Increased Antiplatelet T Helper Lymphocyte Reactivity in Patients With Autoimmune Thrombocytopenia

By John W. Semple and John Freedman

Chronic autoimmune thrombocytopenic purpura (ATP) is a common hematologic disorder in which platelet-specific autoantibodies bind to platelets and enhance their destruction by the reticuloendothelial system. While there has been considerable investigation of the humoral immune abnormalities in ATP, little work has been performed on the cellular immunoregulatory aspects of this autoimmune disorder. We describe here that patients with ATP have lymphocytes that proliferate normally when stimulated by mitogens. However, when stimulated by normal control platelets in 7-day antigen-presenting cell cultures, peripheral blood mononuclear cells (PBMC) from patients with ATP proliferate at significantly higher levels ($P < .001$) and their lymphocytes secrete significantly higher amounts of interleukin-2 (IL-2) ($P < .001$) than do lymphocytes from control subjects. Depletion studies with monoclonal anti-CD8 and complement did not reduce the proliferative capacity of the responding PBMC population, indicating that CD4+ T-helper cells may be responsible for the response. Phenotypic analysis of peripheral blood lymphocyte subsets from patients with ATP showed that there was a significant reduction in CD4Leu8+ T suppressor-inducer cells ($P < .001$) and a concomitant increase in CD3DR+ activated T cells ($P < .001$) and CD19+ B cells ($P < .05$). These data indicate that CD4+ T-helper cells from patients with ATP are stimulated by normal platelet antigen(s) to secrete IL-2 and may modulate the enhanced antiplatelet autoantibody response.

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MATERIALS AND METHODS

Patients. Seventy-nine patients, 54 females and 25 males, with primary or idiopathic chronic ATP ranging in age from 12 to 83 years (mean, 43 ± 18) were studied; 21 had been receiving corticosteroid therapy for a mean duration of 109 ± 107 days. Included among the patients with primary chronic ATP were eight women with unexplained periparturient thrombocytopenia, platelet counts at the time of study in patients with primary ATP ranged from 1 to 135 × 109/L (mean, 69 ± 57 × 109/L). Twenty-three patients, 11 females and 12 males, with secondary ATP (nine associated with systemic lupus erythematosus [SLE], five with lymphoma, three with human immunodeficiency virus 1 [HIV1] infection, three with rheumatoid arthritis [RA], two secondary to drugs, and one associated with ulcerative colitis) were also studied; these patients ranged in age from 27 to 84 years (mean, 54 ± 15) and 13 had received steroids at the time of study for a mean duration of 78 ± 99 days. Platelet counts in patients with secondary ATP ranged from 2 to 121 × 109/L (mean, 41 ± 36 × 109/L). In addition, 18 patients (10 females, eight males; mean age, 54 ± 21 years) with nonimmune thrombocytopenia (NIT) were studied; diagnosis included eight with bacterial infections, two with myelofibrosis, two with hereditary thrombocytopenia, two with metastatic disease to bone marrow, and one patient each with leukemia, multiple myeloma, aplastic anemia, and myelodysplastic syndrome. Thirteen patients (two females, 11 males; mean age, 49 ± 25 years) with nonthrombocytopenic immune diseases (NTID) were also evaluated; these included five patients with acquired circulating anticoagulants, four with autoimmune hemolytic anemia, and one each with autoimmune neutropenia, thyrotoxicosis, diabetes mellitus.

From the Department of Immunohematology, St Michael’s Hospital; and the Departments of Pharmacology and Medicine, University of Toronto, Toronto, Ontario, Canada.

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Address reprint requests to John W. Semple, PhD, Department of Immunohematology, St Michael’s Hospital, 30 Bond St, Toronto, Ontario, Canada M5B 1W8.

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was analyzed using a FACScan flow cytometer and Consort 30 software (Becton Dickinson).

