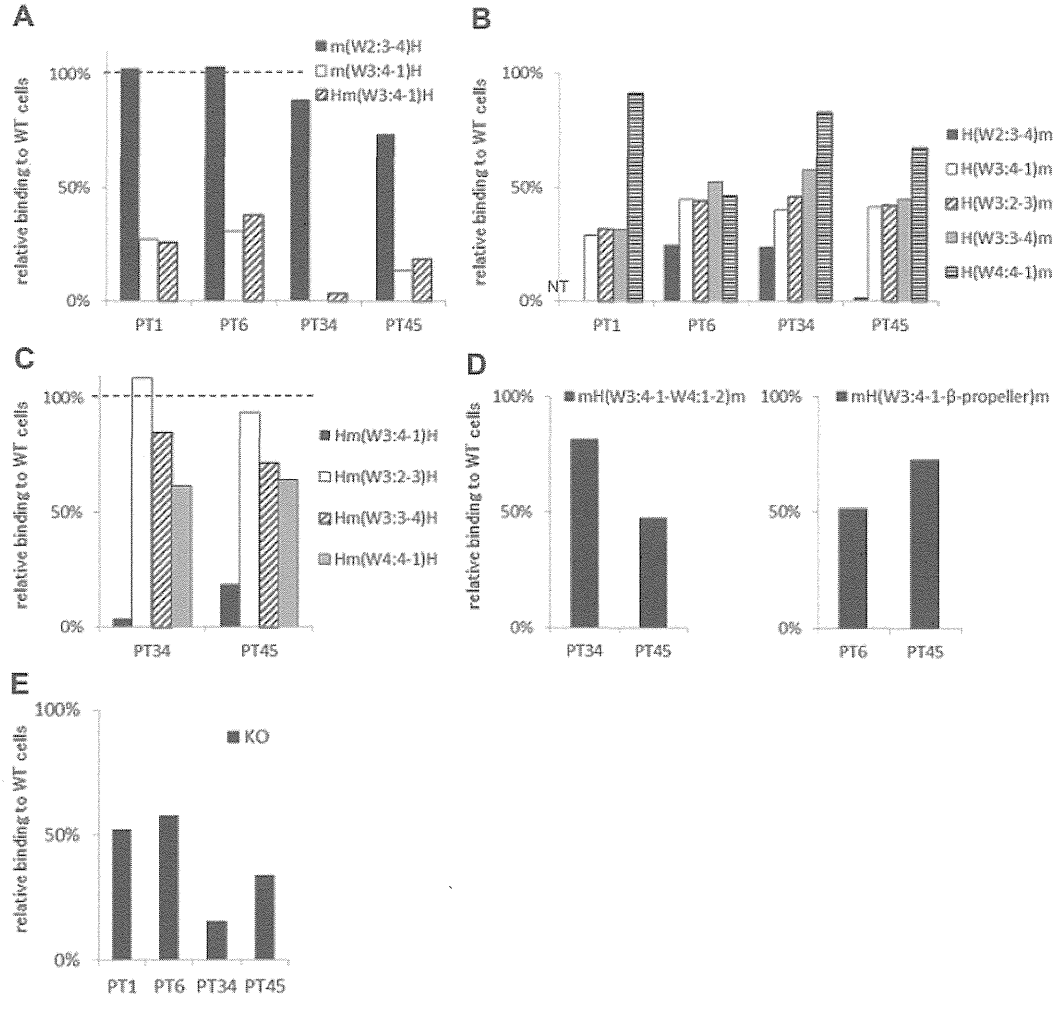

Figure 5. Group C: the W3:4-1 loop is essential for PA anti-αIIbβ3 Ab binding. (A) Relative binding of PA Abs to m(W2:3-4)H (black), m(W3:4-1)H (white), and Hm(W3:4-1)H (shaded) compared with wt αIIbβ3. (B) Relative binding of PA Abs to mouse αIIb replaced from the N-terminus to the indicated loops with the human corresponding sequences. (C) Relative binding of PA Abs to human αIIb replaced the indicated loop with the mouse corresponding sequences. (D) Relative binding of PA Abs to mH(W3:4-1–W4:1-2)m and mH(W3:4-1–β-propeller)m that the mouse αIIb carried the human sequences from W3:4-1 to the C-terminal of the β-propeller domain. (E) Relative binding of PA Abs to 2 amino acids insertion mutant in W3:4-1 loop (KO variant αIIbβ3). Shown were means of ≥ 2 independent experiments.

W2:3-4 loop. Again, we examined the effects of substituting these single amino acids on PA Ab reactivity. We found that the PA Ab reactivity in the sample from PT 36 remained markedly impaired with either the G44N or the P45A mutation in the W1:2-3 loop. However, no mutation in the W1:2-3 loop significantly impaired the PA Ab reactivities in samples from the other 4 patients (Figure 4E). In contrast, the R139G mutation in the W2:3-4 loop impaired reactivity in the samples from all 4 of these patients. In addition, samples from PTs 3 and 12 showed a similarly impaired pattern in the PA Ab reactivities with the P135L, E136Q, and R139G mutations (Figure 4F).

