4 経過

HAMは10～20年の経過で歩行不能になる場合が多いが（緩徐進行例），時に数カ月～2年以内で歩行不能になる例（急速進行例）もあり，重症例では両下肢の完全麻痺，躯幹の筋力低下による座位保持不能で寝たきりとなる例もある．一方，歩行障害が軽度のまま数十年以上症状の進行が乏しい例（軽症例）もある（図）．このように，HAMの経過には個人差が大きいが，その経過は脊髄炎症の程度を反映している場合が多く，病勢の把握は治療方針を決定する指標となる．

5 治療

HAMは病勢に応じた治療が必要である．発症後数カ月単位で階段昇降や歩行に補助が必要となるような急速進行例は，髄液の細胞数やネオプテリンも高く，ステロイドパルス療法とその後の内服療法が有効の場合がある．また症状が緩徐に進行し，髄液所見が炎症活動期と判断される慢性進行例では，ステロイド少量内服やインターフェロンα療法が有効の場合がある．ほとんど進行が認められず髄液所見もおとなしい軽症例は，これら治療薬の必要性に乏しく，排尿・排便障害や痙性に対する対症療法や継続的なリハビリをしながら経過観察が推奨される．また，常に副作用を念頭におき，症状の進行具合や髄液所見を参考に，できるだけ減量や中止の可能性を検討する．特にステロイド性骨粗鬆症には注意が必要で，ガイドライン[1]に基づいた対応が求められる．

6 合併症の治療

HAM患者は多彩な合併症を伴う．排尿障害に関しては，適切な治療薬の選択や間欠的自己導尿を行うことによりADLが大きく改善するので，泌尿器科医と連携した対応が望まれる．痙性に対しては，その程度に応じて抗痙縮薬の量を調整する．下肢の激しい疼痛を伴う場合は，神経障害性疼痛治療ガイドライン[2]に基づいた対応が推奨される．その他，便秘，褥瘡，

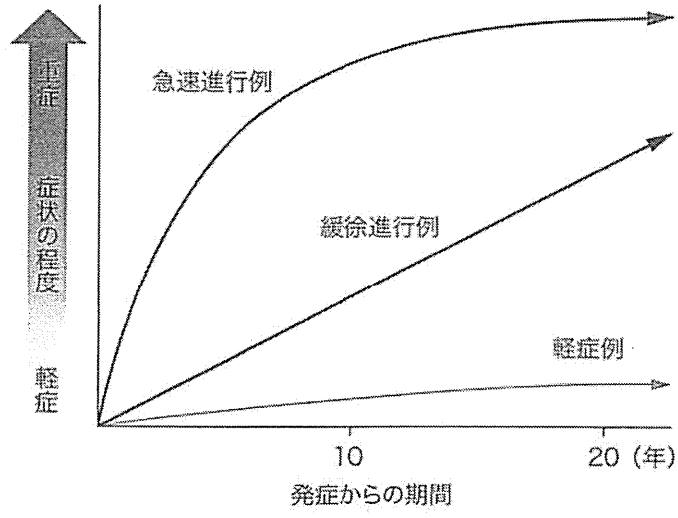

図 HAMの臨床経過の特徴

ブドウ膜炎や肺胞炎などを伴うこともあり，全身検索も忘れてはならない．これら合併症のコントロールや継続的なリハビリは，患者の日常生活を維持するうえできわめて重要であり，他科と連携しながらきめ細かな治療を行う必要がある．

文献

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2）「神経障害性疼痛薬物療法ガイドライン」（日本ペインクリニック学会神経障害性疼痛薬物療法ガイドライン作成ワーキンググループ 編），真興交易医書出版部，2011

3）山野嘉久ら：HTLV-1関連脊髄症（HAM）の治療法を確立していくために―その現状と展望―．日本臨床，70（4）：705-713，2012

a0005

HTLV-1

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Glossary

d0005 **Cytotoxic T cell** A cytotoxic T cell belongs to a subgroup of T lymphocytes with CD8 receptor that are antigen- pecific and capable of inducing the death of virus-infected somatic or tumor cells.

d0010 **Gliosis** Gliosis is the process of scarring in the central nervous system, caused by a proliferation of astrocytes.

d0015 **Oligoclonal band** Oligoclonal bands are bands of immunoglobulins that are seen when a blood serum (or plasma) or cerebrospinal fluid (CSF) is analyzed by protein electrophoresis. The presence of oligoclonal bands in CSF but not in blood serum (or plasma) means the production of immunoglobulins in central nervous system, that is, inflammation in the central nervous system.

Provirus A provirus is the form of the virus which is capable of being integrated into the chromosome of the host cell. d0020

Spastic paraparesis Mild or moderate loss of motor function accompanied by spasticity in the extremities mainly caused by central nervous system (brain and spinal cord) diseases. d0025

p0030 Human T-lymphotropic virus type-1 (HTLV-1) belongs to the *Deltaretrovirus* genus of the Orthoretrovirinae subfamily and infects 10–20 million people worldwide. HTLV-1 can be transmitted through sexual contact, intravenous drug use, and breastfeeding from mother to child. The infection is endemic in south-west Japan, the Caribbean, sub-Saharan Africa, South America, with smaller foci in Southeast Asia, South Africa, and northeastern Iran. HTLV-1 was initially isolated in 1980 from two T-cell lymphoblastoid cell lines and the blood of a patient originally thought to have a cutaneous T-cell lymphoma. It was the first human retrovirus ever associated with a human cancer. Three years before the isolation of HTLV-1, a Japanese group reported adult T-cell leukemia (ATL), a rare form of leukemia endemic to southwest Japan, as a distinct clinical entity. In 1981, the same group demonstrated that ATL was caused by a new human retrovirus originally termed 'ATLV'. Later, ATLV and HTLV have been shown to be identical, and a single name HTLV-1 has been adopted. In the mid-1980s, epidemiological data linked HTLV-1 infection with a chronic progressive neurological disease, which was termed 'tropical spastic paraparesis (TSP)' in the Caribbean and 'HTLV-1 associated myelopathy (HAM)' in Japan. HTLV-1-positive TSP and HAM were subsequently found to be clinically and pathologically identical and the disease was given a single designation as HAM/TSP. HTLV-1 can cause other chronic inflammatory diseases such as uveitis, arthropathy, pulmonary lymphocytic alveolitis, polymyositis, Sjögren syndrome, and infective dermatitis. Only approximately 2–3% of infected persons develop ATL and another 0.25–4% develop chronic inflammatory diseases, while the majority of infected individuals remain lifelong asymptomatic carriers (ACs). Thus, the viral, host, and environmental risk factors, as well as the host immune response against HTLV-1 infection, appear to regulate in the development of HTLV-1-associated diseases. For over two decades, the investigation of HTLV-1-mediated pathogenesis has focused on Tax, an HTLV-1-encoded viral oncoprotein. Tax activates many cellular genes by binding to groups of transcription factors and coactivators and is necessary and sufficient for cellular transformation. However, recent reports have identified another regulatory protein, HTLV-1 basic leucine zipper factor (HBZ), that plays a critical role in the development of ATL and HAM/TSP.

