Extracellular nucleotide degradation was studied in intact human B and T lymphocyte subpopulations and in lymphoblastoid cell lines. Cells of B lymphocyte lineage showed high nucleotide degrading activity, whereas T lymphocytes were unable to degrade extracellular nucleotides. The external surface of B cells contained active sites of ecto-triphosphonucleotidase (ecto-ATPase), ecto-diphosphonucleotidase (ecto-ADPase), and ecto-monophosphonucleotidase (ecto-AMPase). The expression of all three ectoenzyme activities seemed closely associated with B cell development. ATPase and ADPase activities increase continuously during B cell maturation, ecto-AMPase activity, on the other hand, reaches maximal activity in late pre-B cells.

These results combined with our previous studies of intracellular ATP catabolism (Barankiewicz, J., and Cohen, A. (1984) J. Biol. Chem. 259, 15178–15181) provide evidence that extracellular ATP catabolism may represent exclusive source for adenosine in lymphocytes. It is suggested that adenosine may serve as a means of communication between B and T cells in lymphoid organs, B lymphocytes being the sole producers of adenosine and T lymphocytes being the recipients of this signal.

Although the presence of nucleotide degradation enzymes at the extracellular cell surface was reported 40 years ago (1), the metabolic consequences of this discovery received little attention. Nucleotide metabolism was usually discussed as an intracellular process, and extracellular enzyme activities are usually considered as an artificial activity derived from broken cells. This was mainly concluded on the basis that nucleotides are located intracellularly and cannot cross the plasma membrane (2).

Studies of the ectoenzymes concerned with extracellular lymphocyte catabolism focused on ecto-5'-nucleotidase (ecto-AMPase) activity since deficiency in this enzyme is associated with immunodeficiency (3, 4). It has also been reported that ecto-AMPase activity correlates well with T and B cell maturation and may serve as a marker for lymphocyte differentiation (5–9).

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‡ The abbreviations used are: ecto-AMPase, ecto-5'-monophosphonucleotidase; ecto-ADPase, ecto-diphosphonucleotidase; ecto-ATPase, ecto-triphosphonucleotidase; FCS, fetal calf serum.

In contrast to the established view, it has been found that nucleotides, such as ATP can be found in considerable amounts outside of cells, e.g. circulating in plasma (10). Moreover, a variety of cells have also been found to contain extracellular nucleotide degradation enzymes (10–13). Nucleotides which are released from some cells to the extracellular space can reach micromolar concentrations and can modulate many biological processes by acting via specific cell surface receptors.

Lymphocytes are among the cells which have been reported to express ecto-nucleotidase activities (14–16). Although little is known about extracellular enzyme expression and about the role of extracellular nucleotide metabolism in lymphocyte function, some effects of extracellular nucleotides have been suggested. At high concentrations ATP stimulates in vitro DNA synthesis in bone marrow and in thymus cells but it inhibits DNA synthesis in spleen, lymph node, and peripheral blood lymphocytes (17, 18). Extracellular ATP inhibits the activities of natural killer cells (19, 20). On the other hand, adenosine, the degradation product of ATP, acting via both intracellular and extracellular adenosine receptors (21) has been reported to regulate various lymphocyte functions through activation of adenylate cyclase (22–24).

Despite the reported regulatory roles of extracellular adenosine in lymphocyte function (5, 24) the cellular source of adenosine production is not clear. In searching for the potential source of adenosine production in lymphocytes, we have previously shown that adenosine is not produced intracellularly from ATP degradation (25). In the present work we explore the possibility that adenosine may be produced by catabolism of extracellular nucleotides in lymphocyte subpopulations. Toward that end we have conducted a comprehensive study of extracellular nucleotide metabolism in different human B and T lymphocyte subpopulations and in lymphoblastoid cell lines representative of various differentiation stages.

