P2Y<sub>6</sub> Nucleotide Receptor Mediates Monocyte Interleukin-8 Production in Response to UDP or Lipopolysaccharide*

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Michael Warny§§, Samer Aboudola†, Simon C. Robson‡, Jean Sévigny‡, Didier Commun†, Stephen P. Solomon and Ciarán P. Kelly‡

From the §Gastroenterology Division and †Signal Transduction Division, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215 and the ‡Institute of Interdisciplinary Research, Medical School, Université Libre de Bruxelles, Route de Lennik 808, 1070 Brussels, Belgium

Extracellular nucleotides are autocrine and paracrine cellular mediators that signal through P2 nucleotide receptors. Monocytic cells express several P2Y receptors but the role of these G protein-coupled receptors in monocytes is not known. Here, we present evidence that P2Y<sub>6</sub> regulates chemokine production and release in monocytes. We find that UDP, a selective P2Y<sub>6</sub> agonist, stimulates interleukin (IL)-8 release in human THP-1 monocytic cells whereas other nucleotides are relatively inactive. P2 receptor antagonists or P2Y<sub>6</sub> antisense oligonucleotides inhibit IL-8 release induced by UDP. Furthermore, UDP specifically activated IL-8 production in astrocytoma 1321N1 cells transfected with human P2Y<sub>6</sub>. Since lipopolysaccharide has been suggested to activate P2 receptors via nucleotide release, we tested whether IL-8 production stimulated by lipopolysaccharide might result from P2Y<sub>6</sub> activation. P2 antagonists or apyrase, an enzyme which hydrolyzes nucleotides including UDP, inhibit IL-8 production induced by lipopolysaccharide but not by other stimuli. Furthermore, IL-8 gene expression activated by lipopolysaccharide is enhanced by P2Y<sub>6</sub> overexpression and inhibited by P2Y<sub>6</sub> antisense oligonucleotides. Thus, UDP activates IL-8 production via P2Y<sub>6</sub> in monocytic cells. Furthermore, lipopolysaccharide mediates IL-8 production at least in part by autocrine P2Y<sub>6</sub> activation. These findings indicate a novel role for P2Y<sub>6</sub> in innate immune defenses.

Extracellular nucleotides induce a wide range of cellular responses mediated by P2 nucleotide receptors. P2 nucleotide receptors include two distinct subtypes classified as P2X and P2Y receptors. P2X are ligand-gated ion channels permeable to Na<sup>+</sup> and K<sup>+</sup> whereas P2Y are G protein-coupled receptors. Cloned human P2 receptors include seven P2X (P2X<sub>1</sub>–7) and six P2Y (P2Y<sub>1</sub>, P2Y<sub>4</sub>, P2Y<sub>6</sub>, P2Y<sub>11</sub>, P2Y<sub>12</sub> and P2Y<sub>13</sub>) (1–4). P2X are ligand-gated ion channels permeable to Na<sup>+</sup> and K<sup>+</sup> whereas P2Y are G protein-coupled receptors. Cloned human P2 receptors include seven P2X (P2X<sub>1</sub>–7) and six P2Y (P2Y<sub>1</sub>, P2Y<sub>4</sub>, P2Y<sub>6</sub>, P2Y<sub>11</sub>, P2Y<sub>12</sub> and P2Y<sub>13</sub>) (1–4). P2 receptors exhibit a wide tissue distribution and display a very complex pharmacology. For example, ATP activates P2Y<sub>1</sub>, P2Y<sub>12</sub>, and all P2X; ADP activates P2Y<sub>12</sub> and is a potent agonist of P2Y<sub>1</sub> receptor; UDP is the most potent ligand at P2Y<sub>6</sub> and UDP selectively activates P2Y<sub>6</sub> (5–7). Many of these receptors have been cloned recently and their roles in immune responses are still poorly understood.

Monocytic cell line and primary monocytes express several P2X (P2X<sub>1</sub>, P2X<sub>7</sub>) as well as P2Y (P2Y<sub>1</sub>, P2Y<sub>2</sub>, P2Y<sub>4</sub>, and P2Y<sub>6</sub>) receptors (8–10). Many studies of P2 receptors in monocytes have focused on P2X<sub>7</sub>, that is mainly expressed on monocytic cells (11). In monocytic cells or in LPS<sup>1</sup>-primed monocytes, extracellular ATP regulates pro-inflammatory signaling pathways including caspase-1 activation, IL-1β release, and nitric-oxide synthase via P2X7 (12–14). Little is known about the role of the other P2 receptors.

