嘌呤P2受体的免疫调节功能

周金凤[1] 覃朝燕[1] 赖炜明[1] 杜昌升[1,2]*

([1]上海市信号转导与疾病研究重点实验室, 同济大学生命科学与技术学院, 上海 200092;
[2]新药研究国家重点实验室, 中国科学院上海药物研究所, 上海 201203)

摘要 嘌呤P2受体(purinergic P2 receptors)是一类核酸及其衍生物受体, 被激活后可调节免疫反应, 如能够介导免疫细胞向炎症部位的迁移, 影响免疫细胞的增殖、分化和凋亡以及影响其分泌的细胞因子和趋化因子来调节炎症。该文介绍了嘌呤P2受体的分类、在免疫细胞上的分布情况以及它们在调节免疫反应中的功能。

关键词 ATP; 嘌呤P2受体; 免疫

Immunoregulatory Effects of Purinergic P2 Receptors

Zhou Jinfeng[1], Qin Chaoyan[1], Lai Weiming[1], Du Changsheng[1,2]*

([1]*Shanghai Key Laboratory of Signaling and Disease Research, School of Life Sciences and Technology, Tongji University, Shanghai 200092, China*; [2]*State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China*)

Abstract Purinergic P2 receptor is a kind of nucleic acid derivative receptor, it can regulate immune response when activated. The purinergic receptors play important roles in the modulation of proliferation, differentiation, apoptosis and migration of immune cells, as well as the secretion of cytokines and chemokines involved in inflammation. This article introduces the classification of the purinergic P2 receptors, the expression of purinergic P2 receptors on immune cells and their function in modulating immune response.

Keywords ATP; purinergic P2 receptors; immunology

在很长的一段时间里, 人们都认为腺苷三磷酸(ATP)的功能就是作为一种储能物质来参与代谢反应。直到1953年, Holton等[1]发现, 刺激神经末梢时可以释放ATP, 提示胞外ATP也有着重要作用。1972年, Burnstock[2]提出了“嘌呤能神经学说”, 认定ATP为一种神经递质。1978年Burnstock又总结了以往研究成果将胞外核苷酸分子的受体即嘌呤受体并按照激动剂的选择分为Pl和P2受体两大类, P1受体主要的天然配体是腺苷, 又称腺苷受体; P2受体是一类核苷酸极其衍生物受体, 分为P2X(离子通道受体)和P2Y(G蛋白偶联受体)。关于腺苷受体家族成员在免疫中的作用已经在万萍等[3]的文章中做过详细的描述, 本文将对嘌呤P2受体的分类以及在免疫中的功能进行综述。

P2受体分为P2X和P2Y两个亚型。P2X是离子通道型的受体, 是非选择性阳离子通道, 对Na^+、K^+、Ca^{2+}具有通透性。P2X有七种, 分别为P2X1~7。根据与激动剂ATP的亲和力强弱, 分为有高亲和

收稿日期: 2015-04-21 接受日期: 2015-06-16
国家重点基础研究发展规划(973计划)(批准号: 2014CB541903、2012CB910404)、国家自然科学基金面上项目(批准号: 31171348、31371414)、上海市教委科研创新项目(批准号: 14zz042)、新药研究国家重点实验室开放基金资助(批准号: SIMM1302KF-09)和中央高校基本科研业务费专项资金资助的课题
*通讯作者。Tel: 021-659861041, E-mail: duchangsheng@gmail.com
Received: April 21, 2015 Accepted: June 16, 2015
This work was supported by the National Basic Research program of China (973 Program) (Grant No.2014CB541903, 2012CB910404), the National Natural Science Foundation of China (Grant No.31171348, 31371414), the Foundation of Shanghai Municipal Education Commission (Grant No.14zz042), Foundation of the State Key Laboratory of Drug Research (Grant No.SIMM1302KF-09) and the Fundamental Research Funds for the Central Universities
*Corresponding author. Tel: +86-21-659861041, E-mail: duchangsheng@gmail.com
网络出版时间: 2015-07-29 10:58:58 URL: http://www.cnki.net/kcms/detail/31.2035.Q.20150729.1058.001.html

力(EC_{50}=1 μmol/L)的P2X1和P2X3, 较低亲和力(EC_{50}=10 μmol/L)的P2X2、P2X4、P2X5和P2X6, 以及极低亲和力(EC_{50}>300 μmol/L)的P2X7。P2Y是G蛋白偶联受体, 有八种, 分别为P2Y1、P2Y2、P2Y4、P2Y6、P2Y11、P2Y12、P2Y13、P2Y14, 其中, 与Gi偶联的包括P2Y12~14, 其他成员均与Gq偶联。