HTLV-1-Associated Diseases s0005

Adult T-cell leukemia s0010

p0035 ATL is a fatal malignancy of mature CD4+ T cells. It arises in only a small proportion of HTLV-1-infected people (1–5% of infected individuals) after long latency periods following primary infection. ATL shows diverse clinical features, but can be divided into four clinical subtypes: smoldering, chronic, lymphoma, and acute. Each subtype is directly correlated with the prognosis of patients: the smoldering and chronic types are indolent, while the acute and lymphoma types are aggressive and characterized by resistance to chemotherapy and poor prognosis. Development of ATL is characterized by infiltration of various tissues with circulating ATL cells, called 'flower cells', which have conspicuous lobulated nuclei. These cells cause further symptoms including lymphadenopathy, lytic bone lesions, skin involvement, hepatosplenomegaly, and hypercalcemia. Laboratory findings of ATL patients typically reveal a marked leukocytosis, hypercalcemia, high serum levels of lactate dehydrogenase (LDH), and a soluble form of interleukin-2 receptor (IL-2R). In cohort studies of HTLV-1 carriers, the risk factors for ATL appeared to include vertical infection (mother to child transmission), male gender, older age, and increasing numbers of abnormal lymphocytes. Since ATL occurs mainly in vertically infected individuals, but not in those who become infected later in life, the impairment of HTLV-1-specific T-cell responses caused by vertical HTLV-1 infection has been suggested as a possible cause of disease development. The HTLV-1-specific cytotoxic T-cell (CTL) responses from ATL patients are significantly lower than that of HAM/TSP patients. However, insufficient HTLV-1-specific T-cell responses might also occur during and after the onset of

ATL. Although ATL has a poor prognosis, recent advances in its treatment have led to significant gains in response rates and survival. Accumulating evidence suggests that allogeneic bone marrow transplantation and allogeneic peripheral blood stem cell transplantation are potent therapies for aggressive ATL (i.e., the acute and lymphoma type). The combination of the antiretroviral agent zidovudine (AZT) and interferon-alfa (IFN-α) is also beneficial for overall survival in smoldering and chronic (i.e., indolent) ATL, although its efficacy has not yet been confirmed in well-designed prospective studies.

p0040 Since the discovery of HTLV-1, the viral transactivator Tax has been viewed as critical for leukemogenesis, due to its pleiotropic effects on both viral and many cellular genes responsible for cell proliferation, genetic instability, dysregulation of the cell cycle, and apoptosis. However, Tax expression is not detected in about 60% of freshly isolated samples from ATL cases. Recently, the expression of another regulatory protein, HBZ, has been reported in association with all ATL cases. This protein, which is encoded in the minus or antisense strand of the virus genome, promotes proliferation of ATL cells and induces T-cell lymphomas in CD4+ T cells by transgenic expression, indicating involvement of HBZ expression in the development of ATL. In addition, among the HTLV-1-encoded viral genes, only the HBZ gene sequence remains intact, unaffected by nonsense mutations and deletion. Thus, HBZ expression is indispensable for proliferation and survival of ATL cells and HTLV-1-infected cells, and Tax expression is not always necessary for the development of ATL.

s0015 HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis

p0045 HAM/TSP is a chronic progressive myelopathy characterized by spastic paraparesis, sphincter dysfunction, and mild sensory disturbance in the lower extremities. In addition to neurological symptoms, some HAM/TSP cases also exhibit autoimmune-like disorders, such as uveitis, arthritis, T-lymphocyte alveolitis, polymyositis, and Sjögren syndrome. To date, more than 3000 cases of HAM/TSP have been reported in HTLV-1-endemic areas. Sporadic cases have also been described in nonendemic areas such as the United States and Europe, mainly in immigrants from an HTLV-1-endemic area. The lifetime risk of developing HAM/TSP is different among ethnic groups, ranging between 0.25% and 4%. The annual incidence of HAM/TSP is higher among Jamaican subjects than among Japanese subjects (20 vs. three cases/100 000 population), with a 2 to 3 times higher risk for women in both populations. The period from initial HTLV-1 infection to the onset of HAM/TSP is assumed to range from months to decades, a shorter time than for ATL onset. HAM/TSP occurs both in vertically infected individuals and in those who become infected later in life (i.e., through sexual contact (almost exclusively from male to female), intravenous drug use, contaminated blood transfusions, etc.). The mean age at onset is 43.8 years and, like other autoimmune diseases, the frequency of HAM/TSP is higher in women than in men (the male to female ratio of occurrence is 1:2.3).

p0050 The essential histopathological feature of HAM/TSP is a chronic progressive inflammation in the spinal cord, predominantly at the thoracic level. The loss of myelin sheaths and axons in the lateral, anterior, and posterior columns is associated with perivascular and parenchymal lymphocytic infiltration, reactive astrocytosis, and fibrillary gliosis. In addition to HTLV-1 antibody positivity, other laboratory findings of HAM/TSP include the presence of atypical lymphocytes (the so-called flower cells) in peripheral blood and cerebrospinal fluid (CSF), a moderate pleocytosis, and raised protein content in CSF. Oligoclonal bands, raised concentrations of inflammatory markers such as neopterin, tumor necrosis factor (TNF)-α, IL-6 and IFN-γ, and an increased intrathecal antibody synthesis specific for HTLV-1 antigens have also been described in CSF of HAM/TSP patients.

p0055 A previous population association study in HTLV-1 endemic in southwest Japan revealed that one of the major risk factors is the HTLV-1 proviral load (PVL), as the PVL is significantly higher in HAM/TSP patients than in ACs. A high PVL was also associated with an increased risk of progression to disease. Higher PVL in HAM/TSP patients than in ACs was also observed in other endemic areas such as the Caribbean, South America, and the Middle East. In southwest Japan, an association was suggested between possession of the HLA-class I genes HLA-A*02 and Cw*08 and a statistically significant reduction in both PVL and the risk of HAM/TSP. By contrast, possession of HLA-class I HLA-B*5401 and class II HLA-DRB1*0101 predisposed patients in the same population to HAM/TSP. Since the function of class I HLA proteins is to present antigenic peptides to CTL, these results imply that individuals with HLA-A*02 or HLA-Cw*08 mount a particularly efficient CTL response against HTLV-1, which may be an important determinant of HTLV-1 PVL and the risk of HAM/TSP.

p0060 To date, no generally agreed standard treatment regimen has been established for HAM/TSP, as no treatment for HAM/TSP has proven to be consistently effective and long term. Therefore, current clinical practice for treatment of HAM/TSP is based on case series and open, nonrandomized uncontrolled studies. Although mild to moderate beneficial effects have been reported with corticosteroids, immunosuppressants, high-dose intravenous gammaglobulin, antibiotics (erythromycin and fosfomycin), and vitamin C, the clinical benefits are only transient and limited. The complications of steroid use limit their use particularly in postmenopausal females, who are at higher risk of developing HAM/TSP. Only three randomized placebo-controlled trials have been conducted for HAM/TSP treatment. These studies indicate that IFN-α is an effective therapy, with an acceptable side-effects profile. By contrast, no evidence yet exists of any benefit of zidovudine plus lamivudine for treating HAM/TSP. More clinical trials with adequate power are needed in the future.