Preparation of peripheral blood mononuclear cells (PBMC). PBMC were obtained from EDTA-treated or heparinized blood by centrifugation (1,200g for 30 minutes at 20°C) through a 1.077 g/mL Percoll (Pharmacia LKB, Baie d’Urfe, Quebec, Canada) gradient. The PBMC were 18% ± 6% DR+ antigen-presenting cells (APC) (9% ± 5% CD19+ B cells and 8% ± 4% CD14+ monocytes/macrophages), 54% ± 11% CD3+ T cells and 25% ± 5% CD3-CD56+ natural killer (NK) cells. T lymphocyte enrichment was performed by the modified method of Gutierrez et al. Briefly, the washed PBMC were layered onto a discontinuous Percoll gradient consisting of the following densities: 1.091 g/mL (70%), 1.060 g/mL (50%), 1.050 g/mL (40%), and 1.030 g/mL (30%); and then centrifuged at 1,200g for 30 minutes at 20°C. PBMC banding at the 30%/40% Percoll interface were enriched for DR+ APC, 46% ± 12% DR+ APC (13% ± 8% CD19+ and 32% ± 10% CD14+), 7% ± 5% CD3+, and 51% ± 15% CD3-CD56+ of total ungated cells and those banding at the 50%/70% Percoll interface were enriched for T cells, 11% ± 5% DR+ APC (6% ± 3% CD19+ and 5% ± 3% CD14+), 65% ± 8% CD3+, and 22% ± 2% CD3-CD56+ of total ungated cells. Unless otherwise stated, all the in vitro assays were performed in RPMI 1640 medium (GIBCO Laboratories, Grand Island, NY) containing 5% pooled inert human group AB serum, 2 mmol/L L-glutamine (GIBCO), 100 µg/mL penicillin/streptomycin (GIBCO), and 5 x 10^-3 mol/L 2-mercaptoethanol (cRPMI).

Preparation of platelets. EDTA-treated blood from normal controls was centrifuged at 150g for 15 minutes at 20°C and the platelet-rich plasma (PRP) recovered. The PRP was then centrifuged at 550g for 6 minutes at 20°C and the platelet pellet washed twice in normal saline. To reduce possible class I alloreactivity in the PRP, the platelets were annullated with 5% pooled inert human group AB serum, 2 mmol/L L-glutamine (GIBCO), 100 µg/mL penicillin/streptomycin (GIBCO), and 5 x 10^-3 mol/L 2-mercaptoethanol (cRPMI).

Platelet-induced proliferation of mononuclear cells from patients with ATP. As shown in Fig 1, when T-cell-
enriched PBMC from patients with primary ATP were incubated with acid-treated platelets and DR+ PBMC in 7-day APC cultures, a significant increase in proliferation was observed compared with T-cell–enriched PBMC from normal controls or baseline proliferation \( (P < .001 \) at \( 50 \times 10^9 \) platelets/L). Table 1 indicates that 68% of patients with primary ATP showed increased antiplatelet proliferative activity compared with normal controls; these included five of eight patients with unexplained peripartum thrombocytopenia. On the other hand, only 22% of patients with secondary ATP showed increased antiplatelet proliferative activity; these were three of nine patients with SLE, one of three with RA, and one of three with HIV-1–associated immune thrombocytopenia. None of five patients with secondary ATP associated with lymphoma had increased proliferative responses to platelets, whereas both of two patients with immune thrombocytopenia associated with chronic lymphocytic leukemia (CLL) (not shown) showed increased antiplatelet activity. None of the patients with NIT or NTID showed the antiplatelet proliferative response (Table 1). This antiplatelet proliferation of PBMC from patients with primary ATP was not inhibited by depletion of CD8+ T cells from the patient’s PBMC (Table 2).

Of the 79 patients with primary ATP, 21 were on steroid therapy, four were receiving azathioprine, four intravenous (IV) IgG, four danazol, three had had plasmapheresis, and three had previous splenectomy. Thirteen of the 21 patients who had received steroid therapy showed antiplatelet reactivity; 10 of these had received steroids for less than 8 days. In contrast, of the remaining eight patients who had received steroids and showed no antiplatelet reactivity, five were treated for greater than 8 days. Overall, however, there was no significant relation between corticosteroid therapy, patients’ sex, age, platelet count, or presence or absence of detectable platelet-associated IgG and/or C3 and increased antiplatelet reactivity.

