Regulation of adenosine system at the onset of peritonitis

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Abstract

Background. Adenosine, a potent regulator of inflammation, is produced under stressful conditions due to degradation of ATP/ADP by the ectoenzymes CD39 and CD73. Adenosine is rapidly degraded by adenosine deaminase (ADA) or phosphorylated in the cell by adenosine kinase (AK). From four known receptors to adenosine, A1 (A1R) promotes inflammation by a Gs-coupled receptor. We have previously shown that A1R is up-regulated in the first hours following bacterial inoculation. The aim of the current study is to characterize the inflammatory mediators that regulate adenosine-metabolizing enzymes and A1R at the onset of peritonitis.

Methods. Peritonitis was induced in CD1 mice by intraperitoneal injection of Escherichia coli. TNFα and IL-6 levels were determined in peritoneal fluid by enzymelinked immunosorbent assay. Adenosine-metabolizing enzymes and the A1R mRNA or protein levels were analyzed by quantitative PCR or by Western blot analysis, respectively.

Results. We found that CD39 and CD73 were up-regulated in response to bacterial stimuli (6-fold the basal levels), while AK and ADA mRNA levels were down-regulated. Cytokine production and leukocyte recruitment were enhanced (2.5-fold) by treatment with an A1R agonist (2-chloro-N6-cyclopentyladenosine, 0.1mg/kg) and reduced (2.5–3-fold) by the A1R antagonist (8-cyclopentyl-1, 3-dipropylxanthine, 1mg/kg). In contrast to lipopolysaccharide, IL-1, TNF and IFNγ, only low IL-6 levels (0.01ng/ml), in the presence of its soluble IL-6R (sIL-6R), were found to promote A1R expression on mesothelial cells. In mice, administration of neutralizing antibody to IL-6R or soluble gp130-Fc (sgp130-Fc) blocked peritoneal A1R up-regulation following inoculation.

Conclusion. Bacterial products induce the production of adenosine by up-regulation of CD39 and CD73. Low IL-6–sIL-6R up-regulates the A1R to promote efficient inflammatory response against invading microorganisms.

Keywords: A1 Adenosine receptor; C39; CD73; peritonitis; soluble-interleukin (IL)-6 receptor

Introduction

Adenosine is an endogenous purine nucleoside that has been shown to be involved in inflammatory and repair processes [1]. Constitutively, adenosine is present at low concentrations in the extracellular space, but in metabolically stressful conditions its extracellular levels dramatically increase [1–3]. Under these conditions, there is a release of precursor adenine nucleotides (ATP, ADP and AMP) from aggregating platelets, degranulating macrophages, excitatory neurons, injured cells and cells undergoing mechanical or oxidative stress [4]. These nucleotides are dephosphorylated to adenosine by a cascade of two enzymes: nucleotidase triphosphate dephosphorylase (CD39), which converts ATP/ADP to AMP, and 5′-ectonucleotidase (CD73), which converts AMP to adenosine. The half-life of adenosine is <30 s and is rapidly converted to inosine by adenosine deaminase (ADA) or phosphorylated to ATP by adenosine kinase (AK) inside the cell [3]. Adenosine binds to at least four different receptor subtypes. Binding to the A1 receptor (A1R) or to the A3 receptor (A3R) activates G protein G1α/Gqα, which inhibits adenylyl cyclase activity and decreases cAMP levels [5]. Through declining cAMP levels, A1R activates G protein Gqα to inhibit the activation of neutrophil adherence to endothelium [6], chemotaxis [7,8] and phagocytosis [9,10]. In contrast, the A2A receptor (A2AR) interacts with Gs and the A2B receptor (A2BR) interacts with Gq/G11 to induce adenylyl cyclase activity and elevate cAMP levels. Engagement of A2AR inhibits the activation of neutrophils, monocytes, platelets and T cells [9,11,12]. In a previous study using a mice peritonitis model, we demonstrated that, following inoculation with Escherichia coli, adenosine levels increased in the peritoneal cavity with a peak at 24 h [13]. In addition, we found a sequential up-regulation of A1R and A2AR on leukocytes and peritoneal mesothelial cells (PMCs). The peak of the A1R, the pro-inflammatory receptor, occurred in the initial phase of the inflammatory process and its activation was necessary for induction of A2AR, the anti-inflammatory receptor of...
The importance of A1R and A2AR in regulation of inflammation was demonstrated by the shifting of the anti-inflammatory resolution phase after pre-treatment with A1R agonists. The aim of the current study is to characterize the involvement of adenosine in the early stages of inflammation, i.e. how inflammatory mediators regulate adenosine-metabolizing enzymes and A1R at the initial pro-inflammatory phase of peritonitis. For this purpose, we examined the kinetics of adenosine-metabolizing enzymes in an in vivo model of peritonitis, and in vitro on PMCs, we examined the factors that regulate A1R. PMCs were chosen since they form a monolayer on the peritoneal membrane and they play an important role in transferring inflammatory signals from the peritoneal cavity to the blood vessels [15–18]. We were able to show that, in the initial phase of peritonitis, adenosine-producing enzymes are induced and adenosine-degrading enzymes are down-regulated. Moreover, we found that A1R up-regulation was dependent on interleukin-6 (IL-6) activation which requires the presence of soluble IL-6 receptor (sIL-6R).