1 P2X受体

在P2X受体中, 对P2X7受体的免疫学作用研究得最为广泛。P2X7的激活, 可以通过增加免疫细胞分泌的炎性因子来促进炎症反应的发生, 同时可以调节B细胞及T细胞功能来调控免疫反应。还有研究表明, P2X1及P2X4也能够参与免疫反应。

1.1 P2X1受体

P2X1受体在嗜中性粒细胞、单核细胞、巨噬细胞、NK细胞、树突状细胞等细胞上都有表达。对于P2X1在免疫中作用的研究不多, 主要与巨噬细胞分泌IL-6及嗜中性粒细胞的趋化相关。

激活小鼠脾巨噬细胞上的P2X1受体能够抑制IL-6的分泌[4]。同时也发现, P2X1受体的激动剂αβMeATP能够促进人嗜中性粒细胞由IL-8引起的趋化作用和小鼠嗜中性粒细胞由W-肽诱导的趋化作用, 表明激活P2X1受体能够促进嗜中性粒细胞的趋化作用[5]。

1.2 P2X4受体

P2X4受体的表达情况与P2X1大致相同, 也表达于巨噬细胞、NK细胞、嗜中性粒细胞、树突状细胞、T细胞、小胶质细胞。目前研究发现, 巨噬细胞、小胶质细胞和上皮细胞的P2X4受体的激活能够促进炎症反应。

在脑损伤、脊髓损伤中, 巨噬细胞和小胶质细胞中P2X4受体表达上调, 拮抗剂处理后则能减少缺血细胞死亡[6]。激活P2X4受体能够增强巨噬细胞释放前列腺素E2, 由于前列腺素E2是一个重要的炎症介质, 推测抑制P2X4受体可能减轻炎症[7]。最近, 随着炎性体的功能越来越多地被人们所了解, 有研究发现, P2X4受体的拮抗剂处理上皮细胞后能够抑制NLRP3炎性体的组装, 抑制IL-1β、IL-18的分泌[8]。

1.3 P2X7受体

P2X7受体广泛表达于免疫细胞中, 在嗜中性粒细胞、单核细胞、巨噬细胞、NK细胞、B细胞及T细胞上都有表达。

已有报道表明, P2X7受体主要起到促进炎症的作用。激活P2X7受体能促进巨噬细胞中IL-18分泌[9], 引起ASC(apoptosis-associated speck-like protein containing CARD)/NLRP3炎性体的组装和聚集[10], 释放包含MHC-II的外泌体[11], 增强巨噬细胞吞噬抗原的能力[12]。激活上皮细胞上P2X7受体能够激活caspase-1, 促进IL-1β的释放, 并引起其他细胞因子的产生, 如上皮细胞嗜中性粒细胞激活肽ENA-78(epithelial neutrophil-activating peptide-78)和Gro-α(growth-regulated oncogene alpha), 进而诱导嗜中性粒细胞向炎症部位迁移[13]。单核细胞上P2X7受体的激活能够促进IL-1β、VEGF(vascular endothelial growth factor)的分泌[14-16]。激活小胶质细胞上P2X7受体能够促进IL-1β、TNF-α分泌[17-19], 进而加剧炎症反应。

P2X7受体还调控淋巴细胞的功能, P2X7受体的激活能够引起T细胞的增殖和IL-2的分泌[20-21], 也能抑制$CD8^+$T细胞的迁移及Treg的分化和功能[22-23]。而P2受体调节B细胞的功能最近才被报道, BzATP[2',3'-O-(4-benzoyl-benzoyl) ATP]能够激活B细胞上的P2X7受体, 增强B细胞分泌IgM的能力[24]。

P2X7受体也能够通过介导细胞的凋亡来参与免疫反应, 激活P2X7受体能够引起树突细胞[25]和少突胶质细胞的凋亡[26], 同时在小鼠的EAE模型中, 敲除P2X7受体的小鼠中枢神经系统中淋巴细胞的凋亡显著减少, 说明P2X7受体的激活能够增加淋巴细胞的凋亡[27]。

2 P2Y受体

P2Y受体在免疫中的作用集中于影响免疫细胞的招募和迁移。研究发现, 激活P2Y1、P2Y2、P2Y4、P2Y6、P2Y11和P2Y14都能够影响趋化因子的分泌, 从而影响免疫细胞的趋化和迁移。同时, P2Y受体还可以影响细胞因子的分泌、树突状细胞的成熟、NK细胞的细胞毒作用及嗜中性粒细胞的凋亡等来参与免疫反应。

