verified that P2X7R also regulated MyD88/NF-κB and PI3K/Akt/mTOR signaling pathways in innate and adaptive immune responses, which suggested that the key proteins in these pathways can be considered as novel therapeutic targets[177].

**CONCLUSION**

In summary, T cells, the key participant in the intestinal barrier dysfunction, are regulated by P2X7R. The roles and mechanisms of P2X7R are associated with T lymphocytes in the intestinal barrier dysfunction and may be a potential research direction, although there have been few studies on this topic (Figure 4). Furthermore, different specific molecules that inhibit the expression of P2X7R may be
The schematic diagram of the hypothesis of the P2X7 receptor as the regulator of T-cell function in intestinal barrier disruption calls for potential therapeutic drugs in the future.

### FOOTNOTES

**Author contributions:** Jiang ZF and Wu W contributed equally to this work; Zhong M and Zhang L were corresponding authors; Jiang ZF and Wu W wrote the manuscript; Zhang L and Zhong M conceived the topic and reviewed the manuscript; Jiang ZF and Zhang L revised the manuscript; Hu HB and Li ZY reviewed the manuscript; all authors contributed to the article and approved the submitted version.

**Supported by** The National Natural Science Foundation of China, No. 81801943; Shanghai Pujiang Program, No. 21PJ0009; and The Research Grant for Public Health Key Discipline of Shanghai Municipality, China, No. GWV-10.1-XK26.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

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**S-Editor:** Gong ZM
**L-Editor:** Filipodia
**P-Editor:** Gong ZM
Drewe J, Beglinger C, Fricker G. Effect of ischemia on intestinal permeability of lipopolysaccharides. *Eur J Clin Invest* 2002; 32: 25691837 [PMID: 12158300].
2001; 31: 138-144 [PMID: 11168452 DOI: 10.1046/j.1365-2362.2001.00792.x]

Pan P, Song Y, Du X, Bai L, Hua X, Xiao Y, Yu X. Intestinal barrier dysfunction following traumatic brain injury. 
Neurosci Lett 2019; 40: 1005-1110 [PMID: 30771025 DOI: 10.1016/j.neulet.2019.07.045]

Plichta DR, Graham DB, Subramanian S, Xavier RJ. Therapeutic Opportunities in Inflammatory Bowel Disease: 
Mechanistic Dissection of Host-Microbiome Relationships. Cell 2019; 178: 1041-1056 [PMID: 31442399 DOI: 
10.1016/j.cell.2019.07.045]

Wingender G, Kronenberg M. Role of NKT cells in the digestive system. IV. The role of canonical natural killer T cells in mucosal immunity and inflammation. 
Am J Physiol Gastrointest Liver Physiol 2008; 294: G1-48 [PMID: 17947447 DOI: 
10.1152/ajpgi.00437.2007]

Zeissig S, Kaser A, Dougan SK, Nieuwenhuis EE, Blumberg RS. Role of NKT cells in the digestive system. III. Role of 
NKT cells in intestinal immunity. Am J Physiol Gastrointest Liver Physiol 2007; 293: G1101-G1105 [PMID: 
17717040 DOI: 10.1152/ajpgi.00342.2007]

Wang Y, Sedimbi S, Lòbom L, Singh AK, Porcelli SA, Cardell SL. Unique invariant natural killer T cells promote 
intestinal polyps by suppressing TH1 immunity and promoting regulatory T cells. 
Mucosal Immunol 2018; 11: 131-143 [PMID: 28401935 DOI: 10.1038/mi.2017.34]

Selvanantham T, Lin Q, Guo CX, Szurendra A, Fieve S, Escalante NK, Guttman DS, Streutker CJ, Robertson SJ, Philpott 
DJ, Mallevaey JJ. TLR4 in inflammatory bowel disease. 
Cario E, Podolsky DK. Differential alteration in intestinal epithelial cell expression of toll-like receptor 3 (TLR3) and 
adaptor molecules in inflammatory bowel disease. 
Lafleur D, Jerasi J, Wong GK, Madsen K, Carroll MW, Huynh HQ, Dieleman LA, Wine E. 
N Engl J Med 2000; 342: 7010-7017 [PMID: 11083826 DOI: 
10.1016/j.cell.2019.07.045]

Lee SH, Kwon JE, Cho ML. Immunological pathogenesis of inflammatory bowel disease. 
Intest Res 2018; 16: 26-42 [PMID: 
29422795 DOI: 10.5217/ir.2018.16.1.26]

Chang JT. Pathophysiology of Inflammatory Bowel Diseases. 
N Engl J Med 2020; 383: 2652-2664 [PMID: 33382932 DOI: 
10.1053/j.nejmrsr.2002697]