Methods

CD1 mice (Harlan, Jerusalem, Israel) were maintained in the animal laboratory of Soroka Medical Center. Experiments were conducted with the approval of the Israel Committee for Animal Experiments. Recombinant human IL-6, recombinant human sIL-6R, anti-mouse IL-6R and soluble gp130-Fc chimera (sgp130-Fc) were purchased from R&D Systems (Minneapolis, MN). A1R antagonist 8-cyclopentyl-1, 3-dipropylxanthine (DPCPX), A1R agonist 2-chloro-N6-cyclpentyladenosine (CCPA), ADA and lipopolysaccharide (LPS) were purchased from Sigma (Rehovot, Israel).

Induction of peritonitis and treatment protocol

Peritonitis was induced in mice by intraperitoneal (i.p.) inoculation of a sublethal dose of *Escherichia coli* HB-109 (E. coli, 3.6 × 10^8 cfu). Anti-mouse IL-6R (5μg/mouse), sgp130-Fc (250ng/mouse), CCPA (0.1mg/kg) or DPCPX (1mg/kg) were also injected i.p.

Sera fluid collection, leukocyte counting and cytokine detection

Following *E. coli* inoculation, mice were anesthetized by isoflurane, and peritoneal lavage was performed with phosphate-buffered saline containing 2% bovine serum albumin and 5mM EDTA. The supernatants were assayed by enzyme-linked immunosorbent assay (ELISA) for TNFa (Biolegend, San Diego, CA), IL-6 and sIL-6R levels (R&D Systems). Total leukocytes were counted after trypan blue staining using an improved Neubauer haemocytometer. Cell counts and ELISA were performed blindly on coded samples.

Neutrophil purification

A 1-ml syringe flushed with heparin was used to draw intracardial blood from CD1 mice. Neutrophils from blood were separated by Ficoll/Hypaque (Sigma) centrifugation followed by hypotonic lysis of erythrocytes resulting in 85–90% purity [19].

Preparation of PMC’s lysates

Following inoculation, four to five animals per time point were anesthetized, and PMCs were scraped from the peritoneal membrane. After centrifugation at 400 g and 4°C for 10 min, cells were harvested with RNA lysis buffer (Versagen RNA cell kit, Gentra Systems, Minneapolis, MN) for analyzing mRNA levels or with RIPA (150mM NaCl, 50mM Tris-HCl pH 7.4, 1% NP-40, 0.25% Na deoxycholate, 1mM EDTA), including protease inhibitor cocktail (Sigma), for analyzing protein levels.

Isolation of cultured PMC

Peritonitis was removed from eight newborn (2-week-old) CD1 mice, isolated and morphologically inspected, as previously described [20]. Cells were grown in M199 supplemented with 10% heat-inactivated fetal calf serum, 2mM l-glutamine, 100U/ml penicillin and 100μg/ml streptomycin (Biological Industries, Bet Haemek, Israel).