2.1 P2Y1受体

P2Y1受体在单核细胞、巨噬细胞、树突状细胞、嗜中性粒细胞及星形胶质细胞上都有表达。

激活人单核细胞来源的树突状细胞上的P2Y1受体能够抑制MCP-1(monocyte chemoattractant protein-1, 又称为CCL2)和MIP-1α(CCL3)的分泌, 进而抑制其向炎症部位招募单核细胞和未成熟树突状

细胞[28]。同时发现, 大鼠的星形胶质细胞上的P2Y1受体参与调节细胞因子和趋化因子的mRNA转录, P2Y1受体的激动剂MRS 2365能够加重脑梗塞的症状, 激活P2Y1受体能够促进*p-RelA*(phosphorylated-RelA)、*IL-6*、*TNF-α*、*CCL2*及*CXCL-10* mRNA的表达[29]。

2.2 P2Y2/P2Y4受体

P2Y2受体表达于嗜中性粒细胞、巨噬细胞、树突状细胞、NK细胞及星形胶质细胞上。P2Y4受体则在树突状细胞、NK细胞及T细胞上表达。

P2Y2/P2Y4受体主要是通过影响炎性细胞的趋化来介导免疫反应。激活P2Y2受体能够促进上皮细胞分泌ICAM-1(intercellular cell adhesion molecule-1)和CCL20[30-31], 同时也能够诱导嗜中性粒细胞和巨噬细胞向炎症部位的迁移[32-33]。这些现象在许多疾病模型中得到证实, 在小鼠的气囊炎模型中, 敲除P2Y2受体能够抑制单核细胞和巨噬细胞的招募, 抑制凋亡细胞的清除[34]。激活嗜酸性粒细胞上的P2Y2受体能够促进IL-6、IL-8/CXCL8的分泌, 进而介导其向炎症部位迁移[35]。星形胶质细胞上的P2Y2受体能够促进GFAP(glial fibrillary acidic protein)的表达, 增强其迁移能力。也有研究表明, P2Y2受体与α_V整合素的相互作用能够调节UTP(uridine triphosphate)介导的星形胶质细胞迁移[36]。在小鼠的气囊炎模型中, 白细胞和内皮细胞表达的P2Y4受体参与LPS(lipopolysaccharide)诱导的嗜中性粒细胞的招募[37]。

2.3 P2Y6受体

P2Y6受体在嗜中性粒细胞、巨噬细胞、树突状细胞上都有表达, 同时也表达于中枢神经系统中的小神经胶质细胞及星形胶质细胞。

UDP(uridine diphosphate)能够激活P2Y6受体促进趋化因子的表达和分泌。UDP处理能够促进肠上皮细胞、单核细胞及人类角质化细胞中IL-8/CXCL8的分泌[38-40], 引起嗜中性粒细胞的迁移; 促进巨噬细胞中MCP-1(CCL2)的表达[41], 也能上调小神经胶质细胞和星形胶质细胞的中MCP-1(CCL2)及MIP-1α(CCL3)的表达[42], 从而诱导单核/巨噬细胞的招募。UDP还能够促进单核细胞来源的树突状细胞分泌CCL20[31]。

也有研究发现, 激活P2Y6受体能够调节细胞因子的分泌, 如促进人角质化细胞中IL-1α和IL-6的分泌[40]。在小鼠过敏性肺炎中, 激活P2Y6受体能够抑制IL-5、IL-13的分泌从而抑制T细胞的激活[43]。此外, UDP能够激活小神经胶质细胞表面的P2Y6受体, 增强其吞噬作用, 促进中枢神经系统中的死细胞和细胞碎片的清除[44]。

2.4 P2Y11受体

P2Y11受体主要表达于单核细胞、巨噬细胞、树突状细胞、嗜中性粒细胞上。

目前报道P2Y11受体在树突状细胞上的研究最多, 主要与树突状细胞的细胞因子及趋化因子的分泌及迁移相关。树突状细胞上P2Y11受体的激活能够促进IL-8和CCL20的分泌[31,45], 增强TNF-α引起的CD86的表达和IL-12的分泌[46], 从而促进树突状细胞的成熟。也有研究表明, ATP能够激活P2Y11受体, 抑制树突状细胞的迁移[47]。同时也发现, 激活上皮细胞上的P2Y11受体能够促进IL-6的转录[48]。P2Y11受体的激活也能够促进嗜中性粒细胞的凋亡[49], 诱导粒细胞的分化[50], 调节NK细胞的胞毒作用来介导免疫反应[51]。