**IL-2 secretion by platelet-reactive lymphocytes from patients with ATP.** The supernatants of the APC cultures were removed on day 6 and tested for their ability to stimulate the proliferation of the IL-2–dependent cell line CTLL. As shown in Table 1, T lymphocytes from 75% of patients with primary ATP who showed a proliferative response to platelet stimulation secreted significantly higher levels of IL-2 than did lymphocytes from the normal control subjects \( (P < .001 \) at \( 50 \times 10^9 \) platelets/L). On the other hand, only 17% of patients with primary ATP who failed to show antiplatelet proliferative activity had an increased IL-2 secretion. Figure 2 shows the markedly increased IL-2 secretion \( (P < .001 \) at \( 50 \times 10^9 \) platelets/L) of lymphocytes from patients with primary ATP who had an antiplatelet proliferative response, compared with those from patients with no antiplatelet proliferative response and those from normal controls, when stimulated by titrated concentrations of normal platelets. Only three (two with SLE and one quinidine-induced) of 11 patients with secondary ATP had lymphocytes that secreted IL-2 on platelet stimulation (Table 1). Lymphocytes from none of the patients with NIT or NTID and from none of the normal controls secreted IL-2 in response to normal platelet stimulation. There was no correlation between therapy, patients’ sex, age, platelet count, or presence or absence of detectable platelet-associated IgG and/or C3 and increased IL-2 secretion.

### Table 1. PBMC Proliferative Activity and Lymphocyte IL-2 Secretion on Exposure to Platelets in Normal Controls and ATP Patients

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>n</th>
<th>Platelet Reactivity</th>
<th>IL-2 Secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° ATP</td>
<td>79</td>
<td>54/79* (68)</td>
<td>23/40 (58)</td>
</tr>
<tr>
<td>1° ATP platelet-reactive</td>
<td>54</td>
<td>54/54 (100)</td>
<td>21/28 (75)</td>
</tr>
<tr>
<td>1° ATP nonreactive</td>
<td>25</td>
<td>0/25 (0)</td>
<td>2/12 (17)</td>
</tr>
<tr>
<td>2° ATP</td>
<td>23</td>
<td>5/23 (22)</td>
<td>3/11 (27)</td>
</tr>
<tr>
<td>NIT</td>
<td>18</td>
<td>0/18 (0)</td>
<td>0/11 (5)</td>
</tr>
<tr>
<td>NTID</td>
<td>13</td>
<td>0/13 (0)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>Normals</td>
<td>22</td>
<td>0/22 (0)</td>
<td>0/22 (0)</td>
</tr>
</tbody>
</table>

Percentages given in parentheses.

*Positive result/number tested.

### Table 2. Effect of Anti-CD8 and Complement on Antiplatelet Proliferative Activity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1° ATP (n = 15)</th>
<th>Control (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>14,086 ± 9,042</td>
<td>1,626 ± 729</td>
</tr>
<tr>
<td>Rabbit complement alone</td>
<td>15,229 ± 11,398</td>
<td>3,087 ± 1,560</td>
</tr>
<tr>
<td>Anti-CD8 + rabbit complement</td>
<td>13,024 ± 7,011</td>
<td>1,901 ± 933</td>
</tr>
</tbody>
</table>

*At a stimulating dose of 50 × 10^9 platelets/mL.

Anti-Leu 2b.

### Fig 2. IL-2 production by [○] platelet-reactive (n = 21) and [∇] nonreactive (n = 12) lymphocytes from patients with ATP and [●] normal controls (n = 22). Supernatants were harvested on day 6 from a 7-day APC culture and tested for their ability to stimulate the proliferation of the IL-2–dependent cell line CTLL. Results are expressed as [*H]-thymidine incorporation (cpm) ± SD.
Mitogen-induced proliferation of lymphocytes from patients with ATP. To assess the general proliferative capacity of PBMC from patients with ATP, mitogen stimulation assays were performed. Few patients with primary ATP showing antiplatelet proliferative reactivity had a reduced mitogenic response. Table 3 indicates that although some patients with primary ATP had reduced blastogenic response to mitogens, the majority of patients with primary ATP had lymphocytes that could proliferate in response to PHA (78%), Con A (65%), and PWM (71%) in 48-hour mitogen stimulation assays. More than 95% of the normal control subjects showed a proliferative response to the mitogens. Figure 3 shows that no significant difference in the level of proliferative activity was seen when lymphocytes from patients with primary ATP were exposed to titrated doses of mitogens compared with lymphocytes from normal subjects. Table 3 also shows that the proportion of patients with secondary ATP, NIT, and NTID showing a reduced lymphocyte mitogen-induced proliferative activity was higher than that observed for patients with primary ATP overall and the frequency was similar to that obtained for those patients with primary ATP whose lymphocytes did not show antiplatelet reactivity. Of the 28 patients with primary ATP that had received proliferation to any of the mitogens, 12 were receiving steroids, but no relation between the presence of a reduced proliferative response and therapy with corticosteroids was evident in any of the patient groups. Nor was there a correlation between patients’ sex, age, platelet count or presence of detectable platelet-associated IgG or C3 and the finding of reduced proliferative response to mitogens.