Flow cytometry analysis

For flow cytometry analysis, 1 × 10^6 neutrophils or mesothelial cells were incubated with anti-mouse CD32/16 (Fc blocker, Biolegend) for 15 min at 4°C and then stained with 5μg of goat anti-sIL-6R (R&D Systems) for 30 min at 4°C. After 30 min, the cells were stained with fluorescein isothiocyanate-labeled anti-goat (Chemicon International, Temecula, CA) for 30 min at 4°C. Analyses were conducted by flow cytometry (FC500, Beckman Coulter, Fullerton, CA). Fluorescence data were analyzed by the CXP program (Beckman Coulter) and presented in a two-parameter probability plots form.

mRNA analysis

Total RNA was extracted from PMC using the Versagen RNA cell kit (Gentra Systems). cDNA was prepared as previously described [22]. Quantitative real-time PCR (QPCR) assays were carried out in a RotorGene real-time PCR machine (Corbett Research, Northlake, Australia) with the following primers—β-actin sense: 5′-GGG TCA GGA GGA TCT CTA TG-3′, β-actin anti-sense: 5′-GGT CTC ATT GCT GGA CTG ACC-3′; C D 7 3 s e n s e : 5′- TT G TA C T G C C C T CAG C T G T C-3′; C D 7 3 a n t i - s e n s e : 5′-CTG ATT GTG GGA CTG AGC-3′; sIL-6R sense: 5′-AGG TAT GCG TAC TGG GTG GAC CAG-3′; sIL-6R anti-sense: 5′-AAG GAT GCC TGG TAT GAG GAC CAG-3′; CD73 sense: 5′-GGT GTG ATT GTG GGA CTG ACC-3′; CD73 anti-sense: 5′-GCC AGG TAC GCA CCG ATT TCA TCT-3′; MCP-1 sense: 5′-CCC CAA ATG ACC GGT ACC-3′; MCP-1 anti-sense: 5′-GGT ATG GCC CAG TAC ACC-3′; adenosine deaminase sense: 5′-ATG GCC CAG ACA CCC CCA TT-3′, adenosine deaminase antisense: 5′-TCT CTG CAG CCC GAC ACA ACC-3′; A1R sense: 5′-GCG AAT GCA CTC AGT CAG AGG CT-3′; A1R anti-sense: 5′-GGG TCA GGA GGATTC CTA G-3′; IL-6 sense: 5′-CTC ACC TGC TGC TAC TC-3′; IL-6 anti-sense: 5′-GCT TGA GG TGT TGA AAA-3′.

Western blot analysis

Cell lysates were centrifuged at 13 000×g for 30 min and supernatants were collected. Thirty micrograms of total protein from each sample was subjected to 10% sodium dodecyl sulfate–polyacrylamide gel electrophoresis under reducing conditions and heating. The gels were blotted onto a polyvinylidine fluoride membrane (Bio-Rad, Hercules, CA) and probed with one of the following specific antibodies: goat anti-CD73 (Santa Cruz Biotechnology, Santa Cruz, CA), goat anti-CD39 (Santa Cruz Biotechnology), rabbit anti-A1R (Alpha Diagnostic International, San Antonio, TX) and goat anti-β-actin (Santa Cruz Biotechnology). The membrane was then probed with goat anti-rabbit immunoglobulin (IgG) conjugated to peroxidase agent (Jackson ImmunoResearch Laboratories, West Grove, PA). Antigen–antibody complexes were subsequently visualized by the EZ-ECL Chemiluminescence Detection Kit for horseradish peroxidase (Biological Industries).

ADA bioactivity assay

Following inoculation, peritoneal lavage fluid was collected and ADA activity was determined as described by Brady et al. [21].