Other HTLV-1-Associated Diseases s0020

p0065 HTLV-1 has been implicated in the pathogenesis of other inflammatory disorders such as uveitis, arthropathy, infective dermatitis, pulmonary lymphocytic alveolitis, polymyositis, Sjögren syndrome, and autoimmune thyroid diseases, based on the higher HTLV-1 PVL and the higher seroprevalence in patients than in ACs. However, direct evidence for an association between these disorders and HTLV-1 infection is still lacking. Nonetheless, HTLV-1 may be a significant trigger for the development of these autoimmune disorders. AU2

See also: Retroviruses (01323)

Further Reading

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11 ヒトTリンパ球向性ウイルス脊髄症（HAM）

辻野　彰，中村龍文

HTLV-1関連脊髄症［human T-lymphotropic virus type 1（HTLV-1）-associated myelopathy：HAM］は，1986年に納らによって提唱された疾患単位で，HTLV-1感染者（キャリア）に見出される慢性進行性の痙性脊髄麻痺を示す一群である．HTLV-1は，1977年に高月らによって発見された成人T細胞白血病・リンパ腫（adult T-cell leukemia：ATL）の原因ウイルスであるヒトレトロウイルスである．カリブ海諸国で熱帯性痙性麻痺（tropical spastic paraparesis：TSP）患者の一部にもHTLV-1キャリアがいることが明らかとなり，HAM/TSPとして疾患概念が確立した．HAMはHTLV-1キャリアの極一部で発症し，HTLV-1キャリア1,000人に1人位の割合でHAM患者が存在すると報告されている．発症は中年以降の成人が多いが，10歳代，あるいはそれ以前の発症と考えられる例もある．男女比は1：2.3と女性に多い．HTLV-1の感染経路として母乳を介する母子間垂直感染と，輸血，性交渉による水平感染が知られているが，そのいずれでもHAMは発症し，輸血後数週間で発症した例もある．輸血後発症するHAMの存在の指摘を受け

Topics

HAM臨床試験

a) Nishiura Y et al：Disulfide-mediated apoptosis of human T-lymphotropic virus type-I（HTLV-I）-infected cells in patients with HTLV-I-associated myelopathy/tropical spastic paraparesis. Antivir Ther 14：533-542, 2009

b) Araya N et al：Fucoidan therapy decreases the proviral load in patients with human T-lymphotropic virus type-1-associated neurological disease. *Antivir Ther 16*：89-98, 2011

HAMはあくまでもHTLV-1感染症であり，その原因療法を考える場合，HTLV-1感染細胞を標的とした治療法の開発が望まれる．その場合，長期にかつ安全に投与できる薬剤でなければならない．このような観点からの新規治療法の開発をめざした日本における最近の臨床試験の成績について紹介したい．

1．prosultiamine（アリナミン®）療法

prosultiamineはアリシンとチオール型ビタミンB_1で合成されたアリチアミン誘導体の1つである．著者らは本薬剤の中に存在するSS結合に着目し検討を行った結果，prosultiamineで処理されたHAM患者末梢血CD4陽性細胞では，その中のHTLV-1感染細胞がアポトーシスによってHTLV-1プロウイルス量が有意に減少することを明らかにした．この事実を踏まえ，6例のHAM患者に対してprosultiamine 40 mg，14日間連日点滴静注を行い臨床試験を施行した．その結果，短い投与期間にもかかわらず6例全例で末梢血HTLV-1プロウイルス量は30～50%にまで減少した．臨床的には著効は1例であったが，その他の症例でも痙縮を中心に改善がみられた[a]．現在，本薬剤による長期療法をめざし，経口prosultiamineによる臨床試験が進行中である．

2．フコイダン療法

HTLV-1はフリーのウイルスの形では感染は成立せず，感染はcell to cellで伝播していく．Arayaらは，HTLV-1のこのような感染様式での生体内拡大阻止を目的として，13例のHAM患者に対して6gのフコイダンを6～13ヵ月の間，連日経口投与を行った．その結果，末梢血HTLV-1プロウイルス量を約40%減少させ，臨床的にもその間の症状の悪化はなかったと報告している[b]．

これらの報告はあくまでも臨床試験の成績であるが，このように現在いくつかの施設でHTLV-1感染細胞を標的としたHAM治療法の開発へ向けた研究がスタートしている．

て，1986年11月より日本赤十字社の献血に抗HTLV-1抗体のスクリーニングが開始され，以後，輸血後発症はなくなっている．

HTLV-1キャリアは，以前から九州・沖縄地方に多いとされてきた．しかしながら，平成21年度厚生労働科学研究班「本邦におけるHTLV-1感染及び関連疾患の実態調査と総合対策」(研究代表者：国立感染症研究所 血液・安全性研究部 山口一成)の報告[1]では，全国のキャリア数が約108万人と推定され，九州・沖縄地方のキャリアの割合が減少している一方，関東地方と近畿地方の大都市圏での増加が示され，日本のHTLV-1キャリアは依然として多数存在し，全国に拡散する傾向があることが指摘された．HAM患者はHTLV-1キャリアの全国へ拡散とともに，東京や大阪など，人口の集中する大都市では九州に匹敵する数の患者が見出されるようになった．1998年の全国調査では1,422人の患者が確認されていたが，平成21年度の前述の全国調査では人口10万人あたり3人程度(3,000人)の患者数と推定されている．この10年を通して，年間，少なくとも30人以上が新たに発症していることになる．HAMに関しては，その稀少性ゆえに病態解明や治療薬開発のための研究が進展しにくい面があったが，HAM患者およびHTLV-1キャリアの患者会などの多大な尽力により，2008年にHAMが特定疾患(難病)に指定され，難治性疾患克服研究事業の対象疾患として組織的な研究が開始されている．

A 発症機序

HAM患者ではHTLV-1キャリアに比較して末梢血におけるHTLV-1プロウイルス量が有意に多く，このことはHTLV-1感染細胞数が増加していることを意味している．病理学的には，HAM患者脊髄は胸髄全長にわたって萎縮しており，リンパ球・マクロファージの浸潤による慢性炎症が胸髄中・下部に強く認められ，その周囲に脊髄実質の軸索，髄鞘の崩壊変性がみられる，いわゆる慢性脊髄炎である[2]．HTLV-1は脊髄に浸潤しているTリンパ球のみに感染しており，そのプロウイルス量に比例して炎症が強い．以上のことから，脊髄で起こっている病態機序としては，バイスタンダーメカニズム—脊髄に浸潤してきたHTLV-1感染CD4陽性T細胞とHTLV-1特異的細胞傷害性T細胞の相互作用の結果生ずる周囲組織の破壊—が考えられている．つまり，HAMはHTLV-1感染によって惹起されるリンパ球(Th1細胞)の活性化をトリガーとして，脊髄に浸潤するHTLV-1感染CD4陽性T細胞とそれを排除させようとする細胞との凌ぎ合いが脊髄という場所で起こる結果，惹起される疾患と言える．したがって，活性化されて高い組織浸潤能をもったHTLV-1感染Th1細胞の増加がHAMの発症・病態を形成するうえで重要な役割を果たしている可能性がある[3]．