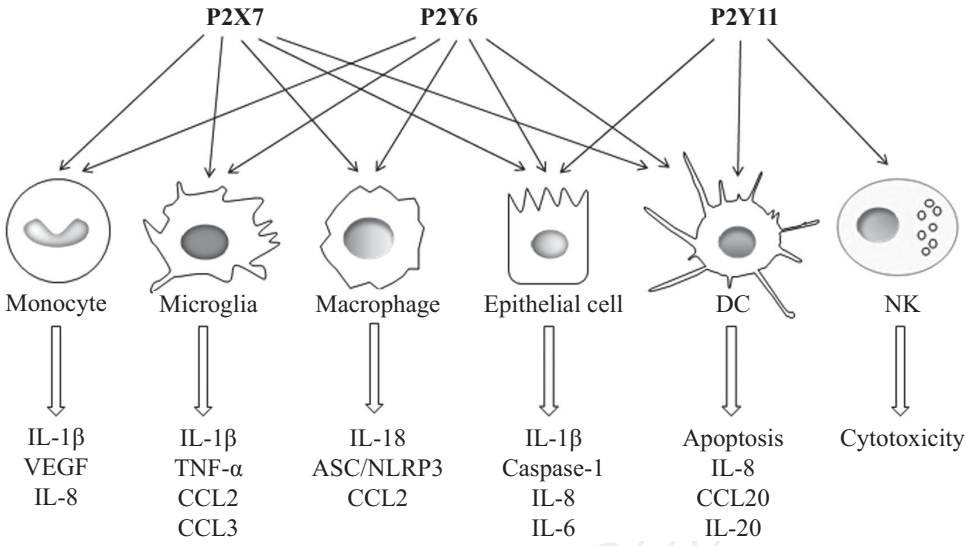
2.5 P2Y12受体

P2Y12受体在单核细胞、树突状细胞、巨噬细胞、T细胞上都有表达。P2Y12受体的研究主要集中于影响血小板炎症因子的分泌。

激活P2Y12受体能够促进血小板炎症因子的分泌, 如IL-1α、IL-2、IL-6、IL-13、IL-10、TNF-α等[52-53]。同时发现, P2Y12受体也可以直接通过影响DC细胞吞噬抗原的能力来调节免疫反应[54]。LTE4(leukotriene E4)能够通过P2Y12受体引起呼吸道过敏小鼠的嗜酸性粒细胞增加和IL-13的分泌增强[55]。在早期的中枢神经系统的损伤中, 敲除P2Y12受体小鼠的小胶质细胞侵润到皮层炎症位点的数量比野生型小鼠少, 表明P2Y12受体能够介导小胶质细胞的趋化作用[56]。

2.6 P2Y14受体

P2Y14受体主要表达于嗜中性粒细胞、树突状细胞及T细胞。UDP葡萄糖能够激活内皮细胞上的P2Y14受体促进IL-8的分泌, 从而促进对嗜中性粒细胞的趋化[57]。P2Y14受体还可以影响巨噬细胞的迁移来参与免疫反应, 用高脂肪饮食来诱导的小鼠的肥胖症模型中, 与野生型小鼠相比, P2Y14受体敲除小鼠的肝脏中浸润的巨噬细胞减少, IL-1β、TNF-α、IL-6的分泌受到抑制[58]。P2Y14受体在人



在单核细胞上, 激活P2X7可以增加IL-1β及VEGF的分泌; 激活P2Y6能够增加趋化因子IL-8的产生。在小神经胶质细胞上, P2X7的激活可以增加促炎性细胞因子IL-1β及TNF-α的分泌; 激活P2Y6可以增加CCL-2及CCL-3的分泌。在巨噬细胞上, 激活P2X7可以增加IL-18的分泌, 也能够介导炎性体ASC/NLRP3的组装; 激活P2Y6能够增加CCL-2分泌。在上皮细胞上, 激活P2X7、P2Y6、P2Y11能够分别增加IL1β、IL-8、IL-6产生。在树突状细胞上, 激活P2X7能够诱导其凋亡; 激活P2Y6能够增加CCL-20分泌; 激活P2Y11能够增加促进IL-8、CCL-20及IL-12分泌。激活自然杀伤细胞上的P2Y11能够增强其细胞毒性作用。

Activation of P2X7 on monocytes induces secretion of IL-1β and VEGF, and increase chemokine IL-8 production by monocytes through the activation of P2Y6. On microglia, activation of P2X7 promotes proinflammatory cytokines IL-1β and TNF-α production and activation of P2Y6 increases chemokines CCL-2 and CCL-3 secretion. Activation of P2X7 on macrophages induces IL-18 production and mediates inflammasome ASC/NLRP3 assembling, activation of P2Y6 also increases chemokines CCL-2 secretion on macrophages. Activation of P2X7, P2Y6 and P2Y11 on epithelial cells increase IL-1β, IL-8 and IL-6 section, respectively. On DCs, activation of P2X7 induces apoptosis of DCs, activation of P2Y6 increases CCL-20 production, activation of P2Y11 promotes section of IL-12, IL-8 and CCL-20. Activation of P2Y11 on NK cells mediate cytotoxicity function.