Statistical analysis

Data are presented as mean ± SEM. Statistical analysis was performed by t-test or analysis of variance followed by Tukey’s post-hoc test. *P*-values <0.05 were considered significant.
Results

Effect of LPS on adenosine-metabolizing enzymes in vitro

Previously, we found that adenosine levels increase in the peritoneal cavity in response to *E. coli* inoculation [13]; therefore, we tested in vitro the regulation of adenosine-metabolizing enzymes in response to LPS. Treatment of PMCs with LPS up-regulated CD39 and CD73 levels. The mRNA of both ectoenzymes peaked at 6h and remained elevated up to 24h after treatment (A–B). In contrast, the levels of adenosine-degrading enzymes were reduced during the first hours of LPS treatment. AK levels were down-regulated after 6h and then slowly increased above basal levels up to 24h (Figure 1C). ADA mRNA levels were down-regulated in response to LPS and remained low up to 24h (Figure 1D).

Expression of adenosine-metabolizing enzymes in the course of peritonitis

Similar to the effect of LPS in vitro, both CD39 and CD73 mRNA levels increased in PMCs shortly after *E. coli* inoculation (A–B, upper panel). mRNA elevation was followed by accumulation of protein, reaching the highest levels 24h after inoculation (Figure 2A–B, lower panel). ADA mRNA levels and activity in the lavage fluid significantly increased at 48h in the late phase of peritonitis (Figure 2C–D). Conversely, we found a decrease in AK mRNA levels up to 12h after *E. coli* inoculation (Figure 2E). At 24h, AK levels were elevated to basal levels and decreased again up to 48h.

Adenosine affects the inflammatory response via A1R

To examine the regulatory role of adenosine and its pro-inflammatory A1 receptor during peritonitis, mice were treated with a specific agonist and antagonist of this receptor. As shown in Figure 3, treatment with A1R agonist (CCPA, 0.1mg/kg) enhanced leukocyte recruitment to the peritoneum in *E. coli*-inoculated mice 1.25-fold compared to vehicle-treated mice (vehicle-treated counts = 5.22 ± 0.85 × 10^6 cells), while treatment with an A1R antagonist (DPCPX, 1 mg/kg) reduced cell counts 1.56-fold from vehicle. Similarly, the A1R agonist and antagonist had reciprocal effects on cytokine levels. Comparing to TNFα levels in vehicle-treated mice (60.42 ± 19.76pg/ml), CCPA treatment increased the levels of TNFα 1.7-fold while DPCPX treatment decreased TNFα 1.8-fold. Similarly, comparing to IL-6 levels in vehicle-treated mice (24.16 ± 3.30ng/ml), CCPA increased the IL-6 levels 1.6-fold and DPCPX reduced its levels 1.49-fold.

IL-6–sIL-6R complex induces the expression of A1R in vitro

Next, the effect of various pro-inflammatory mediators was examined. Stimulation of PMCs with the pro-inflammatory cytokines TNFα, IL-1, IFNγ and IL-6 had no effect on the up-regulation of A1R mRNA levels (A). Interestingly, a combined treatment of IL-6 with its soluble receptor (sIL-6R) effectively increased on PMCs the mRNA levels of A1R and MCP-1 (Figure 4A–B), a chemokine known to be up-regulated by IL-6. The flow cytometry analyses that we have performed (Figure 4C) indicate that, similar to the findings of Hurst *et al.* [22–24], membrane IL-6R is absent...
on PMCs and is highly expressed on neutrophils. Figure 4D shows the dose response of PMCs to increasing concentrations of IL-6 in the presence of constant saturating sIL-6R dose (10 ng/ml). Both levels of A1R mRNA (upper panel) and protein (lower panel) responded in a bell-shaped curve manner to increasing IL-6 concentrations.

Fig. 2. Adenosine-metabolizing enzyme levels during peritonitis. At different time intervals after E. coli inoculation, PMC were scraped from the peritoneum surface and analysed for mRNA by real-time PCR (upper panels of A and B, C and E) or by Western blot for protein levels (lower panels of A and B). mRNA and protein levels were normalized with β-actin levels. Results of protein levels are presented as densitometry of representative protein blot depicted in (A) and (B). (D) Lavage fluid was collected and ADA activity was determined. Results are presented as mean ± SEM of four experiments, fold from time 0, n = 4 for each group. *P < 0.05, **P < 0.01 from time 0.
Induction of A₁R by bacterial products requires the presence of sIL-6R

To examine whether A₁R induction by bacterial LPS requires the presence of sIL-6R, isolated PMCs were incubated with either LPS or sIL-6R separately or in combination. As shown in Figure 5A, neither LPS nor sIL-6R altered A₁R mRNA levels while combined treatment with both LPS and sIL-6R significantly up-regulated A₁R mRNA concentrations.

