P2X7 receptor activation induces CD62L shedding from human CD4+ and CD8+ T cells

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Abstract
The P2X7 receptor is expressed on T cells, however knowledge of its presence and function on human CD4+ and CD8+ subsets is limited. Immunolabeling with an anti-human P2X7 monoclonal antibody and flow cytometry demonstrated that P2X7 is present on the cell-surface of peripheral blood CD4+ and CD8+ T cells. Time-resolved flow cytometry demonstrated that extracellular ATP induced ethidium+ uptake into both T cell subsets. Flow cytometric measurements also demonstrated that ATP induced the rapid loss of CD62L (L-selectin) from CD4+ and CD8+ T cells. ATP-induced ethidium+ uptake and CD62L shedding were dramatically impaired in CD4+ and CD8+ T cells homozygous for the Glu496Ala loss-of-function single nucleotide polymorphism in the P2RX7 gene, demonstrating that both processes were a result of P2X7 activation. In summary, these results show that both human CD4+ and CD8+ T cells express P2X7 receptors, and that ATP activation of this receptor can lead to the rapid shedding of CD62L from these cells.

Keywords
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P2X7 receptor activation induces CD62L shedding from human CD4⁺ and CD8⁺ T cells

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Keywords: T cell; T lymphocyte; purinergic receptor; damage-associated molecular pattern receptor; extracellular ATP; CD62L; L-selectin

Abbreviations: ATP, adenosine 5’-triphosphate; FITC, fluorescein isothiocyanate; IL-6R, interleukin-6 receptor; mAb, monoclonal antibody; PE, R-phycoerythrin; SEM, standard error of the mean; SNP, single nucleotide polymorphism

Introduction

CD62L (L-selectin) is a member of the selectin family of cell adhesion molecules, and plays important roles in the recruitment and migration of leukocytes to lymphoid tissues and sites of inflammation [1]. CD62L directs the entry of naïve and central memory T cells to lymph nodes to promote immune responses [2]. Moreover, CD62L can regulate the migration of certain T cell subsets to sites of cutaneous inflammation [3], as well as to nasal- and gut-associated lymphoid tissues to promote allergy [4] and gastrointestinal inflammation [5], respectively. The expression of CD62L is regulated by a number of mechanisms including proteolytic cleavage from the cell surface, which can limit T cell migration and activation [6]. However, the signaling mechanisms involved in CD62L shedding have not been fully elucidated.

Extracellular adenosine 5’-triphosphate (ATP) is a damage-associated molecular pattern, which mediates its effects through the activation of the P2X7 receptor, a trimeric ATP-gated cation channel [7]. P2X7 activation by extracellular ATP causes the flux of K⁺, Na⁺ and Ca²⁺, as well as the uptake of organic cations including ethidium⁺ [7]. The relative amount of P2X7 function however varies between humans due to a number of single nucleotide
polymorphisms (SNPs) in the P2RX7 gene that code for P2X7 variants with a loss or gain of function [8]. One of the most common P2X7 SNPs is rs3751143, which codes for a glutamic acid to alanine substitution at amino acid 496 (Glu496Ala) and leads to a near-complete loss of receptor function in homozygous dosage [9]. P2X7 is present on mononuclear leukocytes including T cells from various species [10-12]. P2X7 activation on T cells mediates several cell signaling events including the shedding of cell-surface CD62L [13,14]. However, knowledge about the presence and function of P2X7 on human CD4+ and CD8+ T cells is limited. Using peripheral blood lymphocytes from subjects wild-type, heterozygous and homozygous for the Glu496Ala SNP, the current study aimed to investigate the presence of functional P2X7 receptors on human CD4+ and CD8+ T cells, and whether activation of this receptor results in CD62L shedding from these T cell subsets.

Materials and methods

Lymphocytes. Peripheral blood was collected from healthy human volunteers who were previously identified as wild-type, heterozygous or homozygous for the Glu496Ala SNP in the P2RX7 gene [15]. Peripheral blood mononuclear cells were separated by gradient centrifugation using Ficoll-Paque PLUS (Amersham Biosciences, Uppala, Sweden) and cultured in RPMI-1640 medium (Sigma, St. Louis, MO) containing 10% foetal calf serum, 1 mM L-glutamine, 0.1 mM non-essential amino acids, 5.5 x 10-2 mM 2-mercaptoethanol, 5 g/mL gentamycin and 10 mM HEPES (Invitrogen, Auckland, New Zealand) for 2 hours at 37°C and 95% air/5% CO2. The non-adherent cells were collected to obtain lymphocytes. Blood was collected and used in accordance with institutional guidelines and approval from the Wentworth Area Health Service (Penrith, Australia) and University of Sydney (Sydney, Australia) Ethics Committees.

