2つのIGRAでは「判定保留」の意味も異なるなど，違いを認識する必要がある。両者とも生きた細胞を扱うので，検体の扱いを含めた精度管理が重要である。

不適切な治療や患者管理は耐性菌の排出を増加させる可能性がある。耐性結核菌は10種類ある抗結核薬のいずれかに耐性の結核菌を指すが，最も強力な治療薬であるINHとRFPの両剤に耐性である耐性菌による結核を多剤耐性結核(multidrug-resistant tuberculosis：MDR-TB)という。MDR-TBの治療薬としてデラマニドが承認された。しかし，デラマニドの使用については日本結核病学会治療委員会が使用指針を出すことになっている。安易な使用により耐性化をもたらしてはならないので，使用には制限が設けられる。

IGRAについては本誌の別項を参照されたい。

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Memorial Lecture by Imamura Award Winner

# STUDY OF TUBERCULOSIS IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Hideaki NAGAI

**Abstract** The research on tuberculosis (TB) comorbid with human immunodeficiency virus infections (HIV/TB), for which this prize was awarded, began with the author's experience with Japan's first HIV/TB case in 1992. In 1997, the clinical characteristics of six HIV/TB cases were presented in the *Japanese Journal of Thoracic Diseases*. In 2001, the author published a paper in *Kekkaku* on the anti-HIV antibody positive rate of TB patients. As part of a research team with the Japanese Ministry of Health, Labour and Welfare (2011–2013), the author surveyed the HIV/TB patients in the National Hospital Organization, and found a more or less unchanging mean 0.39% HIV-positive rate among TB patients. Among these TB cases, 2.1% were multidrug-resistant TB. In 2007, the results of QuantiFERON®-TB-2G (QFT-2G) HIV/TB analysis were reported in *Kekkaku*, showing the usefulness of QFT-2G in immunosuppression cases. Positive rates obtained with QFT-2G and QuantiFERON®-TB Gold (QFT-3G) declined when the peripheral blood lymphocyte count decreased, thought to be a result of QFT's whole-blood collection methods. The author further studied the usefulness of interferon-gamma release assays (IGRAs) in HIV/TB with another health ministry research team (2009–2011). Enzyme-linked immunospot assay and QFT-3G were compared, which yielded better sensitivity and fewer indeterminate cases with the former. Periodic IGRAs were performed in IGRA-positive patients. Ten such cases (2 received isoniazid) were observed for more than 3 years, but none developed TB; however, IGRA values fluctuated during the observation period. It seems highly likely that immune function recovery through antiretroviral therapy lowered the risk of developing active TB. The author further examined the therapeutic interaction of rifampicin with anti-HIV drugs, confirming the feasibility of combining efavirenz and raltegravir. These results were presented at the annual meeting of the Japanese Society for Tuberculosis in Tokyo in 2012. The author intends to continue research with the hope of reducing HIV/TB incidence and improving prognosis.

**Key words**: Human immunodeficiency virus, Acquired immune deficiency syndrome, Tuberculosis, Interferon-gamma release assay, Multidrug-resistant tuberculosis, Efavirenz, Raltegravir

## Introduction

The risk of developing active tuberculosis (TB) increases in many immunodeficient states but is highest in cases of human immunodeficiency (HIV) infection, which involve a marked decline in cellular immunity.

Japan's TB prevalence has declined to 16.1 cases per 100,000 people (2013); however, among other Western nations, prevalence is no more than five cases per 100,000 people, meaning TB is still moderately prevalent in Japan. The number of HIV/AIDS patients in Japan increased until 2008, eventually exceeding 1,500 new cases per year. Growth plateaued in 2009 but rose again in 2013 to the second-highest number of reported cases ever. In this environment, the number of comorbid HIV/TB cases appears unlikely to decrease.

The author treated Japan's first case of HIV/TB at Tokyo National Hospital in 1992[1]. By 1997, the author's team reported a summary of six cases[2], and, to date, the author has experienced 85 HIV/TB cases. Since that initial case, the author has engaged in a variety of research on HIV/TB. The main findings are described below.

### 1. Surveying changes in HIV-positive rates among TB patients in Japan

The number of HIV/TB patients seen at Tokyo National Hospital has increased yearly since 1992. In most cases, an HIV test is performed if the TB is miliary or nonspecific, but some cases of classical pulmonary TB are found to be HIV-positive purely by chance. Thus, to examine the true extent of HIV-positivity among TB patients, we performed HIV tests on

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all consenting TB patients for 2 years starting in January 1998[3]. In all, HIV tests were performed on 164 TB patients (4 HIV-positive) in 1998 and on 149 patients (6 HIV-positive) in 1999, amounting to a 3.2% HIV-positive rate for the 2 years. Typically not suspected of being HIV-positive, only 1.0% of classical pulmonary TB cases were positive for HIV, but miliary TB cases exhibited a high HIV-positive rate of 28.6%. As TB patients in the Tokyo area may have a high rate of HIV infection, it is important to test TB patients for HIV so infections can be discovered and treatment initiated earlier.