B 臨床像

基本的な臨床症状は緩徐進行性の両下肢痙性不全麻痺で，下肢筋力低下と痙性による歩行障害を示す．膝蓋腱反射，アキレス腱反射は亢進し，病的反射がみられる．通常，上肢は筋力低下などの自覚症状を欠いているが，深部腱反射は亢進していることが多い．感覚障害は運動障害に比して軽度にとどまる例が多く，しびれ感や痛みなど，自覚的なものが多い．一方，自律神経症状は高率にみられ，特に排尿困難，頻尿，便秘などの膀胱直腸障害は病初期よりみられ，主訴となることも多い．その他，進行例では下半身の発汗障害，起立性低血圧，インポテンツなども認められる．これらの症状はいずれも脊髄の傷害を示唆するものであり，HAMの中核症状となっている．それに加え，手指振戦，運動失調，眼球運動障害，あるいは軽度の痴呆を示し，病巣の広がりが想定される例もある．しかし，そのような症例でも中核症状としての両下肢痙性不全麻痺は共通に認められる．

通常は緩徐進行性で慢性に経過するが進行が早い例もみられる．高齢での発症で進行度が早い傾向があり，重症例では両下肢の完全麻痺，体躯の筋力低下による座位障害で寝たきりとなる．一方で，運動障害が軽度のまま長期にわたり症状の進行がほとんどみられない患者も多い．基本的に生命予後は良好であるが，転倒による大腿骨頸部骨折，尿路感染の繰り返しや褥瘡は予後不良の因子として重要である．

C 診断と検査

診断は，緩徐進行性で膀胱直腸障害を伴う痙性対麻痺と，抗HTLV-1抗体が血清，髄液ともに陽性であることによってなされる．髄液では軽度の異常が認められることがあるが，髄液ネオプテリンは高く，活動性炎症を反映しているとされている．末梢血のプロウイルス量は，HTLV-1キャリアに比し高値で，その変動は病勢と連動している．画像診断では，脊髄MRIで通常は正常，重症例では胸髄を中心にびまん性に萎縮していることがあり，局所性病変はみられないことが多い．しかしながら，発症後間もない症例で，びまん性の腫大やT2強調画像での髄内の強信号像が報告されている．また，大脳MRIのT2強調画像で深部白質の異常信号像がみられる例がある．

D 治療の一般方針

1 治療方針の立て方

HAMに対する根本的な治療法は確立されていない．現時点では免疫調節療法が一般的である．すなわち，明らかな症状の進行がみられ，末梢血中プロウイルス高値，髄液ネオプテリン高値などの指標より炎症の活動期と判断される症例ではこの療法が必要とされている．免疫調節療法は，HAM患者において活性化HTLV-1感染リンパ球によって引き起こされた脊髄の慢性炎症を抑制することを目的としている．その治療戦略として，①活性化HTLV-1感染リンパ球の抑制，②脊髄へのリンパ球浸潤の阻止，③種々の炎症性サイトカインやリンパ球の接着因子の制御などがターゲットとして考えられている．HAMに対する治療の中で主体をなしているのが，ステロイドホルモン療法と抗ウイルス効果も併せ持つインターフェロンα療法である．一方，炎症の活動性がほとんどないと考えられる例では，痙性対麻痺や排尿障害に対する対症療法が行われ，継続的なリハビリテーションが推奨される．

2 薬物療法の実際

a) ステロイドホルモン療法

現在でも最も使用されている薬剤である．経口prednisolone（プレドニン®）はHAM患者の7割に有効とされている．活動期のHAM患者ではprednisolone 20～30 mgの隔日投与で改善がみられることが多い．しかしながら，骨粗鬆症，糖尿病，感染症などの副作用のため長期連用が難しく，中止によりしばしば明らかな再燃がみられている．進行性のHAM患者に副腎皮質ステロイドホルモン大量投与（ソル・メドロール®）を500～1,000 mg/日，3～5日連日投与が有効な場合もある．

b) インターフェロンα療法

HAMに対して唯一医療保険適用となっている薬剤である．インターフェロンα（スミフェロン®）は免疫調整作用に加えて抗ウイルス効果を期待して，スミフェロン®の多施設無作為抽出二重盲検法による治験が行われ，HAMに対する効能が2001年1月より保険適用となっている．HAM患者の6～7割に有効とされているが，ステロイドホルモンより効果は劣る．スミフェロン® 300万単位を筋注または皮下注で28日間連日投与し，引き続いて週2～3回投与に移行するか，当初より週2～3回投与を継続する方法が試みられている．この治療でもやはり，副作用に十分注意する必要がある．発熱やうつ状態による長期間の活動性低下は運動機能の低下につながる．

3 その他の治療法

非活動期の治療は痙縮や排尿障害，便秘に対する対症的な薬物療法やリハビリテーションが重要で，腰帯筋・傍脊柱筋の筋力増強やアキレス腱の伸張により，歩行の改善が得られる．間欠自己導尿の導入により外出への不安解消や夜間頻尿による不眠の改善など，ADLの改善が期待される．

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4

Host Immune System Abnormalities Among Patients with Human T-Lymphotropic Virus Type 1 (HTLV-1)-Associated Disorders

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1. Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) is a human retrovirus that causes persistent infection in the host. While most infected persons remain asymptomatic carriers (ACs), 3–5% develop a T-cell malignancy termed adult T-cell leukemia (ATL) (Uchiyama et al., 1977), and another 0.25–3% develop a chronic progressive inflammatory neurologic disease known as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) (Gessain et al., 1985; Osame et al. 1986). Although HTLV-1-associated disorders have been extensively studied, the exact mechanism by which they are induced by HTLV-1 is not completely understood. The proviral load of HTLV-1 could contribute to the development of these disorders, since the circulating number of HTLV-1-infected T cells in the peripheral blood is associated with the risk of developing HAM/TSP and ATL (Iwanaga et al., 2010; Nagai et al. 1998). However, more detail on the precise immune mechanisms controlling HTLV-1-infected cells is still needed.

HTLV-1 preferentially infects $CD4^+$ T cells, the central regulators of the acquired immune system (Richardson et al., 1990). This is known to induce a variety of abnormalities, such as proliferation, cellular activation, and proinflammatory changes (Boxus et al., 2009; Satou et al., 2010; Yamano et al. 2009). These abnormalities, in turn, may deregulate the balance of the host immune system.

HTLV-1 also causes abnormalities among uninfected immune cells. Patients with HTLV-1-associated disorders demonstrate abnormalities in both the amount and function of CD8+ cytotoxic T lymphocytes (CTL), an important component of host immune response against HTLV-1 (Bangham 2009; Kannagi et al., 2011; Matsuura et al., 2010). Patients with ATL and HAM/TSP may also experience reductions in the amount and efficacy of cellular components of innate immunity, which is vital in regulating the immune response against general viral infections and cancers (Azakami et al., 2009; Matsuura et al., 2010). In this chapter, we have summarized the host immune system abnormalities that are associated with HTLV-1 infection.

2. Abnormality of HTLV-1-infected $CD4^+$ T cells

2.1 $CD4^+CD25^+CCR4^+$ T Cells are a major reservoir of HTLV-1-infected T cells, which increase in HAM/TSP and ATL patients

HTLV-1 mainly infects $CD4^+$ T helper (Th) cells, which play a central role in adaptive immune responses (Richardson et al., 1990). $CD4^+$ Th cells recruit and activate other immune cells, including B cells, CD8 T cells, macrophages, mast cells, neutrophils, eosinophils, and basophils (Zhu et al., 2010). Based on their function, their pattern of cytokine secretion, and their expression of specific transcription factors and chemokine receptors, $CD4^+$ Th cells, differentiated from naïve $CD4^+$ T cells, are classified into 4 major lineages: Th1, Th2, Th17, and T regulatory (Treg) cells. To understand the effects of HTLV-1 infection on the function of CD4 Th cells, it is necessary to know which Th population HTLV-1 infects.