Group C: the W3:4-1 loop is essential for PA anti-αIIbβ3 Ab binding. In 4 samples (from PTs 1, 6, 34, and 45) the PA Ab reactivity was markedly impaired with m(W3:4-1)H compared with m(W2:3-4)H. In addition, the PA Ab reactivity was similarly impaired with Hm(W3:4-1)H (Table 2; Figure 5A). These results suggested that the W3:4-1 loop was essential for PA Ab reactivity in these samples. Interestingly, in samples from PTs 1, 34, and 45, the PA Abs showed nearly fully restored reactivity with H(W4:4-1)m (Figure 5B). This suggested that the W4:4-1 loop may also affect PA Ab reactivity. In fact, in PTs 34 and 45, the PA Ab reactivity was markedly impaired with Hm(W3:4-1)H and moderately impaired with Hm(W4:4-1)H (Figure 5C). The sample from PT 1 was not tested because of insufficient sample. The sample from PT 34 showed PA Ab reactivity with mH(W3:4-1–W4:1-2)m that was nearly comparable with its reactivity with wt αIIb (Figure 5D). This supported the notion that both W3:4-1 and W4:4-1 loops were important for PA Ab reactivity in this patient. In contrast, in the sample from PT 45, PA Ab reactivity was not restored with mH(W3:4-1–W4:1-2)m (Figure 5D). Finally, we tested the sample from PT 45 with the mouse αIIb that carried the human sequence from W3:4-1 to the C-terminal of the β-propeller domain, mH(W3:4-1–β-propeller)m. We found that the sample from PT 45 showed reactivity with the mH(W3:4-1–β-propeller)m comparable with reactivity with the wt αIIb. This suggested that the C-terminal half of the β-propeller domain may also contribute to PA Ab binding in the sample from PT 45 (Figure 5D). In the sample from PT 6, PA Ab reactivity was not fully restored with H(W4:4-1)m but was almost fully restored with H(β-propeller)m (Figures 5B and 2E). However, the PA Ab reactivity was impaired with mH(W3:4-1–β-propeller)m (Figure 5D). These results suggested that the N-terminus and the C-terminal portion of the β-propeller domain were important for the PA Ab reactivity in the sample from PT 6.

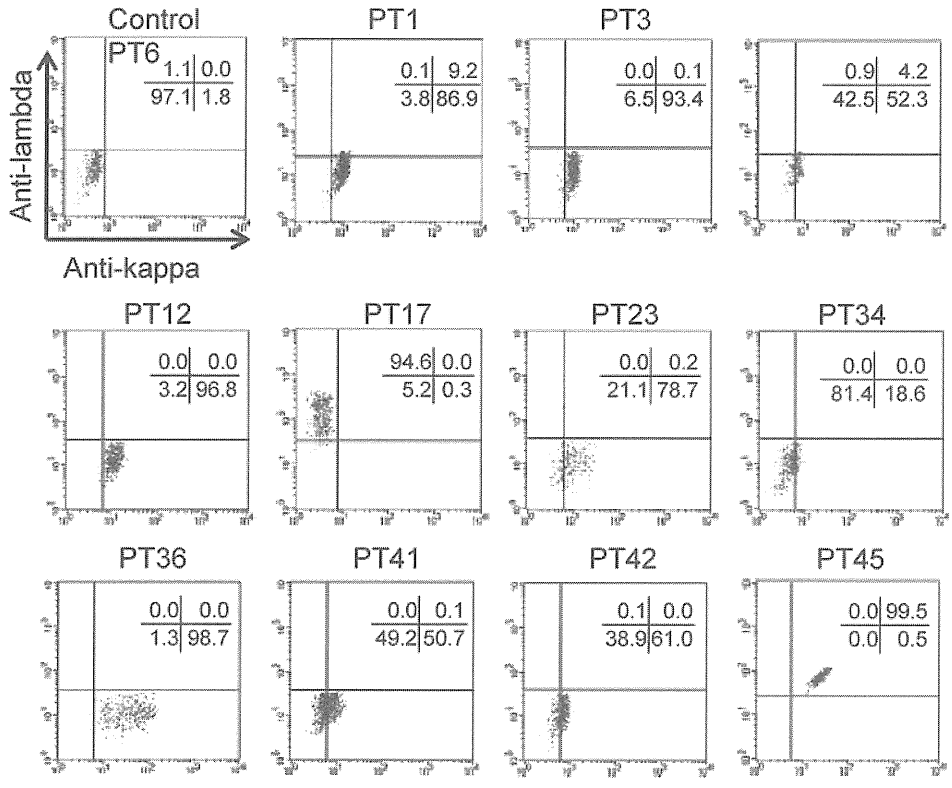

Figure 6. Light-chain usage of PA anti-αIIbβ3 Abs. Platelet eluates were reacted with wt αIIbβ3-expressing 293T cells, followed by the incubation with FITC–anti-κ, PE–anti-λ, and APC–anti-CD61 Abs. Anti-κ (horizontal) and anti-λ (vertical) Abs bindings were analyzed in a subset of cells that were highly positive for CD61. Representative results of ≥ 2 independent experiments are shown.