图1 调节免疫功能的主要嘌呤P2受体

Fig.1 Major P2 purinergic receptors involved in regulation of immune function

单核细胞来源的成熟树突状细胞上基本不表达, 却在未成熟的树突状细胞上高表达, P2Y14激动剂处理能促进共刺激分子CD86的表达, 表明P2Y14受体在树突状细胞的成熟过程中起作用[59]。最新的研究发现, 嘌呤P2受体还能够参与肥大细胞的脱颗粒作用, UDPG和MRS2690能够激活人的肥大细胞上的P2Y14受体促进C3a引起β-Hex的释放, 进而能够促进肥大细胞的脱颗粒作用[60]。

3 展望

嘌呤受体从1978年被发现至今已30多年了, 对其结构、生理特性与功能的研究已经取得了很大的进展。嘌呤受体选择性的激动剂、拮抗剂和敲除了嘌呤受体的动物模型能够对于我们研究嘌呤受体的生物学功能提供了可靠的方法。腺苷受体的拮抗剂茶碱对于治疗哮喘疾病已经取得了很好的疗效。腺苷受体激动剂与拮抗剂在心律失常、类风湿性关节炎等疾病中也已用于临床试验。P2Y受体相关药物氯吡格雷已经应用于动脉粥样硬化和冠心病的临床治疗。但是, 在体内嘌呤受体的激活通过多个信号转导过程会产生复杂的生物学效应还需要进一步研究才能应用于药物研发, 因此嘌呤受体的进一步研究对于治疗炎症和自身免疫病都有重要的意义。

但是, 关于嘌呤P2受体在免疫中的功能研究主要集中于P2X7、P2Y6、P2Y11等受体上(图1), 对于P2X2、P2X3、P2X5、P2X6、P2Y13等在免疫中的作用的研究少之又少, 提示我们对于嘌呤受体的免疫调节功能的研究还有很长的路要走, 同时也给我们留下了很大的研究空间。嘌呤P2受体能够参与多种免疫细胞调节的免疫反应, 并能够很好地契合热点, 如在炎性体功能被深入研究的同时, 参与调节炎性体组装的嘌呤P2受体也很快被报道, 说明随着免疫研究的不断深入, 将会有越来越多的嘌呤P2受体的免疫调节功能将被发掘出来, 对于嘌呤受体在免疫中的作用研究可以为多种疾病的治疗提供重要的药物靶点。

参考文献 (References)

1 Holton FA, Holton P. The possibility that ATP is a transmitter at sensory nerve endings. J Physiol 1953; 119(4): 50-1.

2 Burnstock G, Satchell DG, Smythe A. A comparison of the excitatory and inhibitory effects of non-adrenergic, non-cholinergic nerve stimulation and exogenously applied ATP on a variety of smooth muscle preparations from different vertebrate species. Br J Pharmacol 1972; 46(2): 234-42.

3 万 萍, 陈 昊, 白爱平. 腺苷的免疫调节功能. 世界华人消化杂志(Wan Ping, Chen Hao, Bai Aiping. Immunoregulatory effects of adenosine. World Chinese Journal of Digestology) 2014; 22(17): 2379.

4 Straub RH, Pongratz G, Gunzler C, Michna A, Baier S, Kees F, *et al*. Immunoregulation of IL-6 secretion by endogenous and exogenous adenosine and by exogenous purinergic agonists in splenic tissue slices. J Neuroimmunol 2002; 125(1/2): 73-81.

5 Lecut C, Frederix K, Johnson DM, Deroanne C, Thiry M, Faccinetto C, *et al*. P2X1 ion channels promote neutrophil chemotaxis through Rho kinase activation. J Immunol 2009; 183(4): 2801-9.

6 Zhang Z, Artelt M, Burnet M, Trautmann K, Schluesener HJ. Early infiltration of CD8+ macrophages/microglia to lesions of rat traumatic brain injury. Neuroscience 2006; 141(2): 637-44.

7 Ulmann L, Hirbec H, Rassendren F. P2X4 receptors mediate PGE2 release by tissue-resident macrophages and initiate inflammatory pain. EMBO J 2010; 29(14): 2290-300.

8 Chen K, Zhang J, Zhang W, Zhang J, Yang J, Li K, *et al*. ATP-P2X4 signaling mediates NLRP3 inflammasome activation: A novel pathway of diabetic nephropathy. Int J Biochem Cell 2013; 45(5): 932-43.

9 Gulinelli S, Salaro E, Vuerich M, Bozzato D, Pizzirani C, Bolognesi G, *et al*. IL-18 associates to microvesicles shed from human macrophages by a LPS/TLR-4 independent mechanism in response to P2X receptor stimulation. Eur J Immunol 2012; 42(12): 3334-45.