Phenotypic analysis of PBMC from patients with ATP. Table 4 shows the lymphocyte subset distribution of the PB in the different patient groups and in normal healthy controls. The proportions of total T (CD3+) cells and suppressor/cytotoxic T (CD8+, CD8*CD57+) cells were similar to controls for all patient groups. Mean CD4+ Th cells were reduced in patients with primary ATP whose PBMC showed antiplatelet reactivity, but the reduction was not statistically significant. Patients with primary ATP whose PBMC showed antiplatelet reactivity, however, had a marked reduction in suppressor-inducer (CD4*Leu8+) T cells (11% v 32% in controls, *P < .001), and significant increases in CD4*Leu8- Th cells of B-cell differentiation, activated (CD3*DR+) T cells, and B (CD19+) cells compared with controls (P < .05, *P < .001, and *P < .05, respectively). Similar changes, although to a lesser degree, were seen in the proportion of suppressor/inducer T cells, activated T cells, and B cells in patients with primary ATP with no antiplatelet proliferative activity, patients with 2nd ATP, and patients with NITID. Lymphocyte subset distributions in patients with 2nd ATP, NIT, or NTID were not significantly different from the normal controls.

DISCUSSION

These studies indicate that the majority of patients with primary chronic ATP have PBMC that show normal proliferative responses to mitogens. In contrast, the majority of patients with primary chronic ATP were abnormal in that their CD4+ helper T cells were capable of secreting IL-2 in response to stimulation by platelets. As a group, patients with primary chronic ATP had a decreased proportion of suppressor-inducer T cells, with a concomitant increase in activated T cells and in B cells. Although similar observations were obtained in a few patients with secondary chronic ATP, most patients with secondary chronic ATP, and all those with NIT or NTID, failed to show the changes seen in patients with primary chronic ATP.

Although the etiology of these changes is unclear, the findings support the hypothesis that antiplatelet autoantibody production in patients with primary chronic ATP is regulated and enhanced by a Th cell defect and that the immunopathophysiology of primary chronic ATP may be different from that operative in secondary chronic ATP. The findings suggest that, within the clinical diagnoses of both primary and secondary chronic ATP, there may be subsets of patients in whom the immunopathophysiology of the disease is different. In this regard, it is interesting to note that the majority of women with unexplained peripar- tum thrombocytopenia, a condition of unclear etiology,27 and both patients tested with megakaryocytic thrombocyto- penia (increased megakaryocytes in bone marrow) associated with CLL showed the characteristic cellular immune findings of primary chronic ATP. Patients with megakaryocytic thrombocytopenia associated with lymphoma or with HIV1 infection, on the other hand, did not show these findings. It has been previously suggested that the ‘immune’ thrombocytopenia associated with lymphomas may be pathogenetically different from classical primary ATP.28 Similarly, it is not clear whether those patients with SLE showing increased antiplatelet reactivity or IL-2 secretion represent a different pathophysiology subset from those failing to show these findings.

The production of antigen-specific antibodies by B lymphocytes requires the recognition of the antigen not only by B cells, but also by APC and CD4+ Th lymphocytes. The antigen, whether it be a self or foreign molecule, such as a protein, must first interact with an APC (eg, an Ia-positive macrophage, dendritic, or B cell). The APC can then internalize and proteolytically process the antigen into immunogenic peptides that are presented on the surface of the APC, together with molecules encoded by the major histocompatibility complex (MHC), to Th cells.29,30 The Th

Table 3. Frequency of Reduced Blastogenic Response to Mitogens in Normals and Patients