Armstrong H, Alipour M, Valcheva R, Bording-Jorgensen M, Jovel J, Zaidi D, Shah P, Lou Y, Ebeling C, Mason AL, 
Lafleur D, Jersery J, Wong GK, Madsen K, Carroll MW, Huynh HQ, Dieleman LA, Wine E. Host immunoglobulin G 
selectively identifies pathobionts in pediatric inflammatory bowel diseases. 
Microbiome 2019; 7: 1 [PMID: 30606251 DOI: 
10.1186/s40468-018-0604-3]

Romagnani S. Lymphokine production by human T cells in disease states. 
Ann Rev Immunol 1994; 12: 227-257 [PMID: 
20811282 DOI: 10.1146/annurev.iy.12.040194.001303]

Baumgart DC, Dignass AU. Intestinal barrier function. 
Curr Opin Clin Nutr Metab Care 2002; 5: 685-694 [PMID: 
12394615 DOI: 10.1097/00001575-200211000-00012]

Elson CO, Cong Y, Jugal N, Weaver CT. Immuno-bacterial homeostasis in the gut: new insights into an old enigma. 
Semin Immunol 2001; 13: 187-194 [PMID: 11394961 DOI: 
10.1006/simm.2001.0312]

Rescigno M, Urbano M, Valzasina B, Francolini M, Rotta G, Bonasoro R, Granucci F, Kraehenbuhl JP, Ricciardi- 
Castagnoli P. Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria. 
Nat Immunol 2001; 2: 361-367 [PMID: 11276208 DOI: 
10.1038/3677747]

Shao L, Serrano D, Mayer L. The role of epithelial cells in immune regulation in the gut. 
Semin Immunol 2001; 13: 163-176 [PMID: 
11394959 DOI: 10.1006/smim.2000.0311]

Telega GW, Baumgart DC, Carding SR. Uptake and presentation of antigen to T cells by primary colonic epithelial cells in 
normal and diseased states. 
Gastroenterology 2000; 119: 1548-1559 [PMID: 11111076 DOI: 10.1053/gast.2000.20168]

Cario E, Podolsky DK. Differential alteration in intestinal epithelial cell expression of toll-like receptor 3 (TLR3) and 
TLR4 in inflammatory bowel disease. 
Infect Immun 2000; 68: 7010-7017 [PMID: 
11083826 DOI: 10.1128/iai.68.12.7010-7017.2000]

Holleran G, Lopetuso L, Petitto V, Graziani C, Ianoro G, McNamara D, Gasbarrini A, Scadafarri F. The Innate and 
Adaptive Immune System as Targets for Biologic Therapies in Inflammatory Bowel Disease. 
Int J Mol Sci 2017; 18 [PMID: 
28934123 DOI: 10.3390/ijms18102020]

Bagheri N, Salimzadeh L, Shirzad H. The role of T helper 1-cell response in Helicobacter pylori-infection. 
Microbes Pathog 2018; 123: 1-8 [PMID: 29936093 DOI: 10.1016/j.micpath.2018.06.033]

De Cari M, D’Elissos MM, Zanuoglu G, Romagnani S, Del Prete G. Human Th1 and Th2 cells: functional properties, 
regulation of development and role in autoimmune. 
Autoimmunity 1994; 18: 301-308 [PMID: 7858116 DOI: 
10.1080/08969959409500532]

Shao L, Li M, Zhang B, Chang P. Bacterial dysbiosis incites Th17 cell revolt in irradiated gut. 
Biomed Pharmacother 2020; 131: 110674 [PMID: 
32866810 DOI: 10.1016/j.biopha.2020.110674]

Kitamoto S, Nagao-Kitamoto H, Jiao Y, Gilliland MG 3rd, Hayashi A, Imai J, Sugihara K, Miyoshi M, Brazil JC, Kuffa

https://www.wjgnet.com
P. Hill BD, Rizvi SM, Wen F, Bishu S, Inohara N, Eaton KA, Nusrat A, Lei YL, Giannobile WV, Kamada N. The Intermucosal Connection between the Mouth and Gut in Commensal Pathobiont-Driven Colitis. Cell 2020; 182: 447-462.e14 [PMID: 32758418 DOI: 10.1016/j.cell.2020.05.048]

O’Garra A, Vieira P. Regulatory T cells and mechanisms of immune system control. Nat Med 2004; 10: 801-805 [PMID: 15268761 DOI: 10.1038/nm0804-801]