10 Riteau N, Gasse P, Fauconnier L, Gombault A, Couegnat M, Fick L, *et al*. Extracellular ATP is a danger signal activating P2X7 receptor in lung inflammation and fibrosis. Am J Respir Crit Care Med 2010; 182(6): 774-83.

11 Qu Y, Ramachandra L, Mohr S, Franchi L, Harding CV, Nunez G, *et al*. P2X7 receptor-stimulated secretion of MHC class II-containing exosomes requires the ASC/NLRP3 inflammasome but is independent of caspase-1. J Immunol 2009; 182(8): 5052-62.

12 Correa G, Marques da Silva C, de Abreu Moreira-Souza AC, Vommaro RC, Coutinho-Silva R. Activation of the P2X(7) receptor triggers the elimination of Toxoplasma gondii tachyzoites from infected macrophages. Microbes Infect 2010; 12(6): 497-504.

13 Cesaro A, Brest P, Hofman V, Hebuterne X, Wildman S, Ferrua B, *et al*. Amplification loop of the inflammatory process is induced by P2X7R activation in intestinal epithelial cells in response to neutrophil transepithelial migration. Am J Physiol Gastrointest Liver Physiol 2010; 299(1): G32-42.

14 Hill LM, Gavala ML, Lenertz LY, Bertics PJ. Extracellular ATP may contribute to tissue repair by rapidly stimulating purinergic receptor X7-dependent vascular endothelial growth factor release from primary human monocytes. J Immunol 2010; 185(5): 3028-34.

15 Gu BJ, Saunders BM, Jursik C, Wiley JS. The P2X7-nonmuscle myosin membrane complex regulates phagocytosis of nonopsonized particles and bacteria by a pathway attenuated by extracellular ATP. Blood 2010; 115(8): 1621-31.

16 Castrichini M, Lazzerini PE, Gamberucci A, Capecchi PL, Franceschini R, Natale M, *et al*. The purinergic P2x7 receptor is expressed on monocytes in Behcet's disease and is modulated by TNF-alpha. Eur J Immunol 2014; 44(1): 227-38.

17 Mingam R, de Smedt V, Amedee T, Bluthe RM, Kelley KW, Dantzer R, *et al*. *In vitro* and *in vivo* evidence for a role of the P2X7 receptor in the release of IL-1 beta in the murine brain. Brain Behav Immun 2008; 22(2): 234-44.

18 Sanz JM, Di Virgilio F. Kinetics and mechanism of ATP-dependent IL-1 beta release from microglial cells. J Immunol 2000; 164(9): 4893-8.

19 Suzuki T, Hide I, Ido K, Kohsaka S, Inoue K, Nakata Y. Production and release of neuroprotective tumor necrosis factor by P2X7 receptor-activated microglia. J Neurosci 2004; 24(1): 1-7.

20 Yu T, Junger WG, Yuan C, Jin A, Zhao Y, Zheng X, *et al*. Shockwaves increase T-cell proliferation and IL-2 expression through ATP release, P2X7 receptors, and FAK activation. Am J Physiol Cell Physiol 2010; 298(3): C457-64.

21 Tsukimoto M, Tokunaga A, Harada H, Kojima S. Blockade of murine T cell activation by antagonists of P2Y6 and P2X7 receptors. Biochem Biophys Res Commun 2009; 384(4): 512-8.

22 Lang PA, Merkler D, Funkner P, Shaabani N, Meryk A, Krings C, *et al*. Oxidized ATP inhibits T-cell-mediated autoimmunity. Eur J Immunol 2010; 40(9): 2401-8.

23 Schenk U, Frascoli M, Proietti M, Geffers R, Traggiai E, Buer J, *et al*. ATP inhibits the generation and function of regulatory T cells through the activation of purinergic P2X receptors. Sci Signal 2011; 4(162): ra12.

24 Sakowicz-Burkiewicz M, Kocbuch K, Grden M, Maciejewska I, Szutowicz A, Pawelczyk T. High glucose concentration impairs ATP outflow and immunoglobulin production by human peripheral B lymphocytes: Involvement of P2X7 receptor. Immunobiology 2013; 218(4): 591-601.

25 Nihei OK, de Carvalho AC, Savino W, Alves LA. Pharmacologic properties of P(2Z)/P2X(7)receptor characterized in murine dendritic cells: Role on the induction of apoptosis. Blood 2000; 96(3): 996-1005.

26 Arbeloa J, Perez-Samartin A, Gottlieb M, Matute C. P2X7 receptor blockade prevents ATP excitotoxicity in neurons and reduces brain damage after ischemia. Neurobiol Dis 2012; 45(3): 954-61.