**EXPERIMENTAL PROCEDURES**

**Materials**—Radioactive substrates were purchased from 1) ICN Radiochemicals Inc.: [2,8-3H]ATP, [8-3H]GTP, [5,6-3H]UTP, [8-3H]deoxy-ATP, [methyl-3H]thymidine, [5-3H]uridine, [2,8-3H]adenine, [6-3H]adenosine; 2) Du Pont-New England Nuclear: [8-3H]deoxy-GTP, [5-3H]deoxy-CTP, [G-3H]AMP, [2,8-3H]ADP; 3) Moravek Biochemicals (Brea, CA): [8-3H]hypoxanthine; and 4) Amersham International Ltd. (Amersham, U.K.): 8-3H]inosine. Phytomagglutinin was obtained from Difco. Dipryridamole, kits for pyruvate kinase and phosphatase determinations, nonradioactive purine and pyrimidine nucleotides, nucleosides, and bases were obtained from Sigma. Ficoll 77F was obtained from Du Pont, Canada Inc. (Maitland, Ontario, Canada), and Alamine was a gift from Henkel Corp. (Kahakee, IL). RPMI medium was purchased from Ontario Cancer Institute (Toronto, Ontario, Canada). Fetal calf serum was purchased from Flow Laboratories (McLean, VA). Polyethyleneimine-cellulose TLC sheets were obtained from Fisher Scientific Co. (Don Mills, Ontario, Canada).
Ontario) and 1325-g cellulose TLC sheets with fluorescence indicator from Eastman.

Cells—Fresh human lymphocytes were purified from tonsils and thymus. Mononuclear cells were prepared on Ficoll-Hypaque density gradients (8), resuspended in serum free RPMI 1640 medium, and incubated with radioactive precursors. Fetal calf serum (FCS) was omitted in incubations with nucleotides because even heat-inactivated serum (68 °C, 30 min) contained considerable activities of enzymes participating in nucleotide degradation. When cells were incubated for several hours with other compounds, medium was supplemented with 10% heat-inactivated FCS, but before incubation with radioactive precursors nucleotides were washed 3 times in serum free RPMI. E-rosetting T cells and non-E-rosetting B cells from peripheral blood or tonsils were enriched (>90%) by rosette depletion on Ficoll-Hypaque gradients (8). Briefly, nonseparated lymphocytes were mixed with neuraminidase-treated (37 °C for 30 min) sheep red blood cells (37 °C for 5–10 min) and, after centrifugation at 4 °C (1000 rpm for 10 min), incubated at 4 °C for 30 min. After gentle resuspension, cells were centrifuged on Ficoll-Hypaque (2000 rpm for 30 min at 4 °C). Non-E-rosetting hand was then removed from gradient and washed 3 times with medium. E-rosetting cell pellet was resuspended with Trypan blue dye exclusion and washed with medium. E-rosetting T cell and B and T cells were usually resuspended in RPMI medium containing 10% FCS for 1–2 h (37 °C) before they were used in these studies. B cell fraction contained at least 95% of surface Ig positive cells, whereas the T cell fraction contained at least 95% of OKT3 positive cells.

The presence of attached sheep red blood cell ghosts did not affect the assay, because even in their presence no ectonucleotidase activity was detected.

Lymphoblastoid cell lines of B or T lineage were maintained in logarithmic growth at 37 °C in 5% CO2 in RPMI 1640 supplemented with 10% heat-inactivated FCS. Cells were washed three times in serum-free RPMI medium prior to incubations with radioactive precursors. Where indicated that nucleoside transport was blocked, cells were preincubated with 10 μM dipyridamole (20 min, 37 °C).

Cell Integrity—Cell membrane integrity was determined by trypan blue dye exclusion. In addition, to estimate cell disruption and spill of cytoplasmic enzymes, activities of the cytoplasmic enzymes adenylyl deaminase and pyruvate kinase were measured in culture supernatants. No measurable extracellular activities of these enzymes were found during 2 h incubation of B or T lymphocytes indicative of lack of cell breakage. It was found that as for 5% nontoxic cells (by trypan blue dye exclusion) can produce significant spill of cytoplasmic enzymes, and at least 99% viability was required for the experiments reported. In cases where the viability was less than 99% contaminating dead cells and cytoplasmic enzymes were successfully removed by a second Ficoll-Hypaque gradient centrifugation (8).