Fernandes C, Wanderley CW, Silva CMS, Muniz HA, Teixeira MA, Souza NRP, Cândido AGF, Falcão RB, Souza MHLP, Almeida PRC, Câmara LMC, Lima-Júnior RCP. Role of regulatory T cells in trinitroaniline-induced intestinal mucositis. Eur J Pharm Sci 2018; 115: 158-166 [PMID: 29307857 DOI: 10.1016/j.ejps.2018.01.006]

Geremia A, Biancheri P, Allain P, Corazza GR, Di Sabatino A. Innate and adaptive immunity in inflammatory bowel disease. Autoimmun Rev 2014; 13: 3-10 [PMID: 23774107 DOI: 10.1016/j.autrev.2013.06.004]

Ueno A, Jeffery L, Kobayashi T, Hibi T, Ghosh S, Jijon H. Th17 plasticity and its relevance to inflammatory bowel disease. J Autoimmun 2018; 73: 38-49 [PMID: 29290521 DOI: 10.1016/j.jaut.2017.12.004]

Zundler S, Becker E, Spocinska M, Slawik M, Parga-Vidal L, Stark R, Wiendl M, Atreya R, Rath T, Leppkes M, Hildner K, López-Pedrosas R, Lukassen S, van Gisbergen KJP, Neurath MF. Hobit- and Blimp-1-driven CD4+ tissue-resident memory T cells control chronic intestinal inflammation. Nat Immunol 2019; 20: 288-300 [PMID: 30692620 DOI: 10.1038/s41590-018-0298-5]

Rassendren F, Buell GN, Vinson C, Collo G, North RA, Surprenant A. The permeabilizing ATP receptor, P2X7. Cloning and expression of a human cDNA. J Biol Chem 1997; 272: 5482-5486 [PMID: 9038151 DOI: 10.1074/jbc.272.9.5482]

McCarthy AE, Yoshioka C, Mansoor SE. Full-Length P2X Structures Reveal How Palmitoylation Prevents Channel Desensitization. Cell 2019; 179: 659-670.e13 [PMID: 31587896 DOI: 10.1016/j.cell.2019.09.017]

Surprenant A, Rassendren F, Kawashima E, North RA, Buell G. The cytolytic P2Z receptor for extracellular ATP identified as a P2X receptor (P2X7). Science 1996; 272: 735-738 [PMID: 8614837 DOI: 10.1126/science.272.5262.735]

Zhu X, Li Q, Song W, Peng X, Zhao R. P2X7 receptor: a critical regulator and potential target for breast cancer. J Mol Med (Berl) 2021; 99: 349-358 [PMID: 33486566 DOI: 10.1007/s00109-021-02041-x]

Gu BJ, Zhang W, Worthington RA, Sluyter R, Dao-Ung P, Petrou S, Barden JA, Wiley JS. A Glu-496 to Ala polymorphism leads to loss of function of the human P2X7 receptor. J Biol Chem 2001; 276: 11135-11142 [PMID: 11150303 DOI: 10.1074/jbc.M01033200]

Wiley JS, Dao-Ung LP, Li C, Shemon AN, Gu BJ, Smart ML, Fuller SJ, Barden JA, Petrou S, Sluyter R. An Ile-568 to Asn polymorphism prevents normal trafficking and function of the human P2X7 receptor. J Biol Chem 2003; 278: 17108-17113 [PMID: 12588625 DOI: 10.1074/jbc.M212759200]

Gu BJ, Sluyter R, Skarratt KK, Shemon AN, Dao-Ung LP, Fuller SJ, Barden JA, Clarke AL, Petrou S, Wiley JS. An Arg307 to Gln polymorphism within the ATP-binding site causes loss of function of the human P2X7 receptor. J Biol Chem 2004; 279: 31287-31295 [PMID: 15123679 DOI: 10.1074/jbc.M313902200]

Wesselinus A, Bours MJ, Arts IC, Theunisz EH, Geusens P, Dagnelie PC. The P2X(7) loss-of-function Glu496Ala polymorphism affects ex vivo cytokine release and protects against the cytotoxic effects of high ATP-levels. BMC Immunol 2012; 13: 64 [PMID: 23210974 DOI: 10.1186/1471-2172-13-64]

Ide S, Nishizawa D, Fukuda K, Kasi S, Hasegawa J, Hayashida M, Minami M, Ikeda K. Haplotype of P2RX7 gene polymorphism are associated with both cold sensitivity and analgesic effect of fentanyl. Mol Pain 2014; 10: 75 [PMID: 25472448 DOI: 10.1186/1744-8609-10-75]

Tao JH, Cheng M, Tang JP, Dai XJ, Zhang Y, Li XP, Liu Q, Wang YL. Single nucleotide polymorphisms associated with P2X7R function regulate the onset of gouty arthritis. PLoS One 2017; 12: e0181685 [PMID: 28797095 DOI: 10.1371/journal.pone.0181683]