There are many amino acid differences between human and mouse in the W3:4-1 and W4:4-1 loops (Figure 1A). Therefore, it was difficult to identify critical residues in these regions. However, we previously studied a KO variant of αIIbβ3 with a 2-amino acid (Arg-Thr) insertion between F160 and S161 in the W3:4-1 loop. In that study, we found that this insertion affected PA Ab reactivity as well as ligand binding capacity.[15] In the present study, samples from all 4 patients of group C showed impaired PA Ab reactivity with this mutation (KO; Figure 5E).

Samples from the remaining 4 patients (PTs 2, 5, 7, and 37) could not be classified in the 3 groups described. However, all 4 had PA anti-αIIbβ3 Abs that mainly recognized the N-terminal half of the β-propeller domain of αIIb. In these patients, we did not detect any unique characteristics that might identify an epitope on any specific loop(s).

Light chain–restricted usage of PA anti-αIIbβ3 Abs

Our findings indicated that autoantigenic epitopes may be located on highly restricted regions of αIIb, which also suggested that many PA anti-αIIbβ3 Abs might exhibit clonality. Therefore, we next determined whether PA Abs exhibited restricted κ/λ light chain usage in the 11 eluates that had been classified in 1 of the 3 groups described in the previous paragraphs. We determined that samples from PTs 1, 3, 12, and 36 clearly showed restricted κ-chain usage, and the sample from PT 17 showed restricted λ-chain usage. In contrast, the PA Abs in samples from PT 45 were polyclonal. The samples from the remaining 5 patients also showed κ-chain preference, although the positivity was weak (Figure 6). These results suggested that the PA anti-αIIbβ3 Abs were clonal in many patients with primary ITP.

Discussion

Previous reports have found the importance of the β-propeller domain in αIIb, particularly the W3:4-1 loop, for PA anti-αIIbβ3Ab binding in patients with chronic ITP.[13,15] In this study, we found that samples from 15 patients with primary ITP harbored PA anti-αIIbβ3 Abs that mainly recognized the N-terminal half of the β-propeller domain (L1-W235) of αIIb. A systematic examination with human-mouse αIIb chimeras found 3 main recognition sites: (1) a conformational epitope composed of W1:1-2 and W2:3-4 loops, (2) a region containing the W1:2-3 loop, and (3) a region containing the W3:4-1 loop. We further identified some single residues in these loops that were critical for PA Ab reactivity. Moreover, PA anti-αIIbβ3 Abs in many patients showed restricted κ/λ light chain usage. Our findings indicated that major epitopes of PA anti-αIIbβ3 Abs were localized in highly restricted regions in the β-propeller domain of αIIb and that PA anti-αIIbβ3 Abs may be monoclonal or oligoclonal in many patients with ITP.

It was surprising that PA anti-αIIbβ3 Abs did not bind to mouse αIIbβ3. αIIb and β3 showed 82% and 85% nucleotide sequence homology, respectively, between human and mouse. However, one report suggested that anti–human platelet Abs produced from splenocytes obtained from patients with ITP exhibited low cross-reactivity with mouse platelets.[24] Another report showed that an anti–human αIIb antibody generated in mice exhibited significantly diminished binding to ITP platelets compared with normal platelets.[25] Those results suggested that the reactivity of PA anti-αIIbβ3 Abs may be affected by subtle conformational differences between human and mouse αIIbβ3.