27 Chen L, Brosnan CF. Exacerbation of experimental autoimmune encephalomyelitis in P2X7R$^{-/-}$ mice: Evidence for loss of apoptotic activity in lymphocytes. J Immunol 2006; 176(5): 3115-26.

28 Hanley PJ, Musset B, Renigunta V, Limberg SH, Dalpke AH, Sus R, *et al*. Extracellular ATP induces oscillations of intracellular Ca^{2+} and membrane potential and promotes transcription of IL-6

in macrophages. Proc Natl Acad Sci USA 2004; 101(25): 9479-84.

29 Kuboyama K, Harada H, Tozaki-Saitoh H, Tsuda M, Ushijima K, Inoue K. Astrocytic P2Y(1) receptor is involved in the regulation of cytokine/chemokine transcription an cerebral damage in a rat model of cerebral ischemia. J Cerebr Blood F Met 2011; 31(9): 1930-41.

30 Langlois C, Gendron FP. Promoting MPhi transepithelial migration by stimulating the epithelial cell P2Y(2) receptor. Eur J Immunol 2009; 39(10): 2895-905.

31 Marcet B, Horckmans M, Libert F, Hassid S, Boeynaems JM, Communi D. Extracellular nucleotides regulate CCL20 release from human primary airway epithelial cells, monocytes and monocyte-derived dendritic cells. J Cell Physiol 2007; 211(3): 716-27.

32 Kukulski F, Ben Yebdri F, Bahrami F, Fausther M, Tremblay A, Sevigny J. Endothelial P2Y2 receptor regulates LPS-induced neutrophil transendothelial migration *in vitro*. Mol Immunol 2010; 47(5): 991-9.

33 Cicko S, Lucattelli M, Muller T, Lommatzsch M, de Cunto G, Cardini S, *et al*. Purinergic receptor inhibition prevents the development of smoke-induced lung injury and emphysema. J Immunol 2010; 185(1): 688-97.

34 Elliott MR, Chekeni FB, Trampont PC, Lazarowski ER, Kadl A, Walk SF, *et al*. Nucleotides released by apoptotic cells act as a find-me signal to promote phagocytic clearance. Nature 2009; 461(7261): 282-6.

35 Kobayashi T, Kouzaki H, Kita H. Human eosinophils recognize endogenous danger signal crystalline uric acid and produce proinflammatory cytokines mediated by autocrine ATP. J Immunol 2010; 184(11): 6350-8.

36 Wang M, Kong Q, Gonzalez FA, Sun G, Erb L, Seye C, *et al*. P2Y nucleotide receptor interaction with alpha integrin mediates astrocyte migration. J Neurochem 2005; 95(3): 630-40.

37 Kukulski F, Ben Yebdri F, Bahrami F, Levesque SA, Martin-Satue M, Sevigny J. The P2 receptor antagonist PPADS abrogates LPS-induced neutrophil migration in the murine air pouch via inhibition of MIP-2 and KC production. Mol Immunol 2010; 47(4): 833-9.

38 Grbic DM, Degagne E, Langlois C, Dupuis AA, Gendron FP. Intestinal inflammation increases the expression of the P2Y6 receptor on epithelial cells and the release of CXC chemokine ligand 8 by UDP. J Immunol 2008; 180(4): 2659-68.

39 Kukulski F, Ben Yebdri F, Lefebvre J, Warny M, Tessier PA, Sevigny J. Extracellular nucleotides mediate LPS-induced neutrophil migration *in vitro* and *in vivo*. J Leukoc Biol 2007; 81(5): 1269-75.

40 Uratsuji H, Tada Y, Kawashima T, Kamata M, Hau CS, Asano Y, *et al*. P2Y6 receptor signaling pathway mediates inflammatory responses induced by monosodium urate crystals. J Immunol 2012; 188(1): 436-44.

41 Zhang Z, Wang Z, Ren H, Yue M, Huang K, Gu H, *et al*. P2Y(6) agonist uridine 5'-diphosphate promotes host defense against bacterial infection via monocyte chemoattractant protein-1-mediated monocytes/macrophages recruitment. J Immunol 2011; 186(9): 5376-87.

42 Kim B, Jeong HK, Kim JH, Lee SY, Jou I, Joe EH. Uridine 5'-diphosphate induces chemokine expression in microglia and astrocytes through activation of the P2Y6 receptor. J Immunol 2011; 186(6): 3701-9.

43 Giannattasio G, Ohta S, Boyce JR, Xing W, Balestrieri B, Boyce JA. The purinergic G protein-coupled receptor 6 inhibits effector T cell activation in allergic pulmonary inflammation. J Immunol 2011; 187(3): 1486-95.