Pellegri P. P2X7 receptors and the NLPR3 inflammasome: Partners in crime. Biochem Pharmacol 2021; 187: 114335 [PMID: 33359010 DOI: 10.1016/j.bcp.2020.114335]

Garcia-Marcos M, Pérez-Andrés E, Tandel S, Fontanils U, Kumps A, Kabré E, Gómez-Muñoz A, Marino A, Dehaye JP, Pochet S. Coupling of two pools of P2X7 receptors to distinct intracellular signaling pathways in rat submandibular gland. J Lipid Res 2006; 47: 705-714 [PMID: 16415476 DOI: 10.1194/jlr.M504006-JLR200]

North RA. P2X receptors. Philos Trans R Soc Lond B Biol Sci 2016; 371 [PMID: 27377721 DOI: 10.1098/rstb.2015.0427]

Virgilio F, Sarti AC, Grassi F. Modulation of innate and adaptive immunity by P2X ion channels. Curr Opin Immunol 2018; 52: 51-59 [PMID: 29631184 DOI: 10.1016/j.coi.2018.03.026]
111 Alarcon-Vila C, Pizzuto M, Pelegrin P. Purinergic receptors and the inflammatory response mediated by lipids. *Curr Opin Pharmacol* 2019; 47: 90-96 [PMID: 30952600 DOI: 10.1016/j.coph.2019.02.004]

112 Burnstock G. Purinergic signaling and vascular cell proliferation and death. *Arterioscler Thromb Vasc Biol* 2002; 22: 364-373 [PMID: 11884276 DOI: 10.1161/hq302.105360]

113 Burnstock G. Physiology and pathophysiology of purinergic neurotransmission. *Physiol Rev* 2007; 87: 659-797 [PMID: 17429044 DOI: 10.1152/physrev.00043.2006]

114 Surprenant A, North RA. Signaling at purinergic P2X receptors. *Annu Rev Physiol* 2009; 71: 333-359 [PMID: 18851707 DOI: 10.1146/annurev.physiol.70.113006.100630]

115 Sun X, Zhou R, Lei Y, Hu J, Li X. The ligand-gated ion channel P2X7 receptor mediates NLRP3/caspase-1-mediated pyroptosis in cerebral corticobasal neurons of juvenile rats with sepsis. *Brain Res* 2020; 1748: 147109 [PMID: 32905819 DOI: 10.1016/j.brainres.2020.147109]

116 Bulanova E, Bulfone-Paus S. P2 receptor-mediated signaling in mast cell biology. *Purinergic Signaling* 2010; 6: 3-17 [PMID: 19921464 DOI: 10.1007/s11302-009-9173-z]

117 Ruan Z, Orozco JJ, Du J, Liu W. Structures of human pannexin 1 reveal ion pathways and mechanism of gating. *Nature* 2020; 584: 646-651 [PMID: 32494015 DOI: 10.1038/s41586-020-2357-y]

118 Chekeni FB, Elliott MR, Sandilos JK, Walk SF, Kinchen JM, Lazarowski ER, Armstrong AJ, Penuela S, Laird DW, Salvesen GS, Isakson BE, Bayliss DA, Ravichandran KS. Pannexin 1 channels mediate ’find-me’ signal release and membrane permeability during apoptosis. *Nature* 2010; 467: 867-871 [PMID: 20944749 DOI: 10.1038/nature09413]

119 Barberà-Cremades M, Baroja-Mazo A, Gomez AI, Machado F, Di Virgilio F, Pelegrin P. P2X7 receptor-stimulation causes fever via PGE2 and IL-1β release. *FASEB J* 2012; 26: 2951-2962 [PMID: 22490780 DOI: 10.1096/fj.12-205675]

120 Amores-Iniesta J, Barberà-Cremades M, Martínez CM, Pons JA, Revilla-Nuñ B, Martínez-Alarcon L, Di Virgilio F, Parrilla P, Baroja-Mazo A, Pelegrin P. Extracellular ATP Activates the NLRP3 Inflammasome and Is an Early Danger Signal of Skin Allograft Rejection. *Cell Rep* 2017; 21: 3414-3426 [PMID: 29262323 DOI: 10.1016/j.celrep.2017.11.079]

121 Chen WY, Wang M, Zhang J, Barve SS, McClain CJ, Yoshi-Barve S. Acrolein Disrupts Tight Junction Proteins and Causes Endoplasmic Reticulum Stress-Mediated Epithelial Cell Death Leading to Intestinal Barrier Dysfunction and Permeability. *Am J Pathol* 2017; 187: 2686-2697 [PMID: 28935573 DOI: 10.1016/j.ajpath.2017.08.015]