Previous studies have suggested a role for extracellular nucleotides in regulating cellular responses to lipopolysaccharide (LPS). For instance, extracellular signal regulated kinase (ERK) activation by LPS in macrophages can be inhibited by P2 nucleotide antagonists (15). Moreover, LPS was shown to activate IL-1 secretion via ATP release and autocrine stimulation (16, 17). Monocytes exposed to LPS also synthesize large amounts of IL-8, a potent chemotactant for neutrophils and monocytes (18). Whether LPS-induced IL-8 release is also regulated by extracellular nucleotides is not known.

Previous studies by us and others have reported the presence of P2Y<sub>6</sub> transcripts in human spleen, placenta, thymus, small intestine, and leukocytes (neutrophils, lymphocytes, and monocytes) suggesting that P2Y<sub>6</sub> plays a role in immune defenses (7, 10). However, the physiological responses mediated by UDP and P2Y<sub>6</sub> are not known.

Our initial experiments showed that UDP activated IL-8 release by monocytic cells and led us to explore this new pathway of monocyte activation. Here, we show that in monocytic cells, P2Y<sub>6</sub> mediates IL-8 production and IL-8 gene expression in response to UDP or LPS. Our studies demonstrate a new role for P2Y<sub>6</sub> in chemokine production and innate immune defenses.

MATERIALS AND METHODS

Cell Lines—Human monocytic THP-1 cells (ATCC) were grown in RPMI 1640 supplemented with 5% fetal bovine serum, 10 mM Hepes, 50 units/ml penicillin G, and 50 μg/ml streptomycin (Life Technologies, Inc., Grand Island, NY), in a humid atmosphere containing 5% CO<sub>2</sub>. 1321N1 astrocytoma cells were stably transfected with a pcDNA3 expression vector encoding the human P2Y6 receptor and selected as described previously (7). Transfected 1321N1 astrocytoma cells were cultured in Dulbecco’s modified Eagle’s medium, 10% fetal bovine serum, 100

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† To whom correspondence should be addressed: Gastroenterology Div., Dana Bldg., Rm. 501, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave., Boston, MA 02215. Tel.: 617-667-1944; Fax: 617-667-2767; E-mail: mwarny@caregroup.harvard.edu.

‡ The abbreviations used are: LPS, lipopolysaccharide; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; NTPDase, nucleoside triphosphate diphosphohydrolase; TLR, Toll-like receptor; IL, interleukin; MAP, mitogen-activated protein kinase.
UDP induces IL-8 production and IL-8 gene expression in THP-1 cells. A, THP-1 cells (10⁵/ml) were suspended in complete culture medium and stimulated for 5 h with various concentrations of UDP, UTP, ADP, or ATP. IL-8 concentration was measured by enzyme-linked immunosorbent assay in the supernatant. Means and S.D. of three independent experiments are shown. B, THP-1 cells were transiently transfected with a luciferase reporter gene carrying the IL-8 promoter region. After culture for 48 h, cells (10⁵/ml) were stimulated for 5 h with UDP (0–100 µM). Means and S.D. of two independent experiments run in triplicate are shown. C, human peripheral blood monocytes were cultured in complete culture medium and stimulated for 5 h with various concentrations of UDP, UTP, ADP, or ATP. IL-8 concentration was measured by enzyme-linked immunosorbent assay in the supernatant. Means and S.D. of two independent experiments run in triplicate are shown. D, THP-1 cells were transiently transfected with a luciferase reporter gene carrying the IL-8 promoter region. After culture for 48 h, cells (10⁵/ml) were stimulated for 5 h with UDP (0–100 µM). Means and S.D. of two independent experiments run in triplicate are shown. E, THP-1 cells (10⁵/ml) were suspended in 1 ml of Tris-buffered saline containing 80 µg/mL of DEAE-dextran (Amersham Pharmacia Biotech) and 7 µg of DNA. In co-transfection experiments, total DNA was kept constant at 7 µg using control vector and 1 µg of reporter plasmid DNA was transfected. Following transfection, cells were cultured for 48 h before stimulation. Cell lysis and luciferase assay were performed using the Luciferase Assay System (Promega) following the manufacturer’s instructions. F, THP-1 cells were washed twice in phosphate-buffered saline and resuspended in serum-free culture medium at 2 x 10⁶ cells per conditions) was stopped by adding ice-cold phosphate-buffered saline and cells were lysed in 1 ml of lysis buffer. MAP kinases were immunoprecipitated with 25 µg of rabbit specific IgG to ERK2 (sc-154), p38 (sc-535), or JNK1 (sc-571) and protein G-Sepharose (Santa Cruz Biotechnology). After washing, immunoprecipitates were resuspended in 40 µl of kinase buffer and the kinase reaction was started by addition of 20 µM ATP, 100 µCi/ml [γ-32P]ATP (PerkinElmer Life Sciences, Boston, MA), and 10 µg of myelin basic protein (Sigma) (as substrate for ERK and p38) or 2 µg of glutathione S-transferase c-Jun-(1–79) (Stragatene, La Jolla, CA) (as substrate for JNK1). Samples were subjected to SDS-polyacrylamide gel electrophoresis (12%) and analyzed by autoradiography.