We also conducted fact-finding surveys of National Hospital Organization hospitals nationwide regarding HIV/TB and multidrug-resistant TB (MDR-TB) from 2007 to 2012[4]. Little variation was seen in HIV-positive rates among TB patients, ranging from 0.29% to 0.46% (mean 0.39%) (Table). There were 96 cases of HIV/TB in total, but 82 (85.4%) of these were concentrated in the major urban centers of Tokyo, Osaka, and Nagoya. These regions combined had a 0.91% HIV-positive rate, higher than other, more rural regions. Accordingly, we recommended promoting HIV screening of TB patients in major urban areas. The male-female ratio of the HIV/TB patients was 18:1, and patients' median age was 43 years. In 56% of cases, HIV positivity was discovered owing to TB onset. The mean CD4 count was 156/$\mu$L, with many cases of reduced immune function. There were 48 cases of pulmonary TB, and 39 cases of extrapulmonary TB (25 of which were miliary TB). Side effects due to antitubercular agents were common, occurring in 53 of 83 cases (63.9%). While being treated for TB, 42 patients began antiretroviral therapy (ART). Immune reconstitution inflammatory syndrome was observed in 16 of the 26 patients (62%) who began ART within 8 weeks of starting TB therapy. All seven patients who began ART within 4 weeks of starting TB therapy developed the syndrome. There were two cases (2.1%) of MDR-TB, of which one patient was a foreign national. No cases of MDR-TB have been found since 2009, so there appears to be no increasing trend.

## 2. The usefulness of interferon-gamma release assays (IGRAs) in HIV/TB

The risk of TB infection is extremely high in cases of HIV infection. In recent years, IGRAs have been more frequently used for diagnosing TB infection than the tuberculin skin test (TST). Forms of IGRAs include QuantiFERON®-TB-2G (QFT-2G), QuantiFERON®-TB Gold (QFT-3G), and T-SPOT®TB (T-SPOT); the latter two are currently in use. In 2006, the QFT-2G was the first to be put to use. It has superior sensitivity and specificity, but in cases of HIV infection with markedly reduced cellular immunity, we expected sensitivity to decrease and the number of indeterminate cases to increase. To examine this assumption, we studied the usefulness of QFT-2G in cases of HIV infection[5]. We examined the QFT-2G results, CD4 count, and the TST results in known cases of HIV/TB. In 13 HIV/TB cases, QFT-2G's sensitivity was 76.9%, significantly higher than that of the TST (erythema 38.5%, induration 15.4%). The one indeterminate case had the lowest CD4 count (16/$\mu$L). Thus, we considered QFT-2G highly sensitive and sufficiently useful in HIV/TB, although HIV cases with very low CD4 count may return indeterminate results.

Next, QFT-2G and enzyme-linked immunospot assay (ELISPOT; this study used T-SPOT) were performed simultaneously on 230 pulmonary TB patients with positive tubercle bacilli cultures[6]. Sensitivity was compared based on the lymphocyte count. The overall positive rates were 74% for QFT-2G and 92% for ELISPOT, showing better sensitivity in the latter. In the group with a lymphocyte count of 1,000/$\mu$L or more, QFT-2G's positive rate was 88% and ELISPOT's was 97%. With a lymphocyte count of 500/$\mu$L or less, the positive rate with QFT-2G was 39% and 81% with ELISPOT, a marked decline in QFT-2G's accurate, conclusive positive rate (Fig. 1). A comparison of QFT-3G and ELISPOT produced similar results. That is, when lymphocyte count declined, the positive rate of QFT-3G declined, and the number of indeterminate cases increased (Fig. 2).

We used periodic, simultaneous tests to compare the positive rates of QFT-3G and ELISPOT in HIV-infected patients[7], performing QFT-3G as many as 50 times in 35 HIV-infected patients. Cases that were indeterminate or equivocal using QFT were not found with ELISPOT. There were 13 positive cases diagnosed with QFT versus 22 positive cases with ELISPOT. Patients were grouped per 100/$\mu$L of CD4 to compare QFT-3G and ELISPOT (Fig. 3). In all count groups, the ELISPOT positive rate was the same or higher. In the CD4 200/$\mu$L or less group, three cases were indeterminate by using QFT-3G. No cases were indeterminate by using ELISPOT, which found two negative cases and one positive case.

The results of the previous studies ultimately show that when the CD4 count declines, the sensitivity of QFT-3G decreases, and the number of indeterminate cases increases. The ELISPOT test was not influenced by CD4 count, indicating the effectiveness of this test in cases of reduced immune function.

