Words & terms

核上性 〔288頁〕
脳神経系において，大脳皮質から脳幹の脳神経細胞に至るまでを核上性（上位）ニューロン，脳幹の神経細胞から末梢を核下性（下位）ニューロンという．

他人の手徴候 〔288頁〕
alien hand signともいう．自分の腕が勝手に動き自分で制御できず，視覚情報なしでは自分の腕が自分のものとは認識できない症状（19頁）．

拮抗性失行 〔288頁〕
企図された一方の手の運動に対し，反対側の手が患者の意思に反して妨害的に働き，運動が中断するか，行為が完遂できない状態（19頁）．

非定型抗精神病薬
D2受容体の他に，セロトニン（5-HT_2）受容体なども遮断するため，錐体外路症状が現れにくくなった抗精神病薬．リスペリドン，オランザピンなどがある．

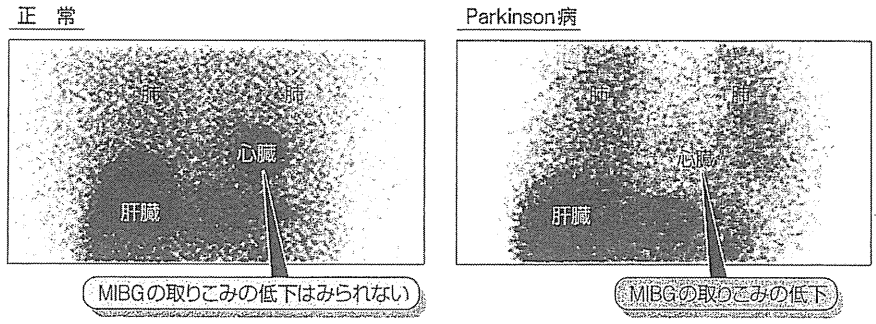
von Economo脳炎 〔287頁〕
嗜眠性脳炎，流行性脳炎ともいう．1920年前後に世界的に流行し，ウイルス感染が疑われたが同定されていない．傾眠，眼筋麻痺，せん妄，錐体外路症状などがみられ，脳炎の後遺症としてParkinson症候群を呈する．現在ではほとんどみられない．

最近注目の診断技術

MIBG心筋シンチグラフィ

- MIBGは生体内でノルエピネフリンと同様の働きをする物質であり，交感神経終末に取りこまれ，貯蔵，放出される．
- 自律神経障害（糖尿病性ニューロパチーなど）では，MIBGの取りこみの低下がみられる．
- Parkinson病では，発症早期から（自律神経障害を認めていなくても）MIBGの取りこみの低下が高率にみられることが知られている．
- 一方，健常人やParkinson症候群（287頁）ではMIBGの取りこみの低下はほとんどみられない．
- このため，MIBG心筋シンチグラフィは，Parkinson病の補助診断として，またParkinson症候群との鑑別のための検査として有用である．

MIBG心筋シンチグラフィ



- 例外として，家族性Parkinson病の一部では，MIBGの取りこみ低下を認めないこともある．また，Lewy小体型認知症ではMIBGの取りこみ低下がみられる．

パーキンソニズム以外の症状も多彩

変性疾患によるParkinson症候群

- Parkinson病以外でパーキンソニズムをきたす変性疾患としては，進行性核上性麻痺，皮質基底核変性症および線条体黒質変性症（MSA-P〔296頁〕）などが挙げられる．
- これらは大脳基底核を中心とした脳の変性により，パーキンソニズムをきたすと考えられている．

	進行性核上性麻痺	大脳皮質基底核変性症	線条体黒質変性症（MSA-P）
特徴的な症状	パーキンソニズム ＋ ❶項筋の緊張亢進（頭部背屈） ❷核上性外眼筋麻痺* ❸偽性球麻痺 ❹認知症	パーキンソニズム ＋ ❶大脳皮質徴候（肢節運動失行，構成失行，他人の手徴候〔19頁〕，拮抗性失行など） ❷不随意運動（ジストニア，ミオクローヌス） ❸認知症	パーキンソニズム ＋ ❶小脳症状 ❷自律神経症状
備　考	• ❶❷のため，Parkinson病と異なり，項部を後屈する姿勢となる．	• パーキンソニズムに加えて失行や認知症など多彩な症状をきたす．	• 多系統萎縮症（MSA）に分類される．
パーキンソニズムの特徴	• 安静時振戦は目立たず，筋強剛が前景に立つ．		
予　後	• 抗Parkinson病薬の効果は乏しく，Parkinson病よりも経過が早い． • 数年以内に寝たきりとなり，感染症，衰弱などで死に至る．		