Extracellular Nucleotide Metabolism—To measure the rate of extracellular nucleotide degradation intact cells (1×10⁶) were incubated with 1 μCi of the respective radioactive nucleotides (500 or 5 μM initial concentrations). Cells were then centrifuged (1500 rpm, 5 min), and supernatants were analyzed for radioactivity in nucleosides, nucleotides, and bases. To detect possible interference by nonspecific phosphatases, cells (1×10⁶) were incubated in RPMI containing 10 mM p-nitrophenyl phosphate for 60 min. Measurement of absorbance (A=410 nm) showed no phosphatase activity outside the cells. The addition of 10 mM p-nitrophenyl phosphate to B cells did not affect ATP degradation.

Intracellular Nucleotide Incorporation—The intracellular incorporation of radioactivity from extracellular nucleotides was examined in cell pellets following three washes in medium. Nucleotides were extracted with 50 μl of 0.4 M perchloric acid for 5 min on ice, centrifuged, neutralized with Alamine-Freon mixture, and analyzed for radioactivity as described (26).

Separation of Nucleotides, Nucleosides, and Bases—Separation of nucleotides was performed using one-dimensional chromatography on polyethyleneimine cellulose TLC in three steps of increasing sodium formate buffer concentrations (0.5, 2, 4 M) (27). Separation of nucleosides and bases was done on one-dimensional cellulose TLC with attached Whatman 3MM paper wick on top in 1-butanol:water:ammonium solvent (60:20:22:1). This chromatography allowed the separation of adenosine, hypoxanthine, and inosine, whereas nucleotides remained at the base line. The radioactivity or separated nucleotides, nucleosides, and bases was measured in a Beckman LS 3801 scintillation counter.

Values reported are averages of duplicate measurements reproducible in at least three experiments. Variation of individual values from the mean was less than 10%.

RESULTS

Extracellular ATP Catabolism by Tonsil Cells—Mononuclear tonsil cells, containing mainly B cells (~65%) and T lymphocytes (~35%) actively degraded extracellular ATP, as well as other extracellular triphosphonucleotides, diposphonucleotides, and monophosphonucleosides (results not shown). To determine the cellular source of these ectonucleotidases, B and T cells were separated and incubated with radioactive ATP. After 30 min of incubation of purified B cells with 500 μM ATP, more than 80% of the extracellular ATP was degraded (Fig. 1A), whereas T cells were unable to degrade any ATP (Fig. 1D). ATP degradation by B cells was accompanied by the accumulation of AMP, ADP (Fig. 1A), and adenosine (Fig. 1B). After 20 min of incubation, the amount of extracellular ADP declined and AMP concentration reached a plateau. Adenosine was the main product of extracellular ATP degradation and its concentrations increased linearly in the medium. Small amounts of hypoxanthine and inosine were also found in the medium (Fig. 1B), but preincubation of tonsil cells with the nucleoside transport inhibitor dipyridamole, completely prevented adenosine and hypoxanthine accumulation (results not shown), indicating that inosine and hypoxanthine were produced exclusively inside the cells. Only a small amount (~1%) of radioactivity was incorporated into intracellular nucleotides, mainly ATP (Fig. 1C).

At a lower initial concentration of extracellular ATP (5 μM), 80% of the ATP added was degraded by 10⁶ purified B cells within 5 min of incubation, with a transient accumulation of a small amount of ADP and AMP (Fig. 2A). Adenosine and inosine were formed transiently and then declined, whereas hypoxanthine was produced in a linear fashion (Fig. 2B). A significant incorporation of radioactivity into intracellular nucleotides was also observed (Fig. 2C). In the presence of dipyridamole, extracellular nucleotide degradation remained unchanged (Fig. 2D), but only adenosine accumulation was measured.