122 Sun S, Duaz Z, Wang X, Chu C, Yang C, Chen F, Wang D, Wang C, Li Q, Ding W. Neutrophil extracellular traps impair intestinal barrier functions in sepsis by regulating TLR9-mediated endoplasmic reticulum stress pathway. *Cell Death Dis* 2021; 12: 606 [PMID: 34117211 DOI: 10.1038/s41419-021-03896-1]

123 Piconese S, Sri G, Trippo C, Musio S, Gorzanelli A, Fossi B, Pedrotti R, Pacilio CE, Colombo MP. Mast cells counteract regulatory T-cell suppression through interleukin-6 and OX40/OX40L axis toward Th17-cell differentiation. *Blood* 2009; 114: 2639-2648 [PMID: 19643985 DOI: 10.1182/blood-2009-05-220004]

124 Proietti M, Coracinechi V, Rezzonico Jost T, Romagnani A, Faliti CE, Perruzza L, Rigoni R, Radaelli E, Caprioli F, Peruzzi S, Brannetti B, Thelen M, McCoy KD, Slack E, Traggiai E, Grassi F. ATP-gated ionotropic P2X7 receptor controls follicular T helper cells number in Peyer's patches to promote host-microbiota mutualism. *Immunity* 2014; 41: 789-801 [PMID: 25464855 DOI: 10.1016/j.immuni.2014.10.010]

125 Proietti M, Perruzza L, Scribano D, Pellegrini G, D’Antuono R, Strati F, Raffaelli M, Gonzalez SF, Thelen M, Hardt WD, Schiavone P, De Falco A, Zotti L. Pannexin-1 hemichannel-mediated ATP release together with P2X1 and P2X4 receptors regulate T-cell activation at the immune synapse. *Cell Death Dis* 2021; 12: 2546-2575 [PMID: 32905819 DOI: 10.1038/s41419-021-03896-1]

126 Wu X, Ren J, Chen G, Wu L, Song X, Li G, Deng Y, Wang G, Gu G, Li J. Systemic blockade of P2X7 receptor protects against sepsis-induced intestinal barrier disruption. *Sci Rep* 2017; 7: 4364 [PMID: 28663567 DOI: 10.1038/s41598-017-04233-5]

127 Jiang H, Gong T, Zhou R. The strategies of targeting the NLRP3 inflammasome to treat inflammatory diseases. *Adv Immunol* 2020; 145: 55-93 [PMID: 32081200 DOI: 10.1016/bs.ai.2019.11.003]

128 Li M, Lv R, Wang C, Ge Q, Du H, Lin S. *Tricholoma matsutake*-derived peptide WFNNAGP protects against DSS-induced colitis by ameliorating oxidative stress and intestinal barrier dysfunction. *Food Funct* 2021; 12: 11883-11897 [PMID: 34738612 DOI: 10.1039/d1fo02806c]

129 Lee GS, Subramanian N, Kim AI, Aksentijevich I, Goldbach-Mansky RS, Sacks DB, Germain RN, Kastner DL, Chae JJ. The calcium-sensing receptor regulates the NLRP3 inflammasome through Ca2+ and cAMP. *Nature* 2012; 492: 123-127 [PMID: 23143333 DOI: 10.1038/nature11588]

130 Tschopp J, Schroder K. NLRP3 inflammasome activation: The convergence of multiple signalling pathways on ROS production? *Nat Rev Immunol* 2010; 10: 210-215 [PMID: 20683318 DOI: 10.1038/nri2725]

131 Hafner-Bratkovič I, Pelegrin P. Ion homeostasis and ion channels in NLRP3 inflammasome activation and regulation. *Curr Opin Immunol* 2018; 52: 8-17 [PMID: 29555989 DOI: 10.1016/j.coi.2018.03.010]

132 Di A, Xiong S, Ye Z, Malireddi RKS, Kometani S, Zhong M, Mittal M, Hong Z, Kangemi TD, Rehman J, Malik AB. The TWIK2 Potassium Efflux Channel in Macrophages Mediates NLRP3 Inflammasome-Induced Inflammation. *Immunity* 2018; 48: 56-65 [PMID: 29958799 DOI: 10.1016/j.immuni.2018.04.032]

133 Voechtle T, Yip L, Lithaih A, Sumi Y, Chen Y, Yao Y, Insel PA, Juenger WG. Pannexin-1 hemichannel-mediated ATP release together with P2X1 and P2X4 receptors regulate T-cell activation at the immune synapse. *Blood* 2010; 116: 3475-3484 [PMID: 20660208 DOI: 10.1182/blood-2010-04-277707]