*進行性核上性麻痺の外眼筋麻痺は，特に下方への眼球運動が制限され（下方注視障害），階段を降りるのが難しくなる．

- この他にパーキンソニズムをきたす変性疾患として，Lewy小体型認知症（350頁）がある．また，Alzheimer型認知症やHuntington病の一部でもみられることがある．

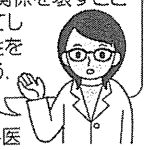
• MIBG：meta-iodobenzylguanidine • MIBG心筋シンチグラフィ：myocardial MIBG scintigraphy • 家族性Parkinson病：familial Parkinson disease • 核上性外眼筋麻痺：supranuclear external ophthalmoplegia • 偽性球麻痺：pseudobulbar palsy (paralysis) • 肢節運動失行：limb-kinetic apraxia • 構成障害（構成失行）：constructional apraxia • ジストニア：dystonia • ミオクローヌス：myoclonus • 下方注視障害：downward gaze palsy • 核上性：supranuclear

ドパミン受容体遮断薬が主

薬剤性パーキンソニズム

- パーキンソニズムを誘発しうる薬剤は以下の表のように多科にわたる.
- よって問診では服薬と合わせて，現在受診中の診療科を聴取することが重要である．原因薬物の投与中止を行えば改善する.

原因薬剤が推定できても，その説明の仕方には十分配慮しましょう．特に精神科で抗精神病薬の処方をされていた場合，患者さんへの伝え方が不適切だとその精神科医と患者さんとの信頼関係を壊すことになりかねず，その後の精神科的治療が難しくなってしまいます．患者さんにはその薬剤が原因である可能性を指摘しつつ，精神科医には薬剤の変更を相談しましょう.


神経内科医

	薬剤	一般名	代表的商品名	パーキンソニズムをきたす薬理作用
精神科	抗精神病薬	クロルプロマジン	ウインタミン，コントミン	• ドパミン受容体（D1，D2ともに）を遮断
		ハロペリドール	セレネース	• ドパミン受容体（主にD2）を遮断
		スルピリド	ドグマチール，アビリット	• ドパミン受容体（D2）を遮断
消化器科	抗潰瘍薬	スルピリド*	ドグマチール，アビリット	• ドパミン受容体（D2）を遮断
		メトクロプラミド	プリンペラン，エリーテン	• ドパミン受容体（D2）を遮断
循環器科	降圧薬	メチルドパ水和物（α-メチルドパ）	アルドメット	• ドパミン産生経路のドパ脱炭酸酵素（DDC）を阻害
		レセルピン	アポプロン	• 線条体でのドパミンの遊離・放出を促進させることでドパミンを枯渇させるとともに，再取りこみをも阻害

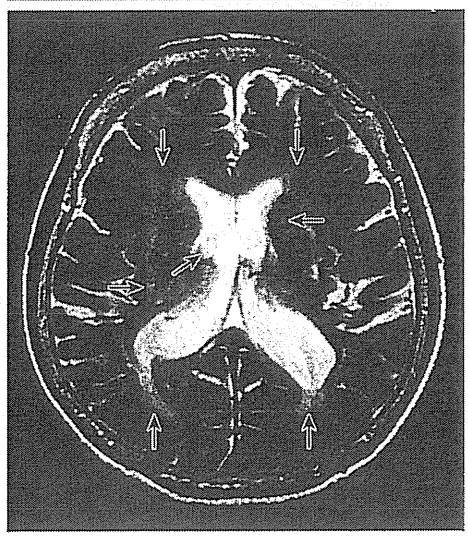
*スルピリドは抗精神病薬の一種だが，抗潰瘍薬としても用いられるため，薬剤性パーキンソニズムの原因となる頻度が最も多い.