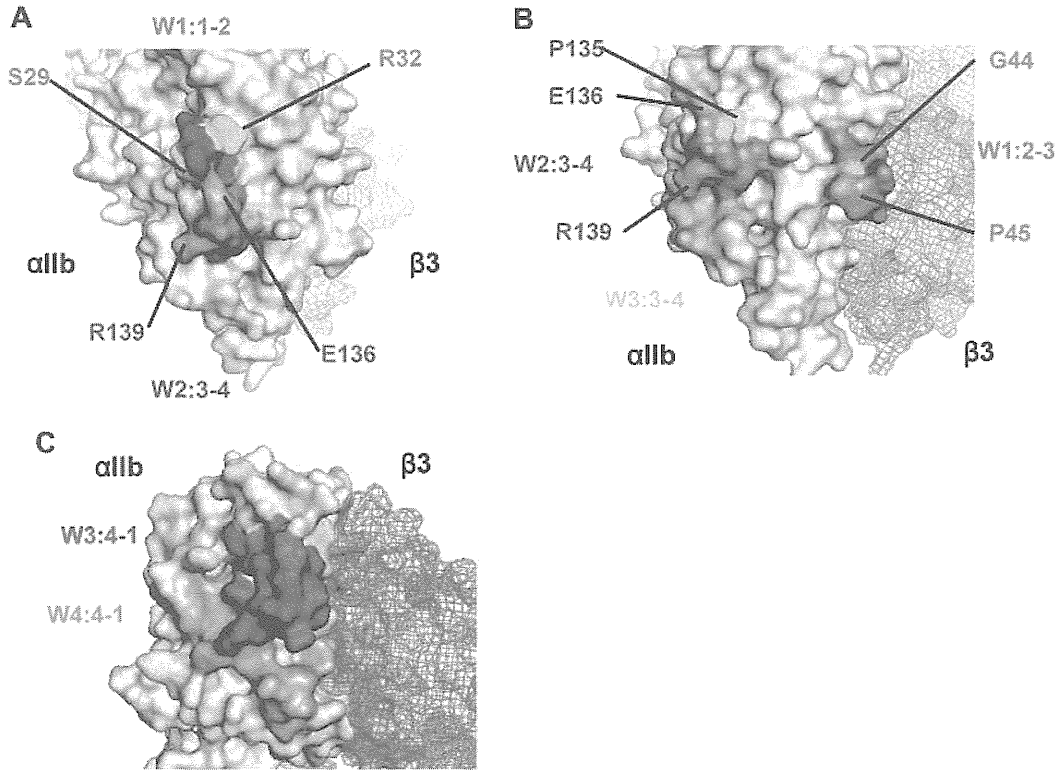

Figure 7. Crystal structure of the recognition sites for the PA Abs. (A) Crystal structure of the recognition sites of group A made by PyMOL Version 1.4 software (DeLano Scientific LLC). W1:1-2 (blue) and W2:3-4 (green) loops and 4 critical residues (S29, R32, E136, R139) for the binding of PA Abs were indicated. (B) Crystal structure of the recognition sites of group B. W1:2-3 loop (orange) is located in the upper surface of αIIbβ3 interface, and W2:3-4 and W3:3-4 loops (green) are in the lower surface. Five critical residues (G44, P45, P135, E136, R139) for the binding of PA Abs were also indicated. (C) Crystal structure of the recognition sites of group C. W3:4-1 (red) and W4:4-1 (pink) loops were indicated. Both loops are located in the upper surface of αIIbβ3 interface, which is near the ligand binding site.

Two patients of group A had PA Abs that recognized the W1:1-2 and W2:3-4 loops. Although these 2 loops are separated by ~ 100 amino acids in the primary αIIb sequence, the crystal structure showed that the W1:1-2 loop was close to the W2:3-4 loop on the lower face of the β-propeller domain (Figure 7A). Furthermore, the binding of PA Abs from PT 17 to wt αIIbβ3 could not be inhibited by linear peptides that corresponded to W1:1-2, W2:3-4, or a mixture of these peptides; this also suggested that the PA Abs recognized a conformational epitope composed of these 2 loops (data not shown). Moreover, the reactivity of Abs was highly affected by single amino acid substitutions (S29K, R32S, E136Q, and R139G) in the W1:1-2 and W2:3-4 loops (Figure 3D-E). Because arginine (R), lysine (K), and glutamic acid (E) are charged amino acids, these substitutions may affect ionic bonds between αIIb and the complementarity determining regions of the PA Abs.

We found that the W1:2-3 loop was critical for the reactivity of PA Abs in 5 patients of group B. However, when epitopes of the mouse αIIb were swapped with the corresponding human N-terminus sequences, recovery of PA Ab binding was heterogeneous among the patient samples (Figure 4B). In particular, the PA Abs from PT 36 appeared to exclusively recognize the W1:2-3 loop, and we further found that the PA Ab reactivity was markedly impaired with a single G44N or P45A substitution in the loop (Figure 4E). Because asparagine (N) has an amino group and proline (P) has a cyclic structure, the presence or absence of these amino acids may have highly affected hydrogen bonding between the Abs in PT 36 and αIIb, and/or they may have disrupted the conformation of the W1:2-3 loop. In addition, swapping human and mouse loop sequences showed that W2:3-4 loop was also important for the reactivity of PA Abs in the eluates of the remaining 4 patients. Finally, the W3:3-4 loop appeared to contribute to PA Ab binding in the eluates from 2 patients, PTs 3 and 12 (Figure 4C). Interestingly, the R139G mutation in the W2:3-4 loop had a profound effect on PA Ab binding in the eluates of the 4 patients in group B and the 2 patients in group A (Figures 3E and 4F). This indicated that R139 may be a critical epitope for many PA Abs. The crystal structure of αIIb showed that the W1:2-3 loop was located on the upper face, and the W2:3-4 and W3:3-4 loops were on the lower face of the β-propeller domain (Figure 7B). Although we could not rule out the possibility that PA Abs may be polyclonal and recognize different epitopes, we hypothesized that PA Abs recognize conformational epitope(s) composed of these multiple loops, based on our findings that PA Ab binding was markedly impaired with a single loop substitution. The crystal structure showed that the W1:2-3 and W2:3-4/W3:3-4 loops were located ~ 30 Å apart; this circumscribes an area consistent with the typical contact areas between protein antigens and their cognate Abs.[26,27] The 3-dimensional structure suggested that these loops formed a relatively flat surface (Figure 7B), also consistent with the observation that Abs typically interact with protein antigens on relatively flat complementarity determining regions.[28]