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Reduced Mitogen Proliferation*</th>
<th>PHA</th>
<th>Con A</th>
<th>PWM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st ATP</td>
<td>17/791 (22)</td>
<td>26/70 (36)</td>
<td>22/77 (29)</td>
<td></td>
</tr>
<tr>
<td>1st ATP platelet-reactive</td>
<td>4/54 (7)</td>
<td>12/25 (23)</td>
<td>8/52 (15)</td>
<td></td>
</tr>
<tr>
<td>1st ATP nonreactive</td>
<td>11/25 (44)</td>
<td>11/25 (44)</td>
<td>12/25 (48)</td>
<td></td>
</tr>
<tr>
<td>2nd ATP</td>
<td>12/23 (52)</td>
<td>13/23 (57)</td>
<td>11/23 (48)</td>
<td></td>
</tr>
<tr>
<td>NIT</td>
<td>7/18 (39)</td>
<td>9/18 (50)</td>
<td>9/18 (60)</td>
<td></td>
</tr>
<tr>
<td>NTID</td>
<td>5/13 (39)</td>
<td>6/12 (50)</td>
<td>5/12 (42)</td>
<td></td>
</tr>
<tr>
<td>Normals</td>
<td>1/22 (5)</td>
<td>0/22 (0)</td>
<td>0/22 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Percentages given in parentheses.

*Less than or equal to 50% of normal controls tested in parallel.

1Number abnormal/number tested.
lymphocytes become activated, proliferate, and secrete lymphokines such as IL-2. These events subsequently stimulate antigen-specific B cells to produce and secrete antibodies. This general mechanism is finely controlled by various regulatory agents, such as T-suppressor cell networks and/or helper and suppressor factors.

The data presented suggest that CD4⁺ Th cells from patients with chronic primary ATP respond abnormally to platelet antigens. These results may be explained by several potential mechanisms. High-affinity autoreactive CD4⁺ Th cells may have escaped thymic selection during T-cell ontogeny and stimulated the antiplatelet autoantibody response. Alternatively, an autoantigenic stimulus may occur in the extrathymic periphery that could stimulate an otherwise normal T-cell repertoire to respond to platelet antigens; this autostimulus could derive from the host's tissues in the form of an altered self antigen or from a cross-reactive environmental stimulus that could mimic self antigens (antigenic mimicry). Furthermore, Table 4 shows a reduced proportion of T suppressor-inducer (Tsi) cells in patients with chronic primary ATP. Tsi cells are responsible for stimulating the production of suppressor T cells to downregulate an immune response, or to tolerate the immune system to self antigens. It is possible that, in chronic primary ATP, Th cells are deregulated due to a relative lack of T-suppressor cells; this possibility is consistent with the findings of Hymes and Karpatkin, who have described decreased T-suppressor cell function in EBV-seropositive patients with ATP. Other autoimmune diseases, such as SLE, RA, and multiple sclerosis, have been shown to have a decrease in Tsi cells. It may be worthwhile to examine specific subsets of CD8⁺ cells to delineate whether a subset of T-suppressor cells is reduced in patients with primary chronic ATP.

In addition to a reduction of Tsi cells, a concomitant increase in activated T cells and in B cells was observed in patients with chronic primary ATP. An increase in activated T cells in patients with ATP was also described by Mizutani et al and may reflect antigenic stimulation by platelet antigens. The increase in B cells in patients with ATP may indicate that the T cell defects stimulate proliferation within the B-cell population. We have recently observed that patients with ATP have a suppressed NK cell activity. Because NK cells can suppress proliferation and antibody production by B cells, it is possible that the defective NK activity in patients with ATP may, in addition