画像検査は必須

脳血管性パーキンソニズム

- 大脳基底核や白質などの血行障害で出現するパーキンソニズムである.
- 具体的には，多発性脳梗塞（ラクナ梗塞〔74頁〕），Binswanger（ビンスワンガー）病（349頁）が挙げられる.

頭部MRI（T2強調像）〔Binswanger病〕



- 大脳白質のびまん性高信号域（➔）と両側側脳室の拡大
- 軽度の大脳皮質の萎縮
- 両側大脳基底核に小梗塞（➔）

治　療

- 脳血管障害の危険因子の検索と治療.
- アスピリンによる脳血栓の予防.
- 症状緩和を目的とした抗Parkinson病薬の投与（効果は乏しい）.

大まかな違いをおさえる

Parkinson病と脳血管性パーキンソニズムの違い

	Parkinson病	脳血管性パーキンソニズム
安静時振戦	• 本症に特徴的にみられる.	• ほとんどない（動作時・姿勢時振戦はときにみられる）.
症状の左右差	• あり	• 目立たない.
歩行障害	• 前かがみで小刻みに歩く.	• 開脚して小刻みに歩く.
L-dopaの効果	• あり	• 少ない.
その他の特徴	• 錐体外路症状に加えて，自律神経症状，抑うつ，認知症がみられることがある.	• 下肢の症状（特に歩行障害）が強い. • 錐体路徴候，偽性球麻痺，認知症，尿失禁の合併がしばしばみられる.

• 拮抗性失行：diagonistic apraxia • von Economo脳炎：von Economo encephalitis • 薬剤性パーキンソニズム：drug-induced parkinsonism • クロルプロマジン：chlorpromazine • ハロペリドール：haloperidol • スルピリド：sulpiride • メトクロプラミド：metoclopramide • メチルドパ水和物：methyldopa hydrate • レセルピン：reserpine • ドパ脱炭酸酵素（DDC）：dopa decarboxylase • 脳血管性パーキンソニズム：arteriosclerotic parkinsonism • 多発性脳梗塞：multiple cerebral infarct

G10

Huntington病

監修
野元　正弘

intro.

多くは30～50歳で発症する常染色体優性遺伝疾患で，徐々に発症し進行する舞踏運動と認知症などの精神症状を主徴とする．特定疾患治療研究対象疾患である．白人における有病率は10万人あたり4～10人であるが，日本での有病率は100万人に1～4人（欧米の10分の1以下）で，まれな疾患である．

Words & terms

ハロペリドール
〔290頁〕
ドパミンD2受容体拮抗作用をもつ抗精神病薬．Huntington病には現在，抗ドパミン薬が（主として不随意運動改善に）用いられているが，種々の副作用があり，効果も長続きしない．

若年型Huntington病
〔290頁〕
若年発症（20歳以下）の場合，病初期から筋強剛を示すものが約1/3を占める．知能低下やけいれん発作などを伴い，進行が速いことが特徴である．

MINIMUM ESSENCE　Huntington disease

❶好発：30～50歳
❷数年の経過で，四肢に何かのしぐさをするような**素早い不随意運動**がみられる（“落ちつきがない”と表現される）．〈舞踏運動〉
❸徐々に**性格変化**，**認知症**，妄想，幻覚を伴うようになる．〈精神症状〉
❹同様の**家族歴**がある．〈常染色体優性遺伝〉
❺**頭部CT・MRIで，尾状核の萎縮を伴う側脳室の拡大**がみられる．
➡ Huntington病 と診断する．

治療 本質的治療法はなく，対症療法が主体．
1. 不随意運動には，**ハロペリドール**，**チアプリド**
2. 精神症状には，ハロペリドール，クロルプロマジンなどを試みる．
※L-dopaで増悪する（Parkinson病とは逆!!）．
※発症後15年ぐらいで感染症で死亡しやすい．

補足事項
- 本疾患は（浸透率がほぼ100％の）常染色体優性疾患で，triplet（トリプレット） repeat（リピート）病（267頁）の1つである．

舞踏様の不随意運動が特徴的 古典型の症状

- 本疾患の主要症状は不随意運動，性格（人格）変化，認知症であり，これら3つのいずれかから発症する．

- はじめは四肢遠位部（手足）を中心に不随意運動が現れる．
- 急に“落ち着きがなくなった”といわれる．
- 緩徐に進行し，性格変化や精神症状，認知症が現れ始める（易怒性，自発性や集中力の低下，妄想，幻覚など）．
- 舞踏運動は，次第に顔や全身にも出現する（口すぼめ，舌うち，しかめ面など）．
- 末期には寝たきりとなり無言無動状態に陥る．
- 発症後15～20年の経過で誤嚥性肺炎などにより死亡することが多い．