In the 4 patients of group C, we confirmed our previous finding that the W3:4-1 loop was one of the main target epitopes for PA anti-αIIbβ3 Abs. The PA Abs from these 4 eluates showed impaired reactivity with the KO variant αIIbβ3.[20,29] We also showed that the W4:4-1 loop was important for the binding of 3 of 4 sample eluates. Again, the 3-dimensional structure (Figure 7C) indicated that the W3:4-1 loop was immediately adjacent to the W4:4-1 loop on the upper face of the β-propeller domain; this suggested that the PA Abs recognized an epitope composed of these 2 loops. Moreover,

the C-terminal half of the β-propeller domain was important for efficient binding of the PA Abs in the samples from PTs 6 and 45. This suggested that the C-terminal region might maintain the proper conformation of the W3:4-1 loop region for the binding of PA Abs.

Our findings that many PA anti-αIIbβ3 Abs in patients with ITP recognized restricted regions of the β-propeller domain in αIIb have some interesting implications. The cause of primary ITP remains obscure; however, it has been suggested that molecular mimicry may trigger an immune response against platelet antigens in some secondary forms of ITP.[14,30] A recent study reported that many bacterial proteins contained the human integrin-type β-propeller domain[31]; this suggested that conformational mimicry between these bacterial proteins and the β-propeller domain in αIIb might be involved in the production of PA anti-αIIbβ3 Abs. Consistent with other reports,[32,33] we observed that many of the PA anti-αIIbβ3 Abs exhibited restricted κ/λ light chain usage, which further suggested that PA Abs might arise from an antigen-derived clonal expansion rather than from polyclonal B-cell activation triggered by nonspecific stimuli.

Of note, all 4 eluates that did not show clear epitopes (PTs 2, 5, 7, and 37) were collected > 6 years after the diagnosis; in contrast, all 5 eluates collected within 1 year after diagnosis were categorized as group B or C (PTs 1, 6, 34, 36, and 45; Table 1). These results suggested that restricted epitopes tended to be more common in the early stages of ITP and that epitopes may spread out in the later, chronic phase of the disease, although in some cases, such as PTs 17 and 23, highly specific epitopes were identified in patients with a long ITP history. This time dependence was also found in other autoimmune diseases.[34,35] In this context, it is intriguing that PA Abs which were categorized as group C were only found in patients with a diagnosis made < 1 year ago in this study. In fact, the PA Abs from PT 12, which showed highly impaired reactivity with the substituted epitopes in the KO mutation in our previous study (PT 6 [patient no. 6] in the previous study[15]), appeared to react with extended or changed epitopes in the W1:2-3, W2:3-4, and W3:3-4 loops in the present study, with eluates collected > 10 years later. These results suggest that W3:4-1 loop may be the target epitope of the early phase of ITP. Clearly, concrete evidence of epitope spreading will require long-term studies of patients with ITP.

This study had several limitations. First, we used human-mouse αIIb chimeras for epitope mapping; thus, we could not evaluate whether identical residues between human and mouse were significant. Second, there was an inevitable bias for patient and sample selection, because patients with severe thrombocytopenia could not provide sufficient platelet eluates for the study. Finally, we analyzed only PA anti-αIIbβ3 Abs; thus, we could not rule out the possibility that PA Abs that recognized other GPs (such as GPIb/IX/V) might play a role in the pathogenesis of ITP in our patients.

In summary, we have shown that PA anti-αIIbβ3 Abs tend to recognize highly restricted regions in the N-terminal half of the β-propeller domain of αIIb with clonality. These results may contribute to a better understanding of the pathogenesis of chronic ITP.

Acknowledgments

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Authorship

Contribution: K.K., H.K., and Y.T. designed the study; K.K. performed most of the experiments and wrote the paper; H.K. and Y.T. edited the paper; T.N. and S.T. performed the transfection studies; and S.H. and Y.K. supervised several aspects of the projects and helped with manuscript preparation.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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【ATLの疫学　現状と課題】