It was recently shown that the chemokine receptor CCR4 is expressed on HTLV-1-infected leukemia cells in ATL patients (Yoshie et al., 2002). CCR4 is selectively expressed on suppressive T cell subsets, such as Treg and Th2 cells, in HTLV-1-seronegative healthy individuals (Yoshie et al., 2001). Using molecular and immunological techniques, we also demonstrated that $CD4^+CD25^+CCR4^+$ T cells were the predominant viral reservoir in both ACs and HAM/TSP patients, and that this T cell subset was increased in HAM/TSP patients (Yamano et al., 2009). Thus, $CD4^+CD25^+CCR4^+$ T cells are a major population of HTLV-1-infected T cells, which increase in number in both HAM/TSP and ATL patients.

The molecular mechanism of HTLV-1 tropism to CCR4 expressing $CD4^+$ T cells was recently uncovered (Hieshima et al., 2008). HTLV-1 Tax, a transcriptional regulator encoded by the HTLV-1 genome, does not induce expression of CCR4, but it does induce expression of CCL22, the ligand for CCR4. Because HTLV-1-infected T cells selectively interact with $CCR4^+CD4^+$ T cells, this results in preferential transmission of HTLV-1 to $CCR4^+CD4^+$ T cells.

2.2 Differences in the fates of $CD4^+CD25^+CCR4^+$ T cells in HAM/TSP and ATL patients

Among $CD4^+$ Th cells, the major reservoir of HTLV-1 is $CD4^+CD25^+CCR4^+$ T cells, including suppressive T cell subsets such as Treg and Th2 under healthy conditions. The exact mechanism by which HTLV-1 induces the deregulation of the host immune system is not completely understood. However, the recent discovery of Treg cells has provided new opportunities and generated increased interest in this issue. In healthy individuals, Treg cells suppress the proliferation of, and cytokine production by, pathogenic T cells, and thereby plays a key role in the maintenance of immune system homeostasis (Sakaguchi et al., 1995). Treg cells can be identified *ex vivo* by the intracellular expression of the transcriptional regulator Foxp3 (Hori et al., 2003), which is critical for the development and function of Treg cells in both mice and humans.

Significant reductions in Foxp3 expression and/or Treg cell function have been observed in several human autoimmune diseases (Sakaguchi et al., 2008), suggesting that defects in Foxp3 expression and/or Treg function may precipitate the loss of immunologic tolerance. Recently, significant reductions in Foxp3 expression and Treg cell function have also been observed in $CD4^+CD25^+$ T cells and/or $CD4^+CD25^+CCR4^+$ T cells from patients with HAM/TSP (Hayashi et al., 2008; Michaelsson et al., 2008; Oh et al., 2006; Ramirez et al., 2010; Yamano et al., 2005). Furthermore, decreased expression levels of the Treg-associated immune suppressive molecules CTLA-4 and GITR were also observed on $CD4^+CD25^+$ T cells in HAM/TSP patients (Ramirez et al., 2010; Yamano et al., 2005). Notably, overexpression of HTLV-1 *tax* can reduce

Foxp3 expression and inhibit the suppressive function of Treg cells (Yamano et al., 2005). Furthermore, because of a Tax-induced defect in TGF-β signaling, HAM/TSP patients experience reductions in Foxp3 expression and impairment of Treg function (Grant et al., 2008). Moreover, a significant reduction in $CD4^+CD25^+Foxp3^+$ Treg cells was demonstrated in HTLV-1-*tax*-expressing transgenic mice, which develop an inflammatory arthropathy (Ohsugi et al., 2011). Thus, HAM/TSP patients display a decreased ratio of $Foxp3^+$ Treg cells within HTLV-1-infected $CD4^+CD25^+CCR4^+$ T cells.

Importantly, a more detailed flow cytometric analysis of Foxp3 expression in $CD4^+CD25^+CCR4^+$ T cells demonstrated that the frequency of "$Foxp3^-$ population" was extraordinary high in HAM/TSP patients (Yamano et al., 2009). Moreover, an analysis of proinflammatory cytokine expression in this $Foxp3^-CD4^+CD25^+CCR4^+$ T cell subset demonstrated that these cells were unique because, in healthy individuals, they produced multiple proinflammatory cytokines such as IL-2, IL-17, and few interferon (IFN)-γ, while $Foxp3^+CD4^+CD25^+CCR4^+$ T cells (Treg cells) did not. Furthermore, HAM/TSP patients were found to exhibit only a few $Foxp3^+CD4^+CD25^+CCR4^+$ T cells that did not produce such cytokines. Rather, these patients had an increased number of $Foxp3^-CD4^+CD25^+CCR4^+$ T cells, which were found to overproduce IFN-γ. Further, given the increase of clinical diseases and severity of HAM/TSP observed in these patients, it appears likely that the frequency of these IFN-γ-producing $Foxp3^-CD4^+CD25^+CCR4^+$ T cells may have a functional consequence (Yamano et al., 2009). Thus, while the $CD4^+CD25^+CCR4^+$ T cell population in healthy patients mainly comprises suppressive T cell subsets such as Treg and Th2, HAM/TSP patients possess an increased proportion of IFN-γ-producing $Foxp3^-CD4^+CD25^+CCR4^+$ T cells, which are rarely encountered in healthy individuals and lead to an overproduction of IFN-γ (Figure 1).

Although Foxp3 expression is decreased by $CD4^+CD25^+$ ($CCR4^+$) T cells in HAM/TSP patients (Hayashi et al., 2008; Michaelsson et al., 2008; Oh et al., 2006; Ramirez et al., 2010; Yamano et al., 2005), it is increased by $CD4^+CD25^+(CCR4^+)$ ATL cells in most ATL patients (Karube et al., 2004; Roncador et al., 2005) (Figure 1). Therefore, it has been hypothesized that ATL cells may be derived from Treg cells (Kohno et al., 2005). Interestingly, some ATL cells exhibit immunosuppressive functions similar to those of Treg cells, which may contribute to the cellular immunodeficiency that has been clinically observed in ATL patients (Chen et al., 2006; Kohno et al., 2005; Matsubar et al., 2006); however, some ATL cells lose this regulatory function (Shimauchi et al., 2008).