134 Voechtle T, Voechtle T, Corridore R, Hirsh M, Chen Y, Inoue Y, Ferrari V, Insel PA, Juenger WG. Autocrine regulation of T-cell activation by ATP release and P2X7 receptors. *FASEB J* 2009; 23: 1685-1693 [PMID: 19211924 DOI: 10.1096/fj.08-126458]

135 Liu Q, Kim CH. Control of Tissue-Resident Invariant NKT Cells by Vitamin A Metabolites and P2X7-Mediated Cell

https://www.wjgnet.com

5277 September 28, 2022 | Volume 28 | Issue 36
Depth. J Immunol 2019; 203: 1189-1197 [PMID: 31308092 DOI: 10.4049/jimmunol.1900398]

Arbonés ML, Ord DC, Ley K, Rateh H, Maynard-Curry C, Otten G, Capon DJ, Tedder TF. Lymphocyte homing and leukocyte rolling and migration are impaired in L-selectin-deficient mice. Immunity 1994; 1: 247-260 [PMID: 7534203 DOI: 10.1016/1074-7613(94)90076-0]

Masopust D, Schenkel JM. The integration of T cell migration, differentiation and function. Nat Rev Immunol 2013; 13: 309-320 [PMID: 23598650 DOI: 10.1038/nm3442]

Mueller SN, Gehhardt T, Carbone FR, Heath WR. Memory T cell subsets, migration patterns, and tissue residence. Annu Rev Immunol 2013; 31: 137-161 [PMID: 23215646 DOI: 10.1146/annurev-immunol-032712-09554]

Foster JG, Carter E, Kilty I, MacKenzie AB, Ward SG. Mitochondrial superoxide generation enhances P2X7R-mediated loss of cell surface CD26L on naive human CD4+ T lymphocytes. J Immunol 2013; 190: 1551-1559 [PMID: 23319734 DOI: 10.4049/jimmunol.1201510]

Grassi F. The P2X7 Receptor as Regulator of T Cell Development and Function. Front Immunol 2020; 11: 1179 [PMID: 32587592 DOI: 10.3389/fimmu.2020.01179]

Wang CM, Ploia C, Anselmi F, Sarukhan A, Viola A. Adenosine triphosphate acts as a paracrine signaling molecule to reduce the motility of T cells. EMBO J 2014; 33: 1354-1364 [PMID: 24843045 DOI: 10.1022/embj.201306666]

Shuyer R. The P2X7 Receptor. Adv Exp Med Biol 2017; 1051: 17-53 [PMID: 28676924 DOI: 10.1007/5854_2017_59]

Tsukimoto M, Maehata M, Harada H, Ikarı A, Takagi K, Degawa M. P2X7 receptor-dependent cell death is modulated during murine T cell maturation and mediated by dual signaling pathways. J Immunol 2006; 177: 2842-2850 [PMID: 16920919 DOI: 10.4049/jimmunol.177.5.2842]

Auger R, Motta I, Benhoud K, Ojius DM, Kannellopoulos JM. A role for mitogen-activated protein kinase(ERK1/2) activation and non-selective pore formation in P2X7 receptor-mediated thymocyte death. J Biol Chem 2005; 280: 28142-28151 [PMID: 15973334 DOI: 10.1074/jbc.M501290200]

Scheuplein F, Schwarz N, Adriouch S, Krebs C, Bannas P, Rissiek B, Seman M, Haag F, Koch-Nothe F. NAD+ and ATP released from injured cells induce P2X7-dependent death of CD26L and externalization of phosphatidylinerine by murine T cells. J Immunol 2009; 182: 2898-2908 [PMID: 19234185 DOI: 10.4049/jimmunol.0801711]

Le Stunff H, Auger R, Kannellopoulos J, Raymond MN. The Pro-451 to Leu polymorphism within the C-terminal tail of P2X7 receptor impairs cell death but not phospholipase D activation in murine thymocytes. J Biol Chem 2004; 279: 16918-16926 [PMID: 14761980 DOI: 10.1074/jbc.M313064200]

Adriouch S, Hubert S, Pechbert S, Koch-Nothe F, Haag F, Seman M. NAD+ released during inflammation participates in T cell homeostasis by inducing ART2-mediated death of naive T cells in vivo. J Immunol 2007; 179: 186-194 [PMID: 17579037 DOI: 10.4049/jimmunol.179.1.186]