**Table** Cases of TB patients with HIV infection in National Hospital Organization hospitals

| Year | No. of TB patients | No. of HIV-positive TB patients | No. of HIV-positive MDR-TB patients |
|---|---|---|---|
| 2007 | 4388 | 15 (0.34%) | 1 |
| 2008 | 4165 | 19 (0.46 ) | 1 |
| 2009 | 4129 | 18 (0.44 ) | 0 |
| 2010 | 4122 | 16 (0.39 ) | 0 |
| 2011 | 4091 | 18 (0.44 ) | 0 |
| 2012 | 3502 | 10 (0.29 ) | 0 |
| Total | 24397 | 96 (0.39 ) | 2 |

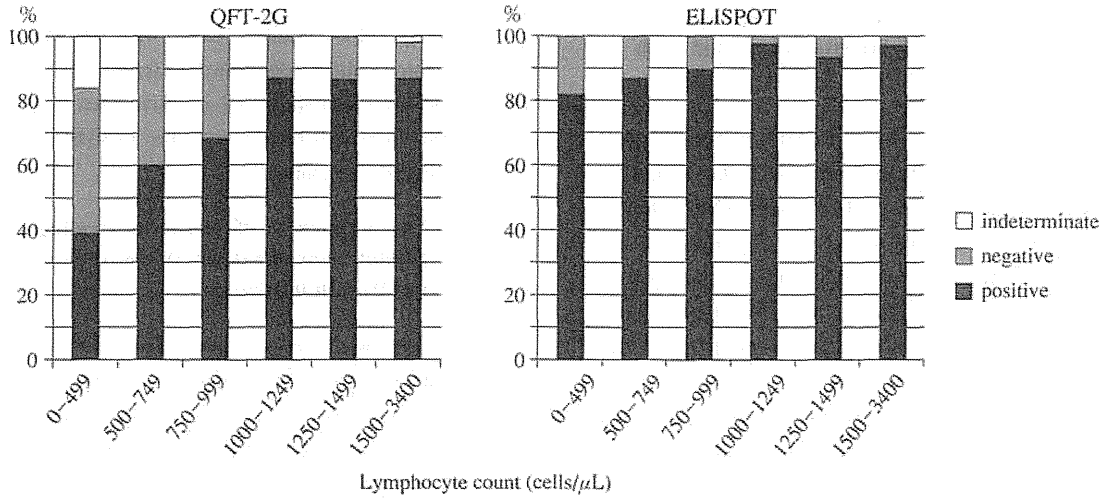


**Fig. 1** Influence of lymphocyte count on QFT-2G and ELISPOT performance in pulmonary TB patients

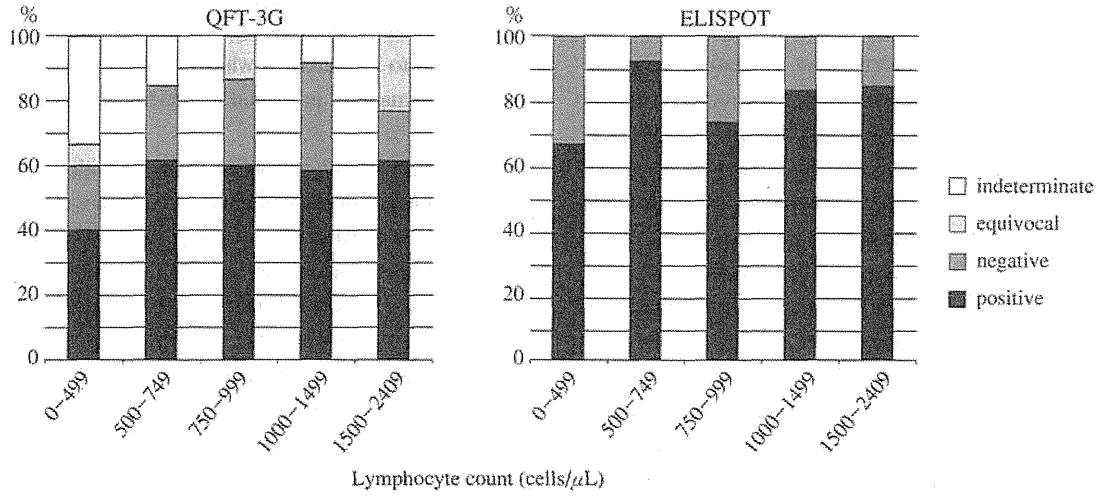


**Fig. 2** Influence of lymphocyte count on QFT-3G and ELISPOT performance in pulmonary TB patients

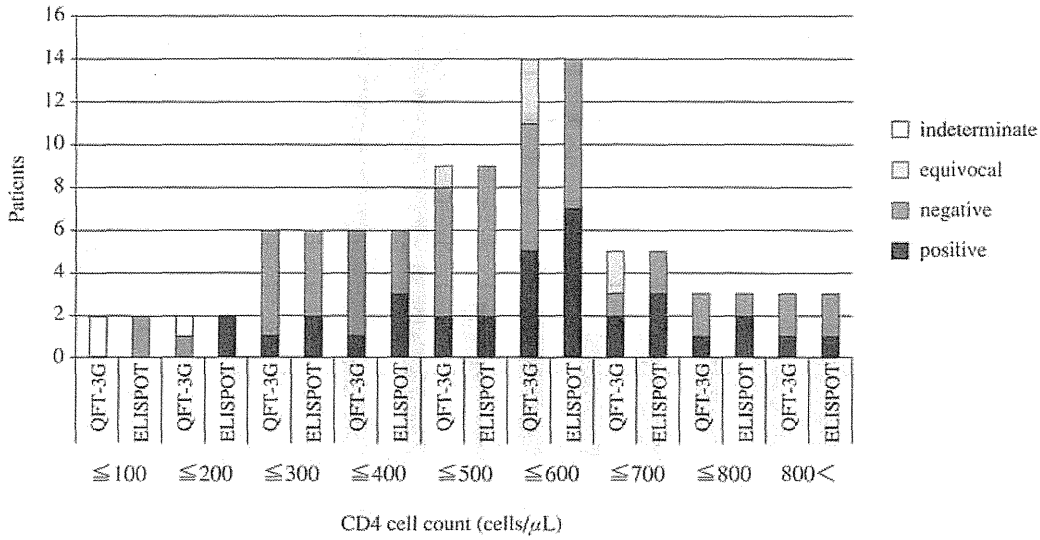


**Fig. 3** Influence of lymphocyte count on QFT-3G and ELISPOT performance in HIV/TB patients

### 3. Research on the early discovery and treatment of latent tuberculosis infection comorbid with HIV infection

As IGRAs can become positive in HIV-infected patients undergoing ART, we sought to determine if TB would unavoidably occur in the future, or if isoniazid (INH) administration could suppress developing active TB in such patients.

We observed six patients with no TB history with positive IGRA results for 3 to 5 years, but none developed TB. In addition, both total conversion to negative results and fluctuations between results were observed.

Of the patients cases with no history of TB that became IGRA-positive during observation, two patients received prophylactic treatment with INH and later became IGRA-negative. The other two patients, observed with no treatment, also became IGRA-negative. For the 3 to 4 years following conversion to IGRA positivity, TB failed to appear in any of these four patients.

Of the 10 aforementioned IGRA-positive cases with no TB history, active TB did not occur over at least 3 years of observation in the eight patients who did not receive INH. It has been reported that repeated IGRA testing can produce variable results regardless of the presence or absence of infection risk, and that this can occur over relatively short time periods[8]. Our hospital confirmed this phenomenon with case