2.3 HTLV-1 may induce plasticity of Foxp3+ cells into exFoxp3+ cell

In HTLV-1-seronegative healthy individuals, $CD4^+CD25^+CCR4^+$ T cells mainly include suppressive T cell subsets such as Treg and Th2 (Yoshie et al., 2001). In ATL patients, most of this subset develops leukemogenesis by maintaining the $Foxp3^+$ Treg phenotype (Figure 1). However, as mentioned above, T cells of this subset become Th1-like cells that overproduce IFN-γ in HAM/TSP patients (Figure 1). Since HTLV-1 may preferentially transmit to $CCR4^+CD4^+$ T cells, these findings suggest that HTLV-1 may intracellularly induce T-cell plasticity of Treg cells into IFN-γ^+ T cells. Indeed, one recent report indicated that loss of Foxp3 in Treg cells and acquisition of IFN-γ may result in the conversion of suppressor T cells into highly autoaggressive lymphocytes (exFoxp3$^+$ cells), which can favor the development of autoimmune conditions (Tsuji et al., 2009; Zhou et al., 2009). Importantly, Toulza et al. (2008) demonstrated that the rate of CTL-mediated lysis was

negatively correlated with the number of HTLV-1-Tax- $CD4^+Foxp3^+$ cells, but not with the number of Tax^+ $CD4^+Foxp3^+$ cells, suggesting that HTLV-1-infected Treg cells lose their regulatory function, while HTLV-1-uninfected Treg cells contribute substantially to immune control of HTLV-1 infection. Additionally, functional impairment of $CD4^+Foxp3^+$ Treg cells was observed in mice that were transgenic mice for the *HTLV-1 bZIP factor* (*HBZ*) gene, which encodes the minus strand of HTLV-1 (Satou et al., 2011). These findings support the hypothesis that HTLV-1 may be one of the exogenous retrovirus genes responsible for immune dysregulation through interference of $CD4^+CD25^+$ Treg cell function. This hypothesis is currently under investigation to elucidate the precise molecular mechanisms by which HTLV-1 influences the fate and function of $CD4^+CD25^+CCR4^+$ T cells, especially $Foxp3^+$ Treg cells.

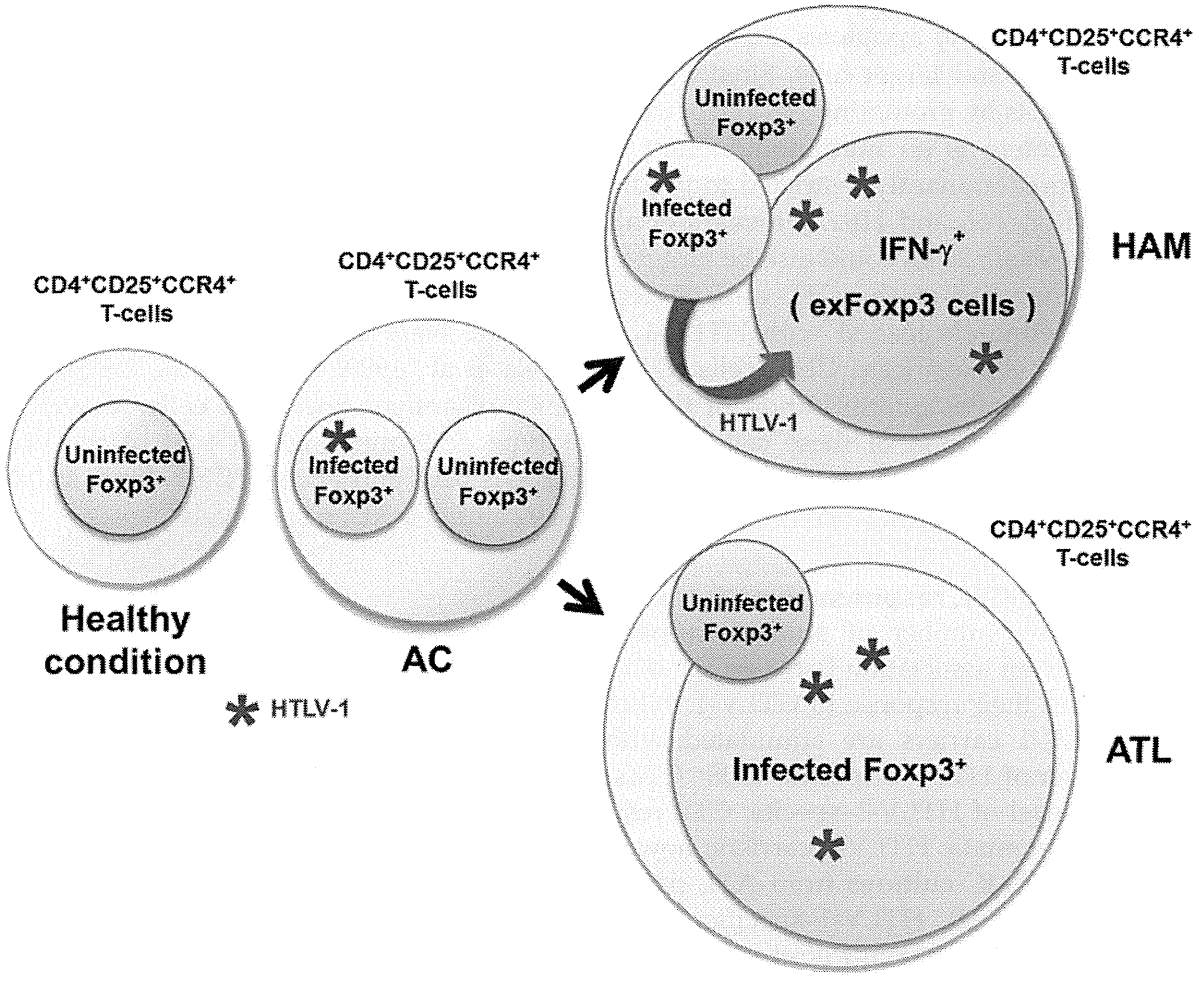

Fig. 1. Cellular components of $CD4^+CD25^+CCR4^+$ T cells in healthy individuals, asymptomatic carriers, ATL, and HAM/TSP patients.

3. Abnormality of cytotoxic T lymphocyte (CTL) response

$CD8^+$ Cytotoxic T lymphocyte (CTL) responses are an effective host defense system against all virus infections and malignancies. CTLs act by killing autologous cells that express viral

or cancer antigen in association with major histocompatibility complex (MHC) class I molecules and by suppressing viral replication and tumor development via IFN-γ secretion. Elucidating the role of HTLV-1–specific $CD8^+$ CTLs has been considered a priority issue in studies of host defense mechanisms involved in HTLV-1 infection (Bangham, 2008; Jacobson, 2002; Kannagi, 2007).

3.1 HTLV-1-specific cytotoxic T lymphocytes

T-cell receptors (TCR) on CTLs recognize peptide fragments derived from viral and tumor antigens that are presented on MHC class I molecules by antigen-presenting cells or virus-infected cells. After TCR binds to the peptide-MHC complex, CTLs are activated and fulfill an effector function. There are 3 main effector mechanisms by which the $CD8^+$ CTL kills virus-infected or tumor cells. One is to release perforin and granzymes. Perforin forms pores in the plasma membrane of the target cells, allowing entry of granzymes; caspases are then activated, leading to apoptosis. Apoptosis may also be induced via a Fas-FasL interaction between CTLs and target cells. Finally, $CD8^+$ cells can produce IFN-γ, which has indirect cytolytic effects by promoting NK cell activity and macrophage activation.