Endotoxin Assay—Endotoxin was measured using amebocyte lysate (QCL-1000 kit, Biowittaker, Walkersville, MD) following the manufacturer’s protocol and standard.

Statistical Analyses—Results are represented as means and S.D. Statistical analyses were performed using the SIGMA-STAT software (Jandel Scientific, San Rafael, CA). Analysis of variance (ANOVA) with protected t test was used for intergroup comparison.

RESULTS
UDP Activates IL-8 Production in Monocytic Cells—To investigate the role of extracellular nucleotides in chemokine production by monocytic cells, THP-1 cells were exposed to various concentrations of ATP, ADP, UTP, or UDP for 5 h. UDP strongly activated IL-8 release (EC50: 3 µM) (Fig. 1A) and IL-8 gene expression in THP-1 cells transiently transfected with a
luciferase reporter plasmid (Fig. 1B). ADP was also active but less potent (EC50: 20 μM), whereas ATP and UTP were inactive even at high concentrations. A similar dose-response curve was observed with another commercial source of UDP (Roche Molecular Biochemicals) (data not shown). In human peripheral blood monocytes, UDP activated IL-8 production in a dose-dependent fashion (EC50: 17 μM). By contrast, UTP, ATP, and ADP had no effect at low concentrations (up to 1 μM) and inhibited spontaneous IL-8 production at higher concentrations (Fig. 1C). Monocytes exposed to 1 mM ATP exhibited cell swelling and a translucent cytoplasm that are typical features of necrosis (23), whereas these alterations were absent in the other conditions (data not shown). We found undetectable levels of endotoxin in UDP when diluted at 100 μM, the optimal concentration. UDP preincubation for 1 h with 13 μg/ml potato apyrase III inhibited IL-8 response by 88% (Fig. 1D). In separate experiments, we found that apyrase hydrolyzes UDP at the rate of 13.7 μmol of UDP/min/mg (data not shown). Heat denaturation (95°, 5 min) abolished apyrase effect. These data indicate that UDP is a potent activator of IL-8 release and IL-8 gene expression both in THP-1 cells and human primary monocytes.

**P2Y6 Mediates IL-8 Production in Monocytic Cells**—We have previously shown that UDP is the most potent agonist of human P2Y6 and that the anthraquino-sulfonic acid derivative reactive blue 2 was a potent P2Y6 antagonist (7). Therefore, we tested whether reactive blue could inhibit UDP-induced IL-8 production in THP-1 cells. As shown in Fig. 2A, reactive blue inhibited IL-8 production by 74% at 100 μM (IC50: 35 μM) but did not prevent IL-1β induced-IL-8 release. Similarly, the P2 nucleotide antagonist suramin caused selective inhibition of UDP-induced IL-8 release (IC50: 5 μM).

To specifically evaluate the role of P2Y6, THP-1 cells were incubated in the presence of various concentrations of P2Y6 antisense S-oligonucleotides (up to 5 μM) complementary to the P2Y6 translation initiation region. Antisense S-oligos prevented IL-8 release by 40% when compared with cells pre-treated with sense S-oligos (Fig. 2B, p < 0.001). By contrast, no inhibition was observed when cells were stimulated with Clostridium difficile toxin A, a 308-kDa protein that activates IL-8 production in human monocytes (20).

To test further whether human P2Y6 mediates IL-8 production in response to UDP, we also used 1321N1 astrocytoma cells stably transfected with a pcDNA3 vector encoding P2Y6. Nontransfected 1321N1 cells have been shown not to respond to UDP (7). In transfected 1321N1 stimulated for 5 h, UDP (up to 1 mM) induced a dose-dependent increase in IL-8 concentration (EC50: 2 μM) whereas control cells did not respond to UDP (Fig. 2C). These results demonstrate that P2Y6 mediates IL-8 gene expression in response to UDP in monocytic cells.

**UDP-Induced IL-8 Production Is Mediated by ERK**—Previous studies by others and us have shown that P2Y receptors signal through MAP kinase (24). To explore the signal transduction mechanism whereby P2Y6 mediates IL-8 gene expression, we investigated the involvement of mitogen-activated protein kinases (MAP), ERK, p38, and JNK. In THP-1 cells, UDP (100 μM) caused rapid and strong ERK activation whereas, p38 and JNK activation was minimal (Fig. 3A). To test whether ERK and p38 were involved in IL-8 gene expression induced by UDP, cells were preincubated in the presence of the MEK1/2 inhibitor PD98059 (20 μM) or the p38 inhibitor SB203580 (2 μM) for 60 min. PD98059 prevented UDP-induced IL-8 production by 50% (Fig. 3B) and blocked ERK activation by UDP (Fig. 3C). By contrast, SB203580 did not prevent IL-8 release in response to UDP. However, it decreased IL-8 release induced by toxin A by 71% (Fig. 3B). Thus, ERK activation by UDP mediates IL-8 production in THP-1 cells.