Immuno labeling and flow cytometry. Fluorescein isothiocyanate (FITC)- and R-phycocerythrin (PE)- conjugated anti-CD4, CD8 and CD62L monoclonal antibodies (mAb) were from BD Biosciences (San Diego, CA). PE-Cy5-conjugated anti-CD3 mAb was from Dako (Carpinteria, CA). FITC-conjugated anti-P2X7 mAb (clone L4) was prepared as described [11]. Lymphocytes (1x10^6) were labeled with fluorochrome-conjugated mAb in the presence of 10% human AB serum for 20 min and washed. CD3+CD4+ or CD3+CD8+ cells within the lymphocyte gate (gated by forward and side scatter) were analysed for P2X7 or CD62L expression using a FACS Calibur flow cytometer and Cell Quest software (BD Biosciences).

Measurement of ATP-induced ethidium+ uptake. ATP-induced ethidium+ uptake into lymphocytes was measured as described [16]. Briefly, 25 M ethidium bromide (Sigma Chemical Co., St. Louis, MO) was added to lymphocytes (2x10^6/mL), pre-labeled with FITC-conjugated anti-CD4 or CD8 mAb, in KCl medium (150 mM KCl, 5 mM D-glucose, 0.1% (w/v) bovine serum albumin, 10 mM HEPES, pH 7.4) at 37°C, followed by the addition of 1 mM ATP (Sigma Chemical Co.) 40 s later. Data was acquired at 5 s intervals for either CD4+ or CD8+ cells within the lymphocyte gate (selected using forward and side scatter) and analysed using WinMDI software (version 2.7; http://www.scripps.edu). ATP-induced ethidium+ uptake was quantitated as the difference in arbitrary units of area under the uptake curves in the presence and absence of ATP during the first 5 min of incubation.

Measurement of CD62L shedding. CD62L shedding from lymphocytes was measured as described [15]. Lymphocytes (2x10^6/mL) were incubated for up to 15 min in KCl medium at 37°C in the presence or absence of 0.5 mM ATP with the incubations stopped by adding two volumes of cold MgCl2 medium (145 mM NaCl, 5 mM KCl, 10 mM MgCl2, 10 mM HEPES, pH 7.4). Cells were washed and the mean fluorescence intensity of CD62L surface expression determined by flow cytometry as above. Results are presented as the percentage of CD62L expression in the presence of ATP compared to CD62L expression in the absence of ATP (control).

Data presentation and statistical analyses. Data is expressed as mean and standard error of the mean (SEM). Differences between groups were compared by the One-way ANOVA (using Tukey’s multiple comparison test) using Prism 5 (GraphPad Software, San Diego, CA) with P < 0.05 considered significant.

Results and discussion

Labeling of CD4+ and CD8+ T cells, from normal human subjects, with anti-P2X7 mAb showed that both cell subtypes expressed P2X7 on the cell surface (Fig. 1). Consistent with previous findings for T and B cells [8] the amount of cell-surface P2X7 between either T cell subset from subjects wild-type, heterozygous or homozygous for the Glu496Ala SNP was similar (Table 1). The amount of cell-surface P2X7 between CD4+ and CD8+ T cells was also similar. The similar but low amounts of P2X7 on both T cell subsets is consistent with the relatively low amount of P2X7 observed previously on CD3+ T cells [11].

Extracellular ATP induced ethidium+ uptake into CD4+ and CD8+ T cells from wild-type subjects with
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Figure 1. P2X7 is present on human CD4^+ and CD8^+ T cells. Lymphocytes wild-type, heterozygous or homozygous for the Glu496Ala SNP were pre-labeled with FITC-conjugated CD4 or CD8 mAb, PE-conjugated CD4 or CD8 mAb, and PE-Cy5-conjugated CD3 mAb, and analyzed by flow cytometry. Representative data from six (wild-type) or three (heterozygous or homozygous) subjects is shown.

Figure 2. P2X7 activation mediates ATP-induced ethidium^+ uptake into human CD4^+ and CD8^+ T cells. Lymphocytes wild-type, heterozygous or homozygous for the Glu496Ala SNP were pre-labeled with FITC-conjugated CD4 or CD8 mAb. Cells were suspended in KCl medium (37°C) and ethidium^+ was added, followed by the addition of 1 mM ATP 40 s later (arrow). Mean fluorescence intensity (MFI) of ethidium^+ uptake was acquired at 5 s intervals by flow cytometry. Ethidium^+ uptake in the absence of ATP was minimal and similar between subsets and subjects (results not shown). Representative data from six (wild-type) or three (heterozygous or homozygous) subjects is shown.

Figure 2. P2X7 activation mediates ATP-induced ethidium^+ uptake into human CD4^+ and CD8^+ T cells. Lymphocytes wild-type, heterozygous or homozygous for the Glu496Ala SNP were pre-labeled with FITC-conjugated CD4 or CD8 mAb. Cells were suspended in KCl medium (37°C) and ethidium^+ was added, followed by the addition of 1 mM ATP 40 s later (arrow). Mean fluorescence intensity (MFI) of ethidium^+ uptake was acquired at 5 s intervals by flow cytometry. Ethidium^+ uptake in the absence of ATP was minimal and similar between subsets and subjects (results not shown). Representative data from six (wild-type) or three (heterozygous or homozygous) subjects is shown.