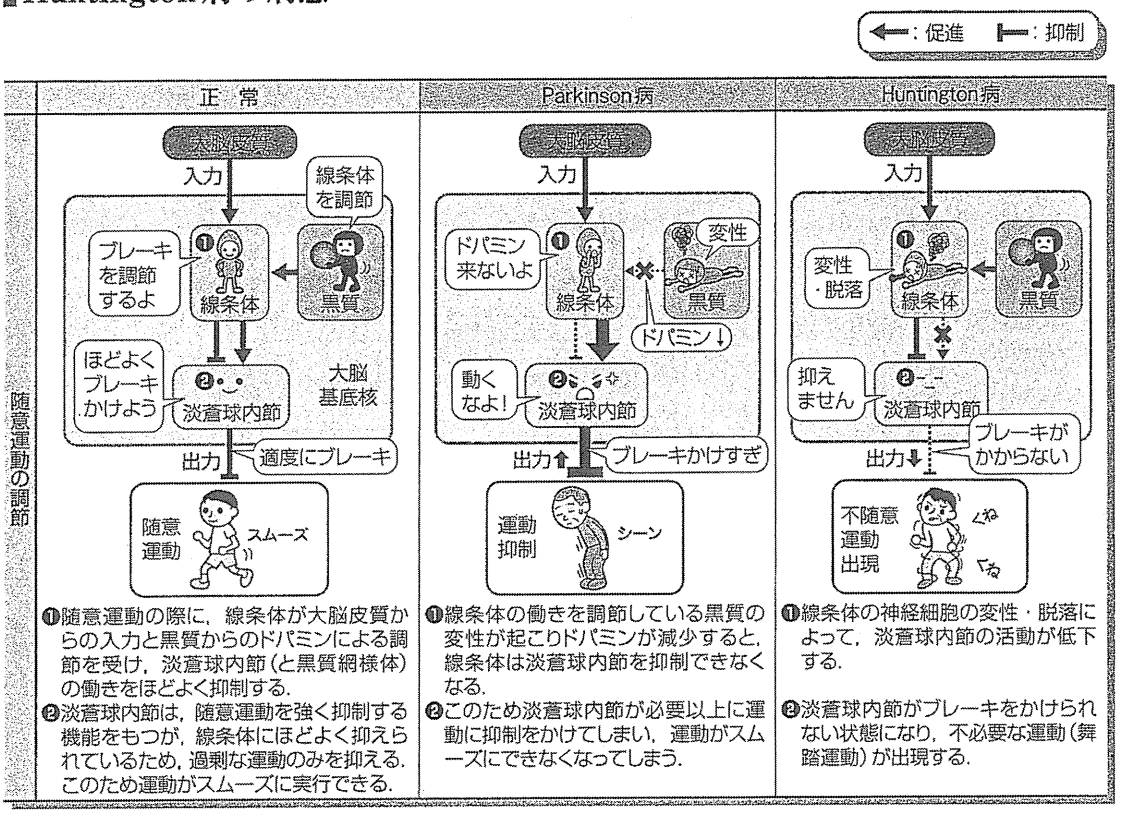
- 経過中にうつ症状や自殺企図がみられることもあり，注意が必要である．
- 発症年齢などによって症状に違いがあり，特に若年発症（若年型Huntington（ハンチントン）病）では病初期から筋強剛を示すものもみられる．上の図に示した古典型（30～50歳代の発症）でも，進行に伴い筋強剛を示すものもある．

- Huntington病（HD）：Huntington disease　- 舞踏運動：choreic movement　- 認知症：dementia　- 尾状核：caudate nucleus　- 側脳室：lateral ventricle　- 誤嚥性肺炎：aspiration pneumonia　- 若年型Huntington病：juvenile Huntington disease　- 筋強剛（固縮）：muscle rigidity　- ハロペリドール：haloperidol