The Tax protein is an immunodominant antigen in HTLV-1 infections. Therefore, CTL activity is predominantly restricted to products of the HTLV-1 Tax gene, although HTLV-1 Env, Pol, Rof, Tof, and HBZ (Elovaara et al., 1993; Hilburn et al., 2011; Macnamara et al., 2010; Pique et al., 2000) could also be target proteins of HTLV-1-specific CTL. In a study that utilized properties of the CTL antigen recognition system, human MHC class I HLA-A2(*0201) tetramers loaded with HTLV-1 Tax peptide were used to detect HTLV-1 Tax specific HLA-A2-restricted $CD8^+$ cells (Bieganowska et al., 1999, Greten et al., 1998). This technique facilitates quantification of the frequency of antigen-specific T cells, as well as direct characterization of these cells. HLA genotype determines which part of the viral protein is presented as an antigen peptide. For HLA-A*0201 and HLA-A*2402, for example, the major epitopes are the Tax 11-19 and Tax 301-309 amino acids, respectively.

3.2 Abnormal CTL response in patients with ATL

An increasing number of studies in patients with HTLV-1-associated disorders have documented an association between the disorders and abnormalities in both the frequency of CTLs and their response to HTLV-1. When peripheral blood mononuclear cells (PBMCs) from HTLV-1 carriers are stimulated with autologous HTLV-1–infected cells *in vitro*, proliferation of HTLV-1-specific $CD8^+$ CTLs is often observed in the presence of IL-2. An increased level of HTLV-1–specific CTL responses occurs in all HAM/TSP patients and in some asymptomatic HTLV-1 carriers; however, HTLV-1–specific CTL responses are rarely induced in PBMC cultures from ATL patients (Jacobson et al., 1990; Kannagi et al., 1984, Parker et al., 1992). HTLV-1–specific CTLs are also present in ATL patients but do not expand sufficiently (Arnulf et al., 2004). Impairment of the HTLV-1 specific CTL response was observed in some individuals during the earlier stages of HTLV-1 infection (AC and smoldering ATL), as well as in advanced ATL patients (Shimizu et al., 2009). This observation suggests that the T-cell insufficiency in ATL patients is present prior to disease onset. In addition, a recent report indicated that, in comparison to ACs, ATL patients have a smaller and less diverse population of HTLV-1 specific $CD8^+$ T cells, as well as lower anti-HTLV-1 $CD8^+$ T cell expression of perforin and granzyme B (Kozako et al., 2006). Thus, the decreased number and functional impairment of CTLs might contribute to the onset and progression of ATL.

Furthermore, Tax-specific CTL responses were strongly activated in some ATL patients who achieved complete remission after hematopoietic stem cell transplantation (HSCT), but were not observed in the same patients before transplantation (Harashima et al., 2004). This suggests that HTLV-1-specific CTLs, including Tax-specific CTLs, play an important role in surveillance against HTLV-1 leukemogenesis.

3.3 Abnormal CTL response in patients with HAM/TSP

One of the most striking features of the adaptive immune system in HAM/TSP patients is the larger number of HTLV-1-specific $CD8^+$ CTLs (Elovaara et al., 1993; Greten et al., 1998; Jacobson et al., 1990; Kubota et al., 2002; Nagai et al., 2001a; Parker et al., 1992). While HTLV-1 specific CTLs are also detectable in the PBMC of ACs (Parker et al., 1992), the magnitude and frequency of these responses are clearly higher in patients with HAM/TSP, particularly in the CSF (Elovaara et al., 1993; Nagai et al. 2001a). In addition, the HTLV-1 proviral load of HAM/TSP patients may be 5- to 16-fold higher than that of ACs (Hashimoto et al., 1998; Kubota et al., 1993; Nagai et al., 1998). While some studies have found a positive correlation between the frequency of HTLV-1-specific $CD8^+$ T cells and HTLV-1 proviral load has been detected in PBMCs from HAM/TSP patients (Kubota et al., 2000, Nagai et al., 2001b, Yamano et al., 2002), this result is not ubiquitous (Wodarz et al., 2001). Thus, the cytolytic activity of CTLs, rather than their frequency, might be impaired in HAM/TSP patients.

There are some methods to measure CTL cytolytic activity. One is the sensitive CD107a mobilization assay, which quantifies the amount of lysosomal membrane protein LAMP-1 (CD107a) present on the CTL surface (CD107a) (Betts et al. 2003). Among studies that have used this method to evaluate CTL function, results are conflicting; while one reported that HTLV-1-specific CTLs of HAM/TSP patients had significantly lower CD107a staining than those of ACs (Sabouri et al., 2008), another study reported the opposite (Abdelbary et al., 2011). Furthermore, higher expression of CD107a/IFN-γ was induced by tax peptide stimulation in the $CD8^+$ T cells of HAM/TSP patients than in those of ACs (Enose-Akahata et al., 2008). Thus, it is not yet clear whether the cytolytic activity of HTLV-1-specific CTL in HAM/TSP patients is insufficient. However, these findings suggest that quantity of HTLV-1-infected cells is not determined by HTLV-1-specific CTL alone; additional factors, such as innate immunity and the proliferative ability of infected cells, must be relevant.

3.4 Pathogenic Role of CTL in HAM/TSP

In HAM/TSP patients, HTLV-1-specific $CD8^+$ CTL levels are extraordinarily high in peripheral blood, and even higher in cerebrospinal fluid (CSF) (Elovaara et al., 1993; Greten et al., 1998; Jacobson et al., 1990; Kubota et al., 2002; Parker et al., 1994; Nagai et al., 2001; Yamano et al., 2002). Immunohistochemical analysis of affected spinal cord lesions in early-stage HAM/TSP patients revealed the presence of infiltrating $CD4^+$ and $CD8^+$ lymphocytes, among which $CD8^+$ cells become increasingly dominant over the duration of the illness (Umehara et al., 1993). The expression of HLA class I antigens (Moore et al., 1989) and the existence of HTLV-1 specific $CD8^+$ CTLs have also been found in such lesions (Levin et al., 1997). In addition, the infiltration of $CD8^+$ CTLs in the affected spinal cord was characterized as positive for TIA-1 that is a marker of CTL (Umehara et al. 1994, Anderson et al. 1990). The number of TIA-1^+ cells was clearly related to the amount of the proviral DNA *in situ*, and the number of infiltrating $CD8^+$ cells appears to correlate with the presence of apoptotic cells.

Tax-specific $CD8^+$ CTL clones secrete various inflammatory cytokines, chemokines, and matrix metalloproteinases (MMP), such as IFN-γ, TNF-α, monocyte inflammatory protein (MIP)-1α, MIP-1β, interleukin(IL)-16, and MMP-9 (Biddison et al., 1997). TNF-α induces cytotoxic damage to endothelial cells, thus decreasing the integrity of the blood-brain barrier. It can also directly injure oligodendrocytes. MIP-1α and 1β can enhance transendothelial migration of lymphocytes into the central nervous system. IL-16 is a chemoattractant for $CD4^+$ cells, which are the major source of IL-2 required by IL-2 non-producer $CD8^+$ cells for proliferation. Therefore, HTLV-1-specific $CD8^+$ CTLs are an important source of proinflammatory soluble mediators that may contribute significantly to the pathogenesis of HAM/TSP. These observations continue to support the hypothesis that HTLV-1-specific $CD8^+$ CTLs are a major contributing factor in the immunopathogenesis of HAM/TSP.