Next, we examined the kinetics of IL-6 and its soluble receptor during peritonitis. We found that both IL-6 and sIL-6R levels increased dramatically in the first hours after inoculation and peaked at 3h (Figure 5B). To test the role of sIL-6R in the induction of A₁R at the onset of peritonitis, we performed sIL-R6 blocking experiments. In accordance with our in vitro findings, the induction of peritoneal A₁R following E. coli inoculation was completely blocked in mice treated with IL-6R-neutralizing antibody which blocks soluble and membrane IL-6R or with sgp130-Fc, a specific inhibitor of the soluble complex IL-6/sIL-6R. Treatment of inoculated mice with isotype-matched controls to anti-IL-6R and sgp130 did not affect A₁R levels (Figure 5C–D).

Discussion

Adenosine is a potent modulator of inflammation, its effect depending on bioavailability and on receptor expression. We have previously demonstrated in a peritonitis model that adenosine levels are up-regulated following E. coli inoculation [13]. In parallel to the induction of adenosine, A₁R levels are up-regulated together with leukocyte recruitment at the initial phase of inflammation [13,14]. The present work focuses on the events that promote the production of adenosine and the expression of A₁R at the first phase of inflammation.

Our data indicate a fast induction of mRNA of the ectoenzymes at 6h, which is followed by protein accumulation at 24h. The time gap between the mRNA and protein peaks could be explained by the different half-lives of mRNA and protein. The induced mRNA of CD39 and CD73 can degrade shortly after its production while protein produced by these mRNA may be stable and continue to accumulate in the peritoneum during the decline of the mRNA levels. Consistent with these results, elevation of CD73 or CD39 was shown in lungs following exposure of mice to aerosolized LPS [25]. Hypoxia, which is common in inflammatory diseases, was shown to induce both CD39 and CD73 mRNA levels and activity [26]. Similarly, in models of colitis [27] and fibrosis [28], CD73 transcript and activity were found to be elevated, and CD39 were shown to significantly increase in both chronic pancreatitis and pancreatic cancer [29].

Generally, the relative levels of ADA and AK which metabolize adenosine were a mirror image to CD39 and CD73 levels. Both ADA and AK levels were reduced in the first hours of peritonitis and up-regulated later at the resolution phase. In accordance with our findings, endothelial AK transcript, protein and function were shown to be repressed in response to hypoxia in vitro and in vivo, enabling the elevation of adenosine [30]. Thus, during the first hours of peritonitis, adenosine-producing enzymes are dominant, leading to accumulation of adenosine, while during the resolution phase adenosine is metabolized due to elevation of adenosine-degrading enzymes.

The A₁R was shown to enhance leukocyte recruitment [6–8,10], phagocytosis [9], generation of reactive oxygen species and NO and cytokine production [7–9,31–34]. We have previously shown on PMCs and peritoneal leukocytes that A₁R is up-regulated shortly after inoculation [13,14],
and we now show that A1R is a potent promoter of inflammation in the peritoneum. Pre-treatment with DPCPX, an A1R antagonist, reduced both leukocyte recruitment and the pro-inflammatory cytokine production as expected; treatment with A1R agonist CCPA has the reverse effects on the inflammatory cytokines. Thus, our data suggest a pro-inflammatory role for A1R.

Different from our results, in two experimental models of chronic inflammation, depletion of A1R increased inflammation as was shown with A1R knockout (KO) mice in a model of allergic encephalomyelitis and in a model of pulmonary injury [35,36].