線条体のニューロンが変性・脱落する

Huntington病の病態

• Huntington病では，線条体細胞の脱落がみられ，運動に対する抑制が効かなくなるため，舞踏運動が起こる．



❶随意運動の際に，線条体が大脳皮質からの入力と黒質からのドパミンによる調節を受け，淡蒼球内節（と黒質網様体）の働きをほどよく抑制する．
❷淡蒼球内節は，随意運動を強く抑制する機能をもつが，線条体にほどよく抑えられているため，過剰な運動のみを抑える．このため運動がスムーズに実行できる．

❶線条体の働きを調節している黒質の変性が起こりドパミンが減少すると，線条体は淡蒼球内節を抑制できなくなる．
❷このため淡蒼球内節が必要以上に運動に抑制をかけてしまい，運動がスムーズにできなくなってしまう．

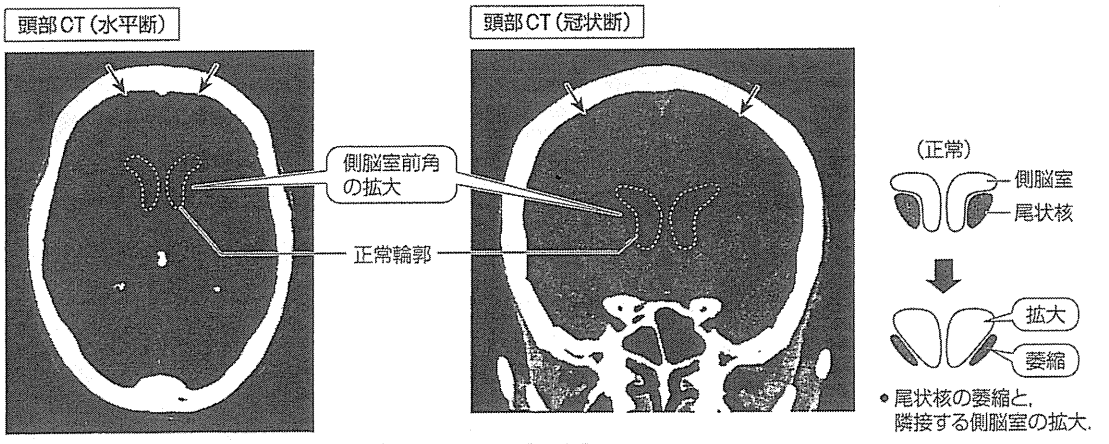
❶線条体の神経細胞の変性・脱落によって，淡蒼球内節の活動が低下する．
❷淡蒼球内節がブレーキをかけられない状態になり，不必要な運動（舞踏運動）が出現する．

• 線条体から淡蒼球への伝達経路には，直接路・間接路の2種類があり，Huntington病では主に間接路のニューロンが変性する．経路の詳細については286頁を参照のこと．

尾状核の萎縮と側脳室の拡大がみられる

CT所見

• Huntington病では線条体細胞の脱落を反映して，脳CT（またはMRI）画像で線条体，特に尾状核の萎縮と側脳室の拡大を認める．



• 尾状核の萎縮と，隣接する側脳室の拡大．

• 進行に伴って，大脳皮質（前頭葉）の萎縮（➔）もみられるようになる．

• 線条体：corpus striatum

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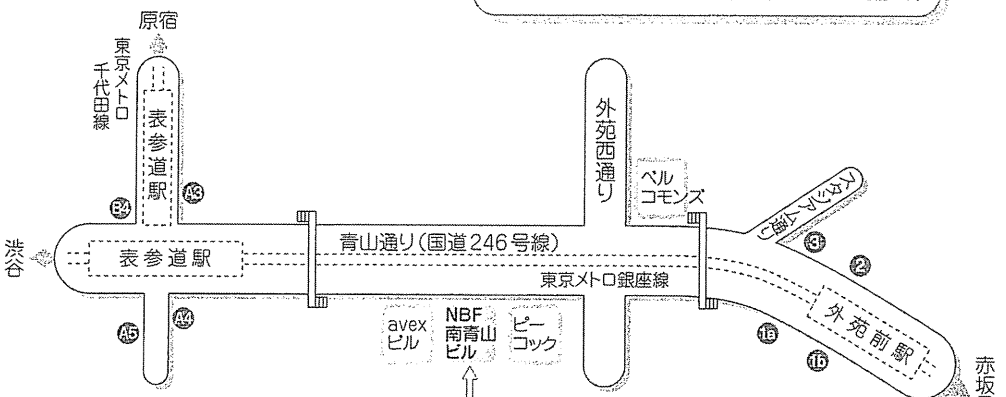

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病気がみえる vol.7

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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.