4. Abnormality of innate immunity

Besides CTLs, there are several cell populations in the human immune system that have cytolytic activity against virus-infected cells, including natural killer (NK) cells, natural killer T (NKT) cells, and γδ T cells, which are cellular components of innate immunity. Dendritic cells (DCs) play an important role in the activation of these cell populations and CTLs. There is little evidence suggesting a role for γδ T cells in the pathogenesis of HTLV-1-associated disorders. Thus, this section focuses solely on the roles of DCs, NK cells, and NKT cells in HTLV-1-associated diseases, by comparing with the role of these cells in HIV-1 infection.

4.1 Dendritic cells and HTLV-1

Immature DCs are located in peripheral tissues and can effectively capture antigens, leading to their maturation via the expression of MHC class I/II and co-stimulatory molecules such as CD80, CD86, and CD40. Mature DCs are professional antigen-presenting cells that are uniquely able to prime naïve T cells. There are 2 main subsets of DCs: myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). These cells play important roles in the regulation of innate and adaptive immunity. mDCs can induce the activation of invariant NKT (iNKT) cells via surface expression of the CD1d/glycolipid complex. After antigen capture, pDCs secrete type 1 IFN, which induces the activation of NK cells and promotes the activation of iNKT cells by mDCs.
An *in vitro* study indicated that cell-free HTLV-1 effectively infects DCs, leading to the transmission and transformation of $CD4^+$ T cells (Jones et al. 2008). In addition to suggesting a mechanism for HTLV-1 transmission, this study also indicated that HTLV-1 infection of DCs plays a role in the pathogenesis of HTLV-1-associated disorders. In fact, HTLV-1-infected DCs are observed in the peripheral blood of HTLV-1-infected individuals (Hishizawa et al., 2004; Macatonia et al., 1992), and infected pDCs have an impaired ability to produce type I IFN (Azakami et al., 2009; Hishizawa et al., 2004). In addition, we recently reported that the frequency of mDCs and pDCs is significantly lower in patients with both HAM/TSP and ATL (Azakami et al., 2009). Cumulatively, these studies imply that decreases in the number and functionality of DCs interfere with innate immunity, thus leading to pathogenesis.

4.2 Natural killer cells and HTLV-1

NK cells are major components of the innate immune system and account for 10–15% of PBMCs in normal individuals. They have direct and indirect cytolytic activity against tumor

cells and virus-infected cells by producing perforins, granzymes, and IFN-γ. Human NK cells can be divided into 2 subsets on the basis of their cell-surface markers: $CD56^+CD16^+$ and $CD56^{bright}CD16^-$ NK cells. $CD56^+CD16^+$ NK cells are the major population of NK cells and have natural cytotoxic activity. $CD56^{bright}CD16^-$ NK cells are not cytotoxic but have the capacity to produce large amounts of IFN-γ upon activation. The activity of NK cells is regulated by a balance between positive and negative signals from different activating and inhibitory NK receptors. CD94/NKG2 receptor family is expressed on $CD8^+$ T cells and γδ T cells as well as NK cells, and is involved in the pathogenesis of HAM/TSP by modulating the activities of those cell populations (Saito et al. 2003, Mosley et al. 2005).
In both HIV-1- and HTLV-1-infected individuals, the number and function of NK cell subsets are impaired (Fortis et al., 2005). Multiple investigators have reported that the numbers of $CD56^+CD16^+$ NK cells in HAM/TSP and ATL patients are significantly lower than those observed in healthy controls (Azakami et al., 2009; Yu et al., 1991). Furthermore, NK cell activity was also lower in HAM/TSP patients than in healthy controls (Yu et al., 1991). When primary $CD4^+$ T cells are infected by HTLV-1, they can escape from NK cell-mediated cytotoxicity; HTLV-1 $p12^I$ downregulates the expression of intercellular adhesion molecule-1 (ICAM-1) and -2 on the surface of infected $CD4^+$ T cells, resulting in a reduced adherence of NK cells to HTLV-1-infected $CD4^+$ T cells (Banerjee et al., 2007).

4.3 Natural killer T cells and HTLV-1

Natural killer T (NKT) cells, a unique T cell subpopulation, constitute a subset of lymphocytes that share the features of innate and adaptive immune cells. Unlike conventional T cells, NKT cells express a TCR that recognizes glycolipids instead of protein antigens. Moreover, these cells share properties and receptors with NK cells. They rapidly produce granzymes and perforins upon stimulation. Among the $CD3^+$ T cells in human blood, 10–25% express NK cell surface molecules such as CD161, and these cells are classified as NKT cells. A small population of T cells within this NKT cell subset expresses a highly conserved Vα24Jα18 TCR chain that preferentially associates with Vβ11; these T cells are referred to as iNKT cells. Activation of human iNKT cells requires the presentation of glycolipids such as α-galactosylceramide (α-GalCer) on the MHC class I-like molecule CD1d. α-GalCer induces the rapid production of cytokines and potent antitumor and antipathogen responses by iNKT cells. $CD4^-$ iNKT cells preferentially induce the Th1 response and are more important than $CD4^+$ iNKT cells in controlling viral infection and cancer (Kim et al., 2002).
HIV-1-infected subjects have fewer iNKT cells in their peripheral blood than healthy donors (Sandberg et al., 2002; van der Vliet et al., 2002). The proliferative potential and INF-γ production of residual iNKT cells are impaired in HIV-1-infected individuals (Moll et al., 2009); likewise, patients with HTLV-1-associated disorders have a decreased frequency of iNKT cells in their peripheral blood (Azakami et al., 2009). Interestingly, in contrast to patterns observed in HIV-1 infections, HTLV-1 infection leads to preferential decreases of $CD4^-$ iNKT cells (Azakami et al., 2009). The production of perforin in iNKT cells is impaired in both ACs and HAM/TSP patients (Azakami et al., 2009). In addition, there is an inverse correlation between the frequency of iNKT cells and the HTLV-1 proviral load in the peripheral blood of HTLV-1-infected individuals (Azakami et al., 2009). Notably, *in vitro* stimulation of peripheral blood cells with α-GalCer leads to an increase in the number of iNKT cells and a subsequent decrease in the number of HTLV-1-infected T cells in samples

from ACs (Azakami et al., 2009). These results suggest that iNKT cells contribute to the immune defense against HTLV-1, and that iNKT cell depletion plays an important role in the pathogenesis of HAM/TSP and ATL.

5. Conclusion

Advances in our understanding of the immune system enhance studies of virus-host relationships. Although HTLV-1 causes 2 different diseases (ATL and HTM/TSP), $CD4^+CD25^+CCR4^+$ T cells are the common viral reservoir in both disorders. According to recent studies, however, characteristics of $CD4^+CD25^+CCR4^+$ T cells are completely different in the 2 diseases: Foxp3+ leukemic cells are found in ATL patients, while Foxp3- IFN-γ-producing cells are found in HAM/TSP patients. The host immune system plays a crucial role in controlling these HTLV-1-infected cells. HTLV-1-specific CTL is activated in patients with HAM/TSP, but not in those with ATL, indicating that impairment of acquired immunity is not universal. However, both ATL and HAM/TSP patients are known to experience decreases in innate immunity via the functional impairment of DCs, NK cells, and iNKT cells, as well as lower overall population numbers of these cell types. These conditions may contribute to inadequate viral control and play an important role in the pathogenesis of HTLV-1-associated disorders.

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