Epidemiology of ATL : Current knowledge and future challenges

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Masako Iwanaga

Key words
HTLV-1キャリア，ATL，疫学，
リスクファクター，プロウイルス量

要　約

HTLV-1感染者が多い地域は偏在しており，世界的には日本，カリブ海沿岸諸国，南米，など，日本国内では九州，沖縄などである。日本には約108万人のHTLV-1キャリアが存在し，毎年約1100人以上のATLが発症し，毎年約1000人がATLにより死亡している。HTLV-1キャリアからの年間ATL発症率は，1,000人あたり男1～1.5，女0.5～0.7，30歳以上のHTLV-1キャリアにおける生涯ATL発症率は，男4～7%，女2～5%と推定されている。ATL発症のリスクファクターとして，母子間感染，男性，加齢，特定のHLA保持者，免疫低下などの宿主側要因や，感染細胞数の多さを反映する白血球増加，異型リンパ球増加，ウイルス抗体価上昇，可溶性IL-2R上昇などの臨床検査値異常や，HTLV-1プロウイルス量の上昇などが報告されている。しかし，ATL発症のリスクファクターの全容解明にはいたっておらず，遺伝的背景，免疫学的背景，分子生物学的特徴などを含むさらなるエビデンスの集積が必要である。

はじめに

白血病やリンパ腫の原因は大半が不明であるが，成人T細胞性白血病・リンパ腫（adult T-cell leukemia-lymphoma, ATL）は，ヒトT細胞性白血病ウイルス（Human T-cell leukemia virus type I, HTLV-1）の持続感染者（HTLV-1キャリア）からのみ発症するウイルス起因性の血液悪性腫瘍である。本稿では疫学的観点から，HTLV-1キャリア数，ATLの発症数や死亡数，HTLV-1キャリアからのATL発症率，発症にかかわるリスクファクターについてこれまでの知見を紹介し，さらに何がまだ未解決の課題として残されているのかを解説する。

1．HTLV-1キャリアの分布と推計数

世界的にみても日本国内でも，HTLV-1キャリアの分布は極めて偏在している。日本，カリブ海沿岸諸国，南米，アフリカ中央部，パプアニューギニア，オーストラリアのアボリジニやアフリカのピグミー族，北米および南米の先住民族，イランの一部の地域などが，HTLV-1感染者の割合が高い地域として知られている（図1）[1]。日本国内でHTLV-1感染者の割合が高い地域は，九州，沖縄，四国や紀伊半島の海岸線地域などであるが，東北や北陸の一部の海岸線地域，北海道の一部の地域でも割合が高いことが報告されている[2]。HTLV-1感染者の地域偏在の原因についてはよくわかっていない。民族移動などの人類学的歴史的背景が考えられている。HTLV-1は3つの遺伝子型，コスモポリタン型，中央アフリカ型，メラネシア型に分けられるが[3]，日本のHTLV-1はコスモポリタン型に属する。コスモポリタン型はさらにA~Eの5つのサブタイプが知られており，日本のHTLV-1はAとBである[4]。HTLV-1の遺伝子型による関連疾患の発症頻度の違いは報告されていない。

世界全体のHTLV-1感染者数は1000～2000万人と推定されているが，推定根拠が不明で正確な数は明ら

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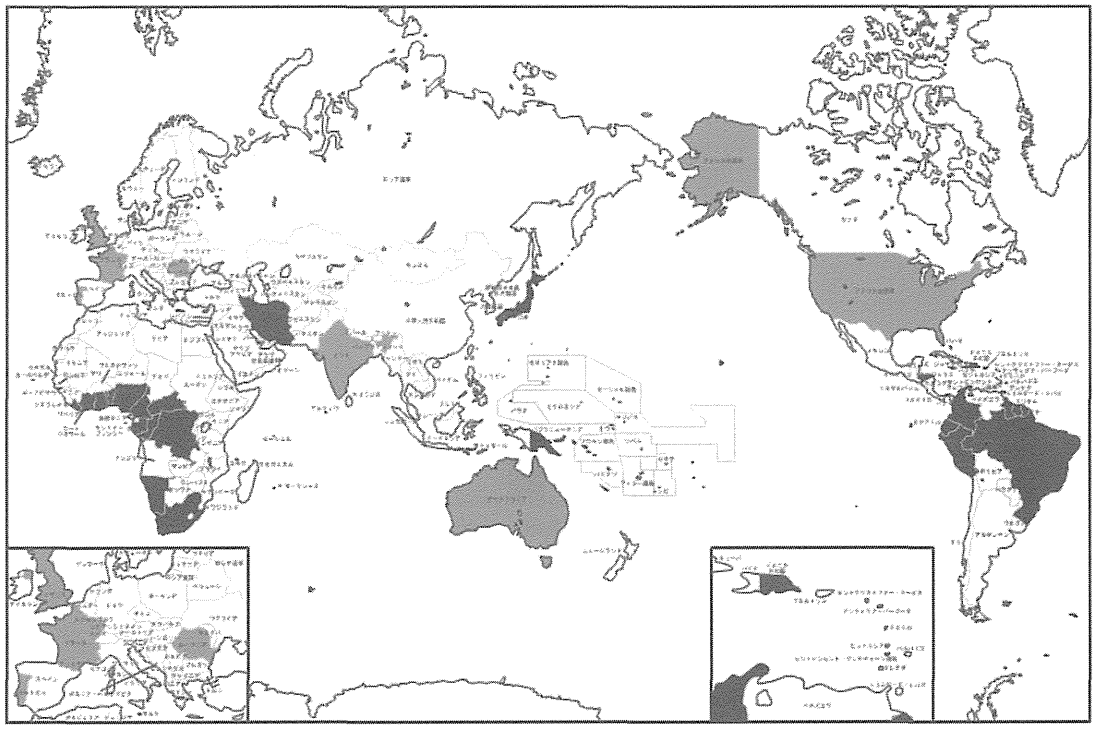