Table 4. Lymphocyte Subpopulation Distributions in Patients and Controls

<table>
<thead>
<tr>
<th>Antibody*</th>
<th>CD</th>
<th>WBC (× 10⁴/L)</th>
<th>Lymphocytes (%)</th>
<th>T-suppressor/cytotoxic cells</th>
<th>T-suppressor/cytotoxic subset</th>
<th>NK cells</th>
<th>Th cells</th>
<th>T-suppressor-inducer cells</th>
<th>Th cells (of B cell differentiation)</th>
<th>Total T cells</th>
<th>Activated T cells</th>
<th>Total B cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leu2⁺</td>
<td>CD8⁺</td>
<td>6.4 ± 2.1</td>
<td>36 ± 9</td>
<td>30 ± 13</td>
<td>7 ± 4</td>
<td>3 ± 3</td>
<td>42 ± 12</td>
<td>32 ± 8</td>
<td>11 ± 5</td>
<td>75 ± 14</td>
<td>4 ± 3</td>
<td>11 ± 8</td>
</tr>
<tr>
<td>Leu2⁺/7⁺</td>
<td>CD8⁺/57⁺</td>
<td>7.1 ± 3.3</td>
<td>30 ± 10</td>
<td>28 ± 10</td>
<td>7 ± 5</td>
<td>3 ± 2</td>
<td>30 ± 11</td>
<td>11 ± 6</td>
<td>20 ± 14</td>
<td>68 ± 10</td>
<td>16 ± 8</td>
<td>19 ± 7</td>
</tr>
<tr>
<td>Leu2⁺/7⁺</td>
<td>CD8⁺/57⁺</td>
<td>7.4 ± 4.2</td>
<td>28 ± 8</td>
<td>10 ± 7</td>
<td>8 ± 4</td>
<td>3 ± 3</td>
<td>39 ± 13</td>
<td>26 ± 9</td>
<td>13 ± 6</td>
<td>61 ± 20</td>
<td>9 ± 4</td>
<td>15 ± 8</td>
</tr>
<tr>
<td>Leu3⁺</td>
<td>CD4⁺</td>
<td>6.3 ± 2.0</td>
<td>31 ± 10</td>
<td>29 ± 12</td>
<td>8 ± 4</td>
<td>2 ± 1</td>
<td>35 ± 10</td>
<td>32 ± 14</td>
<td>13 ± 7</td>
<td>63 ± 10</td>
<td>8 ± 4</td>
<td>15 ± 7</td>
</tr>
<tr>
<td>Leu3⁺/8⁺</td>
<td>CD4⁺/Leu8⁺</td>
<td>7.4 ± 4.3</td>
<td>29 ± 13</td>
<td>32 ± 14</td>
<td>30 ± 10</td>
<td>4 ± 2</td>
<td>41 ± 9</td>
<td>30 ± 10</td>
<td>11 ± 6</td>
<td>69 ± 14</td>
<td>5 ± 3</td>
<td>10 ± 3</td>
</tr>
<tr>
<td>Leu3⁺/8⁺</td>
<td>CD4⁺/Leu8⁺</td>
<td>7.4 ± 4.3</td>
<td>32 ± 14</td>
<td>30 ± 10</td>
<td>22 ± 14</td>
<td>5 ± 2</td>
<td>38 ± 8</td>
<td>22 ± 6</td>
<td>16 ± 9</td>
<td>70 ± 11</td>
<td>5 ± 4</td>
<td>9 ± 6</td>
</tr>
</tbody>
</table>

* Number of patients given in parentheses.

**Becton Dickinson nomenclature.

1 Antiplatelet proliferative activity (+ or −).
to the Th cell defects shown here, enhance the proliferation of B cells in ATP, with subsequent antiplatelet autoantibody production.

Proliferation and IL-2 secretion by lymphocytes in response to platelet stimulus was also observed in some patients with secondary ATP; these patients, however, had associated immune diseases (three SLE, one RA, and one drug-induced) that could account for their overall autoimmune reactivity. Because none of the patients with NIT or NTID had any significant antiplatelet reactivity, it would appear that antiplatelet Th cell reactivity is relatively specific for ATP.

The nature of the platelet autoantigen(s) recognized by Th cells in patients with ATP is unclear. In the current study, normal random donor platelets (devoid of HLA class I antigens) were used as the platelet stimulus. The specificity of antiplatelet autoantibodies in ATP is commonly directed toward public antigenic sites contained within platelet membrane glycoproteins IIb-IIIa and Ib-IX. It is possible that Th cell immunogenic epitopes also lie within these glycoproteins. Identification of Th cell epitopes within platelet glycoproteins will have important implications with respect to the autoantigenic initiation of the antiplatelet antibody response and will allow for a better understanding of the autoimmune events leading to ATP. We are currently studying the immunogenic T-cell epitopes within these glycoproteins to define and map these potential autoantigenic sites.

In conclusion, patients with chronic primary ATP have Th lymphocytes that proliferate and secrete IL-2 when stimulated by normal platelets. This stimulation may reflect an immunoregulatory abnormality that can enhance antiplatelet autoantibody production, leading to elevated platelet destruction.

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JW Semple and J Freedman