The large differences between these chronic models and our acute bacterial inflammation model make them difficult to compare. As we have shown in the current and previous studies [13,14], adenosine receptors are dynamic and their levels change during the different phases of inflammation. It is possible that prolonged exposure to adenosine in chronic pathologies affects the levels or desensitizes the pro-inflammatory signals produced by the A1R. In addition, we have recently shown that A1R activation is necessary for the induction of the A2AR, which is the main receptor associated with the anti-inflammatory effects of adenosine [14]. It is possible that part of the A1R-protect
tive role is mediated by the induction of A2A R which is lacking in A1R KO mice used in these studies. Although it has been shown that A1R has a role in the inflammatory process, its regulation has been poorly investigated. Biber et al. suggested an important role for IL-6 in induction of neuronal adenosine A1R, with relevant consequences to synaptic transmission and neuroprotection [37]. In accordance, we have now found that induction of A1R required the presence of sIL-6R. Interestingly, while LPS, TNFα, IL-1, IFNγ or IL-6 alone failed to up-regulate A1R, sIL-6R combined with either LPS or IL-6 effectively up-regulated A1R mRNA and protein levels. Since LPS also requires sIL-6R, it seems that the effect on A1R induction is secondary to its induction of IL-6.

We have previously shown that A1R mRNA peaks at 6 h from inoculation [13]. Thus, IL-6 and sIL-6R that peak at 3h from inoculation have a period of time that is sufficient to up-regulate A1R. To directly examine the role of IL-6/sIL-6R in the induction of A1R, we used two types of blocking experiments. The induction of A1R was effective-

![Fig. 5](https://academic.oup.com/ndt/article-abstract/25/3/931/1910580)

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ly blocked either by neutralizing antibodies against the soluble and membrane-bound forms of IL-6-R or by sgp130-Fc, a specific blocker of IL-6/sIL-6R.

Thus, our in vitro data, kinetics experiments as well as blocking experiments strongly support the involvement IL-6/sIL-6R in the induction of A1R.

PMCs, similar to other types of cells such as T cells [38] and endothelial cells [39], fail to respond to IL-6 since they do not express the IL-6-binding chain of the IL-6 receptor as we have confirmed by flow cytometry. sIL-6R is probably shed from activated neutrophils as suggested by Hurst et al., who have shown that sIL-6R from neutrophils binds to IL-6 and trigger the cellular activation of PMCs [22–24]. Other leukocyte types may also shed sIL-6R as described by Chalaris et al. [40], but we assume that at the source of sIL-6R at the onset of peritonitis are neutrophils that constitute the main cell population at this inflammatory phase.

Interestingly, the dose response to A1R induction by IL-6 was in a bell-shaped curve manner. A1R elevation was effectively achieved by low concentrations of IL-6 (0.01 ng/ml) while at higher concentrations of IL-6 A1R levels were reduced. This can be explained by the evidence that suppressors of cytokine signaling (SOCS) proteins are rapidly induced by elevated IL-6 levels [41]. Further experiments should be done to test the involvement of SOCS or other inhibitors of IL-6 in the bell-shaped response to increasing doses of IL-6.

These results may clarify the fast induction of A1R by low concentrations of IL-6 at the onset of the inflammation and its down-regulation later on which correspond to the rise in IL-6 levels [13,14]. Our findings indicate a partial positive feedback loop between IL-6 and A1R: (i) IL-6 and sIL-6R are induced by bacterial product and pro-inflammatory cytokines, (ii) IL-6–sIL-6R trans-signaling complex up-regulated the A1R which exhibits the highest affinity for adenosine ($K_i = 10nM$) [42], suggesting that A1R is the first receptor to be activated by low levels of adenosine; (iii) elevated A1R levels increase the IL-6 production; and (iv) the positive loop is ended by elevated IL-6 levels.

To conclude, the present study demonstrates for the first time the concerted regulation of adenosine-metabolizing enzymes and adenosine high affinity receptor in the pro-inflammatory phase of peritonitis. Bacterial products induce the production of adenosine by up-regulation of CD39 and CD73. IL-6/sIL-6R up-regulates the A1R, promoting efficient leukocyte recruitment and production of pro-inflammatory cytokines which are key elements in effective response against invading microorganisms.

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Conflict of interest statement. The results presented in this paper have not been published previously, in whole or part, except in abstract format.

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