図 1　HTLV-1 感染者の世界分布
文献[1]より引用改変。黒塗りは HTLV-1 感染者率 1-5%，灰色は 1% 以下を示す。

かではない。日本全体の HTLV-1 感染者数把握は，厚生労働省班研究として全国の初回献血者における地域別・年齢別 HTLV-1 抗体陽性率の結果と人口動態統計資料をもとに 1988 年と 2008 年に実施された。1988 年の報告では，1988 年単年の献血者の抗体陽性率を用いて日本全体の HTLV-1 感染者数は約 120 万人と推定されたが[2]，HTLV-1 感染者のほとんどが九州，沖縄，に集中しており，かつ若年者の陽性率が極めて低いことより，日本における HTLV-1 感染者数は将来自然減するものと予測されていた。しかし，2006-2007 年の献血者の抗体陽性率を用いた 2008 年の報告では，日本全体の HTLV-1 感染者数は約 108 万人と推定され[5]，この 20 年間日本における HTLV-1 感染者数はほとんど減少しておらず，1988 年と比べ 2008 年では，九州・沖縄の感染者数は減少し，大都市圏の感染者数が増加していたことが判明している（図 2）[5]。

一般に HTLV-1 感染の大半は新生児期の母乳によって感染し，出生年時代の母乳哺育方法や家族構成の違いが影響し，HTLV-1 感染率は年齢が高い（出生年が早い）ほど高い。また成人期以降は，女性の感染率が男性より上回るため，夫婦感染ルートによる感染率増加が示唆されている。ちなみに ATL 発症率は男性が高く，HAM/TSP 発症率は女性が高い。

2．ATL の発症数と死亡数

ATL 患者の地域分布は HTLV-1 感染者の分布とほぼ等しいため割愛する。日本全体の ATL による年間死亡実数は，厚生労働省人口動態統計によると，1999 年から 2010 年まで毎年ほぼ一定で約 1000 人である。しかし日本全体の ATL 発症実数は，人口動態統計では報告されていない。全国 T・B リンパ系腫瘍研究グループは日本全体の ATL 発症実数を把握するために，1988 年から 1999 年まで基幹病院を対象とした ATL 全国実態調査を行い，日本における ATL の年発症数は約 700 例と推定した[6]。しかし 2010 年に実施された厚生労働省班研究の報告では，年発症者数は約 1100 人と推定されている[7]。両者の発症数の違いは研究手法の違いによると思われ，日本全体の年間発症数は年間死亡数より 1 － 2 割ほど多いと推測されるが，正確な発症数は不明である。ATL の診断時年齢の平均値は，1990 年調査時 58.3 歳，1999 年調査時 61.1 歳，2009 年調査時 66.0 歳としだいに高齢化していることが判明している[7]。

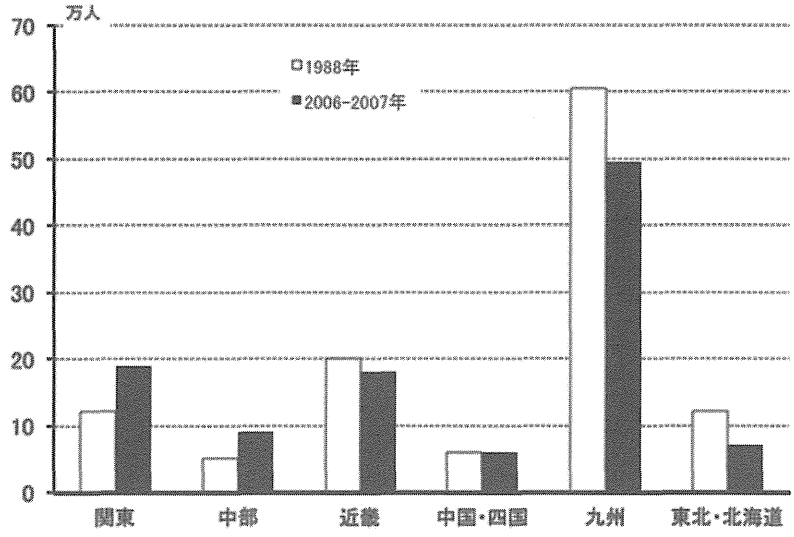

図2　日本におけるHTLV-1感染者数の推計値の地域別分布

文献[5]より引用改変。白カラムは1988年当時のHTLV-1感染者推計数を，黒カラムは2008年当時のHTLV-1感染者推計数を示す。

地域がん登録を行っている一部の県や市では，より詳細なATLの発症実数と人口10万人あたりの発症率が毎年報告されている。HTLV-1キャリアが多い長崎県がん登録の報告では，2000-2007年のATLの発症実数は，毎年男性51～65人，女性30～62人，2007年の県内粗罹患率は10万人あたり男性9.1，女性6.8であり，男性の発症率は同年の白血病罹患率（男性9.7，女性3.9）とほぼ肩を並べている。