Fig. 1. Extracellular ATP catabolism by B and T lymphocytes. Tonsil cells were separated to non-E-rosetting B lymphocytes and E-rosetting T lymphocytes. Cells (1×10⁶) were incubated in 0.1 ml with 1 μCi of [2,8-3H]ATP (500 μM initial concentration). After 60 min of incubation, nucleotides, nucleosides, and bases were analyzed separately in the medium and in cell extracts as described under "Experimental Procedures." A, extracellular nucleotide degradation during ATP catabolism by non-E-rosetting tonsil cells. B, extracellular nucleotides and bases produced during ATP catabolism. Hyp, hypoxanthine; Ado, adenosine; Ino, inosine. C, incorporation of radioactive into intracellular nucleotides during extracellular ATP catabolism. D, extracellular ATP catabolism by tonsillar T cells.
Extracellular Nucleotide Catabolism in Lymphocytes

**Fig. 2.** Extracellular catabolism of low concentrations of ATP by tonsillar B cells. Cells \((1 \times 10^6)\) were incubated with 1 µCi of \([2,8-\text{H}]\text{ATP}\) \((5 \mu\text{M initial concentration})\). After incubation, nucleotides, nucleosides, and bases were analyzed separately in the medium and in the cell extracts as described under "Experimental Procedures." A, extracellular nucleotides; B, extracellular nucleosides and bases. Hyp, hypoxanthine; Ado, adenosine; Ino, inosine. C, intracellular nucleotides. Cells preincubated with 10 µM dipyridamole: D, extracellular nucleotides; E, extracellular nucleosides and bases; F, intracellular nucleotides.

Extracellular nucleotide catabolism seems to be of low specificity, with comparable degradation of dATP, GTP, dGTP, and dCTP (Fig. 3). However, the activity toward ribonucleotides seemed to be higher than that for deoxyribonucleotides. Mg\(^{2+}\) was found to stimulate \((400 \mu\text{M MgCl}_2, \text{optimal concentration})\) degradation of extracellular ATP. No activities of ecto-AMP deaminase or ecto-AMP kinase and ecto-ADP kinase were found on either B or T cells (results not shown).

During 90 min of incubation of tonsillar B lymphocytes there was no release of any ectonucleotidase activities into the extracellular medium (results not shown), indicating that ectonucleotidases are integral cell surface membrane enzymes.

**Fig. 3.** Nucleotide specificity of extracellular catabolism in tonsillar B cells. Cells \((1 \times 10^6)\) were incubated with 1 µCi of radioactive dATP, GTP, dGTP, and dCTP \((A, B, C, \text{and } D, \text{respectively})\) \((500 \mu\text{M final concentration})\). After the indicated incubation times, radioactivity in triphosphonucleosides, diphosphonucleotides, and monophosphonucleotides was analyzed in medium.

Extracellular ATP and AMP Catabolism by Various B and T Lymphocytes—Extracellular degradation of ATP (Table I) and other nucleotides (results not shown), similar to that described above for B lymphocytes from tonsil, were also found in peripheral blood B lymphocytes, and in various B lymphoblastoid cell lines. In contrast, all cells of the T lymphocyte lineage such as thymocytes, peripheral blood T lymphocytes, and various T lymphoblastoid cell lines showed no or very little ability to degrade extracellular nucleotides (Table I). Also, extracellular AMP was fast degraded by different B lymphocyte subpopulations, whereas cells of T lymphocyte lineage showed practically no such abilities (Table II). Human red blood cells showed no ability to degrade extracellular nucleotides (results not shown).