**LPS-Induced IL-8 Production Is Modulated by Extracellular Nucleotides**—Previous studies have implicated nucleotide receptor signaling as a component of monocyte/macrophage activation by LPS (15, 16, 17). Therefore, we investigated whether extracellular nucleotides might regulate IL-8 production induced by LPS in THP-1 cells. First, we tested whether nucleotide receptor antagonists might prevent IL-8 production specifically induced by LPS. We found that suramin and reactive blue inhibited IL-8 release induced by LPS (100 ng/ml) but not by IL-1β (Fig. 4A).

Next, we observed that the enzyme potato apyrase grade III (2 units/ml) that degrades tri- and diphosphate nucleotides, inhibited LPS-induced IL-8 production by 70% and IL-8 gene
expression by 71%. By contrast, apyrase had no effect on IL-8 production stimulated by C. difficile toxin A or IL-1β (Fig. 4B).

However, apyrase failed to significantly inhibit IL-8 production in the presence of very high LPS concentrations (10 µg/ml; data not shown).

Finally, we tested whether LPS stimulates the release of extracellular nucleotides in the system tested. Unfortunately, UDP release from monocytes could not be assessed because of a lack of an appropriately sensitive method. However, apyrase failed to significantly inhibit IL-8 production in the presence of very high LPS concentrations (10 µg/ml; data not shown).

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**DISCUSSION**

This study demonstrates that UDP stimulates IL-8 release via P2Y6 in human mononuclear cells. It also shows that P2Y6 regulates IL-8 production induced by LPS. This is the first...
UDP release was demonstrated by the observation that addition of $[^{32}P]ATP$ in extracellular medium resulted in the accumulation of $[^{32}P]UTP$, presumably via membrane diphosphokinase. However, identification of the mechanisms that regulate nucleotide release in basal conditions or in response to LPS will help to better understand the physiological role of UDP.

Peracellular nucleotide concentration is also regulated by ecto-apyrases including CD39, the prototype nucleoside triphosphate diphosphohydrolase (or NTPDase-1) (33, 34). This enzyme is the major NTPDase expressed by monocytes-macrophages and is expressed on THP-1 cells. In endothelial cells, CD39 overexpression can block ATP release induced by LPS and prevent subsequent maturation and release of IL-1α (17). Since CD39 hydrolyzes diphosphonucleotides, this enzyme may regulate inflammatory responses mediated by UDP in monocytes. Another potential player in regulating UDP and P2Y$_6$ activity is CD39-L4 (or NTPDase 5), a CD39 analogue (35). In contrast to CD39, CD39-L4 is secreted and its role is not known. Interestingly, CD39-L4 transcripts were found only in macrophages. In addition, this enzyme was specific for diphosphate nucleotides and exhibited a maximal activity for UDP (35). Therefore, CD39-L4 might regulate inflammation and UDP-induced chemokine release.

Our finding that LPS triggers ATP release from THP-1 cells and primary macrophages is consistent with previous studies in microglial cells (16), HUVEC cells (17), and Raw 264.7 macrophagic cells (13). However, two other studies did not detect ATP release from a murine macrophage cell line (36) or from THP-1 cells (37). The reasons for these discrepancies are unclear, but in our experiments we have excluded artifactual ATP release by physical stimuli (medium change, shaking, or pipetting).

This study extends previous reports implicating extracellular nucleotides in the regulation of intracellular responses induced by LPS in monocytes/macrophages (15, 16, 27). Moreover, it is now well established that Toll-like receptor 4 (TLR4) mediates LPS signaling. In concert with CD14 and MD-2, TLR4 plays a key role in mediating IL-8 production in response to LPS (38, 39). In vivo, TLR4 mutations are associated with hyporesponsiveness to LPS in mice and humans (40, 41). However, TLR4 has not been shown to be the only signaling mechanism for LPS. Our finding that IL-8 production induced by LPS can be partially inhibited by nucleotidases or by P2Y$_6$ antisense S-oligos suggest that UDP and perhaps other extracellular nucleotides act synergistically with TLR4. Whether TLR4 or CD14 might be implicated in regulating UDP and P2Y$_6$ activity is not known.

In summary, this study demonstrates that UDP activates IL-8 gene expression and IL-8 release via P2Y$_6$ in monocytes. Furthermore, it shows that LPS-induced IL-8 production is at least in part mediated by autocrine P2Y$_6$ activation. These findings indicate a novel role for P2Y$_6$ in inflammation and innate immune defenses.

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$^{2}$ M. Warny, S. C. Robson, and J. Sévigny, unpublished observations.
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