Hubert S, Rissiek B, Klages K, Huehn J, Sparwasser T, Haag F, Koch-Nothe F, Boyer O, Seman M, Adriouch S. Extracellular NAD+ shapes the Foxp3+ regulatory T cell compartment through the ART2-P2X7 pathway. J Exp Med 2010; 207: 2561-2568 [PMID: 20975043 DOI: 10.1084/jem.20091154]

Iyer SS, Latner DR, Zilliox MJ, McCausland M, Akondy RS, Penaloza-Macmaster P, Hale JS, Ye L, Mohammed AU, Yamaguchi T, Sakaguchi S, Amara RR, Ahmed R. Identification of novel markers for mouse CD4(+) T follicular helper cells. Eur J Immunol 2013; 43: 3219-3232 [PMID: 24030473 DOI: 10.1002/eji.201334369]

Borges da Silva H, Beura LK, Wang H, Hanse EA, Gore R, Scott MC, Walsh DA, Block KE, Fonseca R, Yan Y, Hippen KL, Blazar BR, Masopust D, Kelekar A, Vulchanova L, Hogquist KA, Jameson SC. The purinergic receptor P2RX7 directs metabolic fitness of long-lived memory CD8+ T cells. Nature 2018; 559: 264-268 [PMID: 29973721 DOI: 10.1038/s41586-018-0282-0]

Wanhaïnen KM, Jameson SC, da Silva HB. Self-Regulation of Memory CD8 T Cell Metabolism through Extracellular ATP Signaling. Immunometabolism 2019; 1 [PMID: 31428464 DOI: 10.2090/immetabolism20190009]

Herzig S, Shaw RJ. AMPK: guardian of metabolism and mitochondrial homeostasis. Nat Rev Mol Cell Biol 2018; 19: 121-135 [PMID: 28974774 DOI: 10.1038/nrm.2017.95]

Roncarolo MG, Gregori S, Battaglia M, Bacchetta R, Fleischhauer K, Levings MK. Interleukin-10-secreting type 1 regulatory T cells in rodents and humans. Immunol Rev 2006; 212: 28-50 [PMID: 16903904 DOI: 10.1111/j.0909-1849.2006.00420.x]

Mascarenho ID, Takenaka MC, Yeste A, Patel B, Wu Y, Kenison JE, MacKenzie AB, Ward SG, Hippen KL, Blazar BR, Masopust D, Kelekar A, Vulchanova L, Hogquist KA, Jameson SC. The purinergic receptor P2RX7 directs metabolic fitness of long-lived memory CD8+ T cells. Nature 2018; 559: 264-268 [PMID: 29973721 DOI: 10.1038/s41586-018-0282-0]

Fernández D, Flores-Santibañez F, Neira J, Osorio-Barrios F, Tejón G, Nuñez S, Hidalgo Y, Fuenzalida MJ, Meza D, Ureta G, Lladser A, Pacheco R, Acúa-Castillo C, Guixé V, Quintana FJ, Bono MR, Roseblatt M, Sauma D. Purinergic Signaling as a Regulator of Th17 Cell Differentiation. PLoS One 2016; 11: e0157889 [PMID: 27322617 DOI: 10.1371/journal.pone.0157889]

Del Prete A, Scutera S, Sozanni S, Musso T. Role of osteopontin in dendritic cell shaping of immune responses. Cytokine Growth Factor Rev 2019; 50: 19-28 [PMID: 31126876 DOI: 10.1016/j.cytogfr.2019.05.004]

de Jong EC, Smits HH, Kapsenberg ML. Dendritic cell-mediated T cell polarization. Springer Semin Immunopathol 2005; 26: 289-307 [PMID: 15609005 DOI: 10.1007/s00281-004-0167-1]

la Sala A, Ferrari D, Corini S, Cavan A, Di Virgilio F, Girolomoni G. Extracellular ATP induces a distorted mature dendritic cells and inhibits their capacity to initiate Th1 responses. J Immunol 2001; 166: 1611-1617 [PMID: 11160202 DOI: 10.4049/jimmunol.166.3.1611]

la Sala A, Sebastiani S, Ferrari D, di Virgilio F, Idzko M, Norgauer J, Girolomoni G. Dendritic cells exposed to extracellular adenosine triphosphate acquire the migratory properties of mature cells and show a reduced capacity to attract type 1 T lymphocytes. Blood 2002; 99: 1715-1722 [PMID: 11861288 DOI: 10.1182/blood.v99.5.1715]