44 Koizumi S, Shigemoto-Mogami Y, Nasu-Tada K, Shinozaki Y, Ohsawa K, Tsuda M, *et al*. UDP acting at P2Y6 receptors is a mediator of microglial phagocytosis. Nature 2007; 446(7139): 1091-5.

45 Meis S, Hamacher A, Hongwiset D, Marzian C, Wiese M, Eckstein N, *et al*. NF546 [4,4'-(carbonylbis(imino-3,1-phenylene-carbonylimino-3,1-(4-methyl-phenylene)-carbonylimino))-bis(1,3-xylene-alpha,alpha'-diphosphonic acid) tetrasodium salt] is a non-nucleotide P2Y11 agonist and stimulates release of interleukin-8 from human monocyte-derived dendritic cells. J Pharmacol Exp Ther 2010; 332(1): 238-47.

46 Wilkin F, Duhant X, Bruyns C, Suarez-Huerta N, Boeynaems JM, Robaye B. The P2Y11 receptor mediates the ATP-induced maturation of human monocyte-derived dendritic cells. J Immunol 2001; 166(12): 7172-7.

47 Schnurr M, Toy T, Stoitzner P, Cameron P, Shin A, Beecroft T, *et al*. ATP gradients inhibit the migratory capacity of specific human dendritic cell types: Implications for P2Y11 receptor signaling. Blood 2003; 102(2): 613-20.

48 Yu J, Sheung N, Soliman EM, Spirli C, Dranoff JA. Transcriptional regulation of IL-6 in bile duct epithelia by extracellular ATP. Am J Physiol Gastrointest Liver Physiol 2009; 296(3): G563-71.

49 Vaughan KR, Stokes L, Prince LR, Marriott HM, Meis S, Kassack MU, *et al*. Inhibition of neutrophil apoptosis by ATP is mediated by the P2Y11 receptor. J Immunol 2007; 179(12): 8544-53.

50 van der Weyden L, Conigrave AD, Morris MB. Signal transduction and white cell maturation via extracellular ATP and the P2Y11 receptor. Immunol Cell Biol 2000; 78(4): 369-74.

51 Gorini S, Callegari G, Romagnoli G, Mammi C, Mavilio D, Rosano G, *et al*. ATP secreted by endothelial cells blocks CX(3)CL 1-elicited natural killer cell chemotaxis and cytotoxicity via P2Y(1)(1) receptor activation. Blood 2010; 116(22): 4492-500.

52 Muhlestein JB. Effect of antiplatelet therapy on inflammatory markers in atherothrombotic patients. Thromb Haemost 2010; 103(1): 71-82.

53 Hermann A, Rauch BH, Braun M, Schror K, Weber AA. Platelet CD40 ligand (CD40L)–subcellular localization, regulation of expression, and inhibition by clopidogrel. Platelets 2001; 12(2): 74-82.

54 Ben Addi A, Cammarata D, Conley PB, Boeynaems JM, Robaye B. Role of the P2Y12 receptor in the modulation of murine dendritic cell function by ADP. J Immunol 2010; 185(10): 5900-6.

55 Paruchuri S, Tashimo H, Feng C, Maekawa A, Xing W, Jiang Y, *et al*. Leukotriene E4-induced pulmonary inflammation is mediated by the P2Y12 receptor. J Exp Med 2009; 206(11): 2543-55.

56 Haynes SE, Hollopeter G, Yang G, Kurpius D, Dailey ME, Gan WB, *et al*. The P2Y12 receptor regulates microglial activation by extracellular nucleotides. Nat Neurosci 2006; 9(12): 1512-9.

57 Arase T, Uchida H, Kajitani T, Ono M, Tamaki K, Oda H, *et al*. The UDP-glucose receptor P2RY14 triggers innate mucosal immunity in the female reproductive tract by inducing IL-8. J Immunol 2009; 182(11): 7074-84.

58 Xu J, Morinaga H, Oh D, Li P, Chen A, Talukdar S, *et al*. GPR105 ablation prevents inflammation and improves insulin sensitivity in mice with diet-induced obesity. J Immunol 2012; 189(4): 1992-9.

59 Skelton L, Cooper M, Murphy M, Platt A. Human immature monocyte-derived dendritic cells express the G protein-coupled receptor GPR105 (KIAA0001, P2Y14) and increase intracellular calcium in response to its agonist, uridine diphosphoglucose. J Immunol 2003; 171(4): 1941-9.

60 Gao ZG, Wei Q, Jayasekara MP, Jacobson KA. The role of P2Y(14) and other P2Y receptors in degranulation of human LAD2 mast cells. Purinergic Signal 2013; 9(1): 31-40.