mean arbitrary units of uptake (SEM) of 1664 (510) and 3478 (1263), respectively (n = 6; Fig. 2). ATP also induced ethidium^+ uptake into CD4^+ and CD8^+ T cells from heterozygous subjects with mean arbitrary units of uptake (SEM) of 509 (356) and 1155 (391), respectively (n = 3), which on average was one-third lower than that observed for wild-type CD4^+ and CD8^+ T cells (Fig. 2). In contrast, ATP induced only minimal ethidium^+ uptake into CD4^+ and CD8^+ T cells from homozygous subjects with mean arbitrary units of uptake (SEM) of 47 (23) and 295 (105), respectively (n = 3; Fig. 2). Comparison of CD4^+ and CD8^+ T cells showed that ATP-induced ethidium^+ uptake tended to be higher in CD8^+ T cells than in CD4^+ T cells for each genotype, but this difference did not reach statistical significance. However, comparison between the subsets is complicated by the ability to gate only FITC-labeled CD4^+ or CD8^+ T cells, as ethidium^+ interferes with the far-red channel and prevented the use of PE-Cy5-conjugated CD3 mAb on our single laser flow cytometer. Natural killer cells, which have higher P2X7 function than T cells [11], can also express CD8 [17], and thus would have been included in the CD8^+ gate to potentially contribute to the greater P2X7 function of CD8^+ T cells compared to CD4^+ T cells. Nevertheless immunolabeling with an anti-P2X7 mAb and measurements of ATP-induced ethidium^+ uptake demonstrate that both human CD4^+ and CD8^+ T cells express P2X7.

Extracellular ATP also induced a rapid loss of CD62L from the cell-surface of CD4^+ and CD8^+ T cells from wild-type subjects in a near-identical and time-dependent fashion (Fig. 3). In contrast to ATP-induced ethidium^+ uptake (Fig. 2), ATP induced a loss of CD62L from CD4^+ and CD8^+ T cells from heterozygous subjects that was only marginally slower than that observed for wild-type T cells (Fig. 3). This rate of loss of cell-surface CD62L from CD4^+ and CD8^+ T cells from subjects of either genotype was similar to that previously reported for human CD4^+ T cells [18], and for human B and T cells [13]. In contrast, the ATP-induced loss of CD62L was dramatically impaired from homozygous T cells compared to wild-type or heterozygous T cells (Fig. 3). Although the shedding of CD62L into the extracellular medium was not directly assessed, ELISA measurements of soluble CD62L have confirmed that P2X7 activation induces the shedding of CD62L from human B cells [13]. Collectively, the above data demonstrates that P2X7 activation induces the rapid shedding of CD62L from both human CD4^+ and CD8^+ T cells.

The cell signaling events that mediate P2X7-induced
shedding of CD62L from T cells remain to be determined. Human P2X7 activation induces the rapid shedding of CD23 and CXCL16 from malignant B cells [19-21], as well as the shedding of the interleukin-6 receptor (IL-6R) from human epithelial cells or murine fibroblasts co-transfected with human P2X7 and human IL-6R [22]. Human P2X7-induced CD23, CXCL16 and IL-6R shedding is primarily mediated by ADAM10 [21,22], however it is likely that ADAM17 is the principle sheddase involved in P2X7-induced CD62L shedding from human CD4+ and CD8+ T cells. It has previously been shown that P2X7-induced CD62L and CD23 shedding from malignant B cells is mediated by different metalloproteases [20], and that ADAM17 is the principle sheddase for both calcium- and ATP-induced CD62L shedding from murine B cells [23]. Furthermore, P2X7-induced CD62L shedding from malignant B cells is impaired by the zinc-metalloprotease inhibitor, Ro 31-9790, [20] which indirectly supports a role for ADAM17 in this process.

Despite the known involvement of ADAM10 and ADAM17 in P2X7-induced shedding of cell-surface molecules, the cell signaling mechanisms involved in this process have remained far more elusive. Attempts using inhibitors of candidate enzymes predicted to mediate P2X7-induced CD62L and CD23 shedding have failed to show a role for various intracellular signaling enzymes [15,18,24]. In contrast, use of 4,4’-disothiocyanatosilbene-2,2’-disulphonic acid, an inhibitor of phosphatidylserine translocation, indicates that P2X7-induced CD62L shedding from murine CD4+CD45RB+T cells is dependent on phosphatidylserine exposure [25], although the precise mechanism involved in this signaling axis remains to be determined. Moreover, mitochondrial but not NADPH oxidase superoxide formation has been shown to enhance P2X7-induced CD62L shedding from human CD4+ T cells, but despite this observation P2X7-induced CD62L shedding appears to be independent of mitochondrial superoxide formation [18]. Thus, further studies are required to ascertain the cell signaling pathways involved in P2X7-induced metalloprotease activation and the subsequent shedding of cell-surface molecules including CD62L. Further studies are also required to determine the physiological significance of P2X7-induced CD62L shedding in inflammation.

In summary, the current results show that both human CD4+ and CD8+ T cells express P2X7, and that activation of this receptor by extracellular ATP can lead to the rapid shedding of CD62L from these cells.

**Conflict of interests**

The authors declare that they have no conflicting interests.

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