Li R, Wang J, Li R, Zhu F, Xu W, Zha G, He G, Cao H, Wang Y, Yang J. ATP/P2X7-NLRP3 axis of dendritic cells participates in the regulation of airway inflammation and hyper-responsiveness in asthma by mediating HMGB1 expression and secretion. Exp Cell Res 2018; 366: 1-15 [PMID: 29545090 DOI: 10.1016/j.yexcr.2018.03.002]
Demon? Savio LEB
Infect Microbiol Signaling Blockade Reduces Lung Inflammation and Necrosis During Severe Experimental Tuberculosis.
MVP, Lasunskaia E, Hirata MH, Alves-Filho JCF, Nakaya HI, Alvarez JM, D'Império Lima MR. P2x7 Receptor
Santiago-Carvalho I
10.3390/ph15010089
Alpha-Sarcoglycan Muscular Dystrophy.
Minetti C, Gazzerro E, Bruno C. P2X7 Receptor Antagonist Reduces Fibrosis and Inflammation in a Mouse Model of
32668623
Acuña-Castillo C, Bono MR, Sauma D. P2X7 Receptor at the Crossroads of T Cell Fate.
Rivas-Yáñez E
J Cell Biol
Sharma D
Front Pharmacol
Zhou J
Disease.
Shokoples BG
purinergic receptor P2X7.
Hashimoto-Hill S
[T cells to nucleotides indicates P2X7 as a regulator for intestinal T cell responses.
Heiss K
2020;
Tindemans I, Joosse ME, Samsom JNII. Dissecting the Heterogeneity in T-Cell Mediated Inflammation in IBD. Cells
2020; 9: [PMID: 31906479 DOI: 10.3390/cells9010110]
Heiss K, Jänner N, Mähnss B, Schumacher V, Koch-Nolte F, Mittrücker HW. High sensitivity of intestinal CD8+
T cells to nucleotides indicates P2X7 as a regulator for intestinal T cell responses. J Immunol 2008; 181: 3861-3869
[PMID: 18768840 DOI: 10.4049/jimmunol.181.6.3861]
Hashimoto-Hill S, Friesen L, Kim M, Kim CH. Contraction of intestinal effector T cells by retinoic acid-induced
purinergic receptor P2X7. Mucosal Immunol 2017; 10: 912-923 [PMID: 27966552 DOI: 10.1038/mi.2016.109]
Shokoples BG, Paradis P, Schiffrin EL. P2X7 Receptors: An Untapped Target for the Management of Cardiovascular
Disease. Arterioscler Thromb Vasc Biol 2021; 41: 186-199 [PMID: 32998520 DOI: 10.1161/ATVBAHA.120.315116]
Zhou J, Zhou Z, Liu X, Yin HY, Tang Y, Cao X. P2X7 Receptor-Mediated Inflammation in Cardiovascular Disease.
Front Pharmacol 2021; 12: 654425 [PMID: 33995071 DOI: 10.3389/fphar.2021.654425]
Sharma D, Kanneganti TD. The cell biology of inflammasomes: Mechanisms of inflammasome activation and regulation.
J Cell Biol 2016; 213: 617-629 [PMID: 27325789 DOI: 10.1083/jcb.201602089]
Rivas-Váíz E, Barrera-Avalos C, Parra-Tello B, Briceøo P, Rosenblatt MV, Saavedra-Almarza J, Rosenblatt M,
Acuña-Castillo C, Bono MR, Sauma D. P2X7 Receptor at the Crossroads of T Cell Fate. Int J Mol Sci 2020; 21 [PMID:
32668623 DOI: 10.3390/ijms21144937]
Raffaghello L, Principi E, Baratto S, Panicucci C, Pintus S, Antonini F, Del Zotto G, Benzi A, Bruzzone S,
Scudieri P, Principi E, Baratto S, Panicucci C, Pintus S, Antonini F, Del Zotto G, Benzi A, Bruzzone S, Scudieri P,
Minetti C, Gazzerro E, Bruno C. P2X7 Receptor Antagonist Reduces Fibrosis and Inflammation in a Mouse Model of
Alpha-Sarcoglycan Muscular Dystrophy. Pharmaceuticals (Basel) 2022; 15 [PMID: 35056146 DOI: 10.3390/15010089]
Santiago-Carvalho I, de Almeida-Santos G, Bomfim CCB, de Souza PC, Silva JCSE, de Melo BMS, Amaral EP, Cione
MVP, Lasunskaia E, Hirata MH, Alves-Filho JCF, Nakaya H, Alvarez JM, D'Império Lima MR. P2x7 Receptor
Signaling Blockade Reduces Lung Inflammation and Necrosis During Severe Experimental Tuberculosis. Front Cell
Infect Microbiol 2021; 11: 672472 [PMID: 34026666 DOI: 10.3389/fcimb.2021.672472]
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: 52 [PMID: 29467654 DOI: 10.3389/fphar.2018.00052]