Extracellular Nucleotide Degradation during B Cell Maturation—To examine the expression of ecto-nucleotidase activities within the framework of human B cell development, a
but absent light chain gene rearrangement or expression. B cell clones, whereas those of ATPase and ADPase were cells expressed high activities of all three nucleotide-degrading enzymes. The activities of AMPase were maximal in late pre-B cells, whereas those of ATPase and ADPase were

**TABLE I**

**Extracellular ATP catabolism in various B and T lymphocytes**

Human lymphocytes or lymphoblastoid cells (1 x 10⁶) were preincubated for 20 min with 10 μM dipyridamole and then incubated with 1 μCi of radioactive ATP (500 μM initial concentration) for 60 min. Incorporation of radioactivity into extracellular nucleotides, nucleosides, and bases was measured. PBL, peripheral blood lymphocytes. Hyp, hypoxanthine.

| Cell line         | ATP → ADP → AMP → Ado → Ino → Hyp (%) |
|-------------------|----------------------------------------|
| B cells           |                                        |
| PBL B lymphocytes | 1.2                                    |
| 34L83C B lymphoblasts | 0.2                                    |
| Tonsil B lymphoblasts | 0.3                                    |
| HSC-3 B lymphoblasts | 0.5                                    |
| M, B lymphoblasts | 0.9                                    |
| B lymphoma cells  | 0.4                                    |
| T cells           |                                        |
| Thymocytes        | 99.7                                   |
| PBL T lymphocytes | 99.6                                   |
| Molt-3 T lymphoblasts | 89.1                                   |
| Jurkat T lymphoblasts | 89.1                                   |
| HSB-2 T lymphoblasts | 92.4                                   |
| CEM T lymphoblasts | 91.6                                   |

**TABLE II**

**Extracellular AMP catabolism in various B and T lymphocytes**

Human lymphocytes or lymphoblastoid cells (1 x 10⁶) were preincubated for 20 min with 10 μM dipyridamole and then incubated with 1 μCi of radioactive AMP (500 μM initial concentration) for 60 min. Incorporation of radioactivity into extracellular nucleotides, nucleosides, and bases was measured. PBL, peripheral blood lymphocytes. Hyp, hypoxanthine.

| Cell line         | Radioactivity (%) AMP → Ado → Ino → Hyp |
|-------------------|-----------------------------------------|
| B cells           |                                        |
| PBL B lymphocytes | 26.3                                    |
| 34L83C B lymphoblasts | 29.1                                    |
| Tonsil B lymphoblasts | 38.6                                    |
| HSC-3 B lymphoblasts | 40.3                                    |
| M, B lymphoblasts | 86.0                                    |
| T cells           |                                        |
| Thymocytes        | 99.8                                    |
| PBL T lymphocytes | 99.1                                    |
| Molt-3 T lymphoblasts | 98.2                                    |
| Jurkat T lymphoblasts | 97.3                                    |
| HSB-2 T lymphoblasts | 96.2                                    |
| CEM T lymphoblasts | 99.5                                    |

**Fig. 4. Ecto-nucleotidase activities during B cell ontogeny.** Cells (1 x 10⁶) (Epstein-Barr virus-transformed, fetal pre-B, and B cell lines) were incubated with [2,8-3H]ATP, [2,8-3H]ADP, or [G-3H]AMP at 500 μM initial concentration). After 30 min of incubation, radioactive nucleotides, nucleosides, and bases were analyzed in the medium and the sum of all radioactive products calculated.

somewhat lower in late pre-B cells as compared to the more mature B cell lines. Interestingly, the levels of ecto-AMPase expressed on mature B cells were very low and comparable to that found on the most immature clones in this series.

**DISCUSSION**

The importance of nucleotide degradation pathways to lymphocyte function has been evident from the association of severe immunodeficiencies with defects of nucleotide degradation enzymes, adenosine deaminase, and purine nucleoside phosphorylase (5). The relevance of ectoenzymes of the nucleotide degradation pathway expressed on the cell surface of lymphocytes and their potential significance to immune function has attracted attention only more recently (10–13, 28–30). Although one of these ectoenzymes, ecto-5'-nucleotidase (AMPase), has been studied more widely (31), understanding of its biological function awaits a more complete description of extracellular purine catabolism.

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2 M. Hui, T. Hibi, and H. -M. Dosch, manuscript in preparation.