3．HTLV-1キャリアからのATL発症率とリスクファクター

四国宇和島市（人口290,464, HTLV-1感染率；男5.4%，女8.3%）の調査研究では，30歳以上のHTLV-1キャリア10万人あたりのATL発症率は男性145，女性55.2，HTLV-1キャリアの生涯ATL発症率は男性6.9%，女性3.0%と推計されている[8]。長崎県の某諸島(人口26,870人，HTLV-1感染率；男14.3%，女17.9%）の調査研究では，30歳以上のHTLV-1キャリア10万人あたりのATL発症率は男性137.7, 女性57.4，HTLV-1キャリアの生涯ATL発症率は男性6.6%，女性2.1%と推計され[9]，宇和島の結果とほぼ同じである。その他の報告も含め，HTLV-1キャリア1,000人あたり年間ATL発症率は男性1～1.5，女性0.5～0.7，30歳以上のHTLV-1キャリアにおける生涯ATL発症率は男性4～7%，女性2～5%と推定されている。　このようにATLは一部のHTLV-1キャリアからしか発症せず，大半のキャリアは無症状で過ごし「無症候性HTLV-1キャリア」と呼ばれている。

ATL発症にかかわるリスクファクターとしてこれまで報告されてきたさまざまの因子を**表1**にまとめる。母子間感染，男性，加齢，特定のHLA保持者，免疫の状態などの宿主側の要因や，感染細胞数の多さを反映する白血球増加，異型リンパ球増加，ウイルス抗体価上昇，可溶性IL-2R上昇などの臨床検査値の異常や，HTLV-1プロウイルス量の上昇などが報告されている。特にHTLV-1プロウイルス量はダイレクトに感染細胞数を反映していると考えられ，HTLV-1プロウイルス量の増加はキャリア状態からATL進展への重要なマーカーと考えられている[10]。しかし，HAM/TSPへ進展するキャリア症例でもHTLV-1プロウイルス量は高く，HTLV-1プロウイルス量の増加がATL進展にかかわる役割については未解明な部分が残っている。HTLV-1キャリア実数は女性が多いが，ATL発症率は男性が高く，一方HAM/TSP発症率は女性が高いこと，プロウイルス量が高値の無症候性キャリアが存在すること，ATL発症者には糞線虫感染者が多いこと，免疫抑制剤投与中のHTLV-1キャリアから高率にATLが発症したという報告があることなどから，キャリアの免疫状態がATL発症を制御している可能性が示唆されている。

4．今後の課題

ATLは予後不良の血液悪性腫瘍であることから，発症予防や早期治療という戦略のためには，キャリアの中でATLを発症するリスクファクターを明確にし，発症のハイリスクグループを同定することが重要な課題である。しかし，どのようなHTLV-1キャリアが発症しやすいか，あ

表　日本人 HTLV-1 キャリアから ATL 発症に関わるリスクファクターのまとめ

宿主の感受性	
	乳児期の母子感染
	50 歳以上の到達年齢
	男性
	HLA-A*26, HLA-B*4002, HLA-B*4006, HLA-B*4801
	糞線虫（*Strongyloides stercoralis*）感染
	免疫力低下
ウイルス感染量	
	HTLV-1 プロウイルス量の増加（100 PBMCs 中 4 コピー以上）
臨床検査マーカー	
	sIL-2R の上昇（500 U/mL 以上）
	抗 HTLV-1 抗体 titer の上昇（1,024 倍以上）
	末梢血異常リンパ球の増加（0.6% 以上）
	抗 Tax 活性低下
	白血球数の増加（9,000/μL 以上）
	単クローン性感染細胞の増加
	細胞表面マーカー発現の異常（CD26 発現の低下）

ATL = adult T-cell leukemia = 成人 T 細胞性白血病
HTLV-1 = human T-cell leukaemia virus type 1 = ヒト T 細胞性白血病ウイルス
HLA = human leukocyte antigen = ヒト白血球抗原
PBMC = peripheral blood mononuclear cell = 末梢血単核球細胞
sIL-2R = soluble interleukin-2 receptor = 可溶性インターロイキン 2 レセプター
さまざまの文献からの拾い上げ

るいは宿主側から見た ATL 発症のリスクファクターは何かということについては全容解明にはいたっていない。遺伝的背景，免疫学的背景，分子生物学的特徴などを含む HTLV-1 キャリアの大規模コホート調査などを行い，ATL 発症のリスクファクター解明についてさらなるエビデンスを積み重ねる必要がある。

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－平成 24 年度総括研究報告書－

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