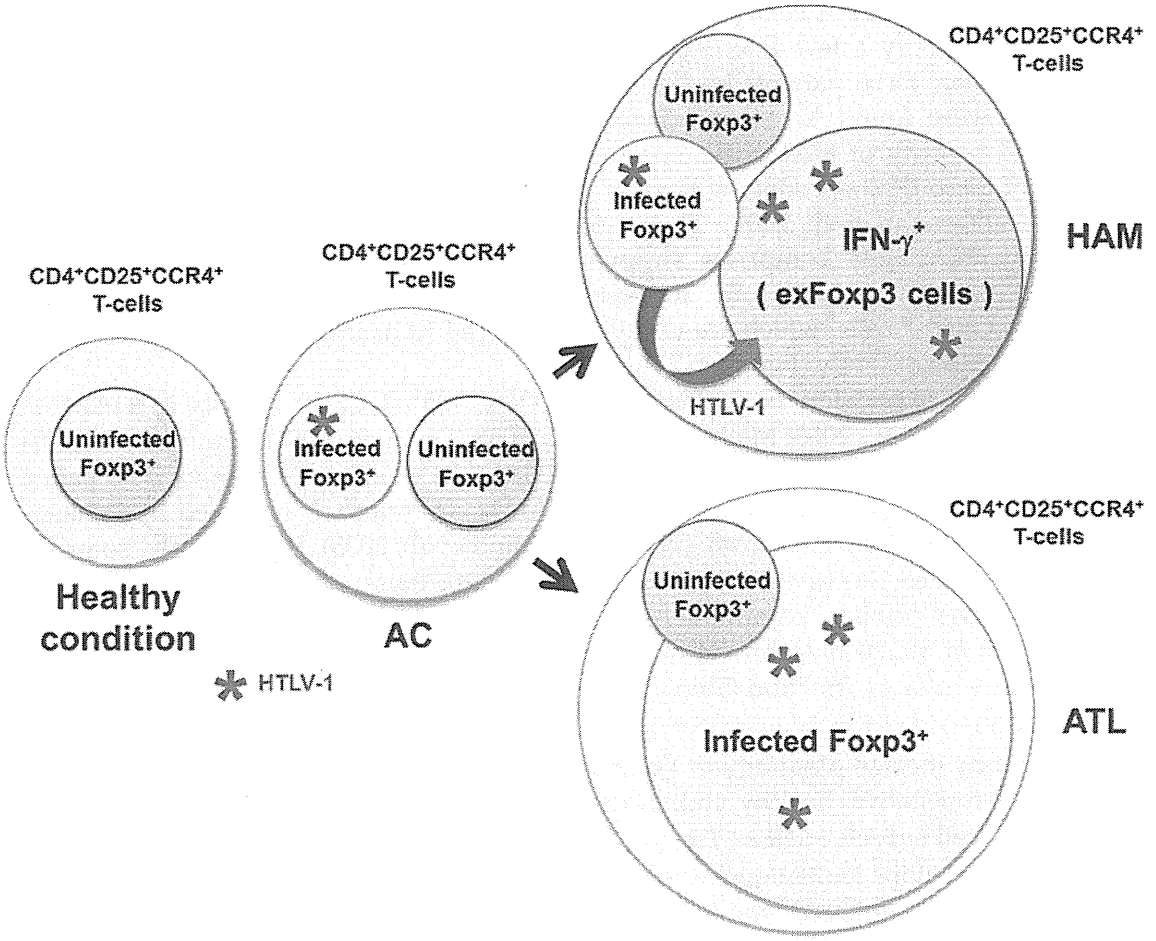

Fig. 1. Cellular components of CD4$^+$CD25$^+$CCR4$^+$ T cells in healthy individuals, asymptomatic carriers, ATL, and HAM/TSP patients.

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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