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Series of Epstein-Barr virus transformed, fetal pre-B, and B cell lines generated in our laboratories were used. The earliest B lineage cells (early pre-B lymphocytes) were characterized by the presence of Epstein-Barr virus receptor and surface markers characteristic of B cell lineage but absent in immunoglobulin gene rearrangements. Late pre-B cells were characterized by immunoglobulin heavy chain gene rearrangements, cytoplasmic expression of IgM heavy chain, but absent light chain gene rearrangement or expression. Mature B lymphocytes were characterized by the rearrangements and expression of complete IgM and/or IgD immunoglobulin molecules.² The most immature clones in this series, the early pre-B lymphocytes, showed at best little extracellular ATPase, ADPase, and AMPase activities (Fig. 4). In contrast, late pre-B cells expressed high activities of all three nucleotide-degrading enzymes. The activities of AMPase were maximal in late pre-B cell clones, whereas those of ATPase and ADPase were...
### Extracellular ATP Catabolism in Lymphocytes

**Scheme 1.** Extracellular and intracellular ATP catabolic pathways in human B lymphocytes. Extracellular enzymes: 1, ecto-ATPase; 2, ecto-ADPase; 3, ecto-AMPase (ecto-5'-nucleotidase). Intracellular enzymes: 4, ATPase; 5, ADPase; 6, AMP-deaminase; 7, 5'-nucleotidase; 8, purine nucleoside phosphorylase.

Human B-lymphocytes and lymphoblastoid cell lines can actively hydrolyze exogenous triphosphonucleotides, diphosphonucleotides, and monophosphonucleotides, whereas T lymphocytes and T cell lines have at best little ability to do so (Tables I and II). It was reported previously that certain T cell populations exhibit 5'-nucleotidase activity (6–9). However our experience shows that (a) only T cell preparations with less than 95% viability and with detectable extracellular activity of cytoplasmic enzymes exhibit ecto-AMPase activity, and (b) complete elimination of dead cells removed ecto-AMPase activity in all T cells examined (Table I, see also "Experimental Procedures").

Within the B cells examined, the expression of ATPase/ADPase ectoenzyme(s) appears to be closely associated with B cell differentiation, increasing continuously with maturation (Fig. 4). AMPase activity, on the other hand, reaches a maximum at an intermediate stage of early B cell development and declines in mature B cells. This specific pattern of ecto-nucleotidase expression may indicate that different extracellular nucleotidases participate at different stages of B cell differentiation (32).

There are significant differences between extracellular and intracellular catabolism of ATP. Intracellular ATP catabolism proceeds exclusively via AMP deamination, and, therefore, under physiological conditions adenosine is not formed (25). Hypoxanthine, the end product of this intracellular catabolic pathway, can be salvaged back into intracellular nucleotide pools or excreted. In contrast, extracellular ATP catabolism proceeds exclusively via AMP dephosphorylation, resulting in the formation of adenosine as the end product (Scheme 1). Taken together, these results indicate that the exclusive source for adenosine in lymphoid tissues is extracellular ATP catabolism by B lymphocytes. Adenosine formed this way can act either as an extracellular physiological modulator through specific membrane receptors or, alternatively, it can enter the cells and participate in nucleotide synthesis.

The results reported here (Table I), together with our previous observations (25), demonstrate that only B lymphocytes, and not T lymphocytes, can produce adenosine from ATP. On the other hand, only T lymphocytes, and not B lymphocytes, express the cell surface receptor for adenosine (33). A similar dichotomy has been observed in the interaction between endothelial cells (adenosine producers) and heart muscle cells (expressing adenosine receptors (34)). It has been suggested that this cellular dichotomy of adenosine production versus utilization may serve as a regulatory cycle controlling the interaction between adenosine producing endothelial cells and the recipient muscle cells (34). Similarly, in lymphoid tissues an adenosine regulatory cycle may operate between certain adenosine producing B cells and T cells expressing the adenosine receptor, but this needs more studies.

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