fluctuations from positive to negative. The reasons for these fluctuations are unclear, though factors such as instability of test methods, variable interpretations of results, and immune system changes unrelated to infection are thought to play a role. Owing to these IGRA variations, uniformly administering INH to IGRA-positive patients in periodic testing may be premature. In the above cases, it is highly likely that immune function recovery (CD4 $\geqq 200\,\mu$/L) due to ART lowered the risk of developing active TB.

Among ELISPOT-positive cases with TB history at our hospital, three patients continued to test positive for 7 to 13 years, and four patients tested negative after 8 to 15 years. Clearly, it takes substantial time for ELISPOT to become negative in HIV/TB patients.

### 4. Examination of efavirenz and raltegravir plasma concentrations during rifampicin (RFP) administration

Rifampicin (RFP) induces cytochrome P450 in the liver, which accelerates the metabolism of a variety of drugs and reduces their plasma concentration, including that of key anti-HIV drugs. This phenomenon can make anti-HIV drug selection difficult. The nonnucleoside reverse transcriptase inhibitor efavirenz (EFV) or the integrase inhibitor raltegravir (RAL) are often selected, as these key drugs are not easily affected by RFP. An effect is still present, however, as the plasma concentration of both drugs were shown to decline when combined with RFP. Thus, it was thought the doses of both drugs need to be increased when combined with RFP, but the pharmacodynamics in Japanese patients have not yet been clarified.

To help clarify this phenomenon, we examined the achievement of optimal doses in patients who received EFV or RAL combined with RFP by measuring EFV and RAL plasma concentration[9]. Plasma concentrations of EFV and RAL were measured in 15 patients with HIV/TB. Patients received RFP combined with EFV or RAL at our hospital from 2001 to 2011. There were 14 men and one woman (14 received EFV and one received RAL) who received 600 to 800 mg/day of EFV. Blood samples were taken, on average, 13.7 hours after EFV administration. The median plasma concentration of EFV was 1,696 ng/mL (900–12,685 ng/mL), which was

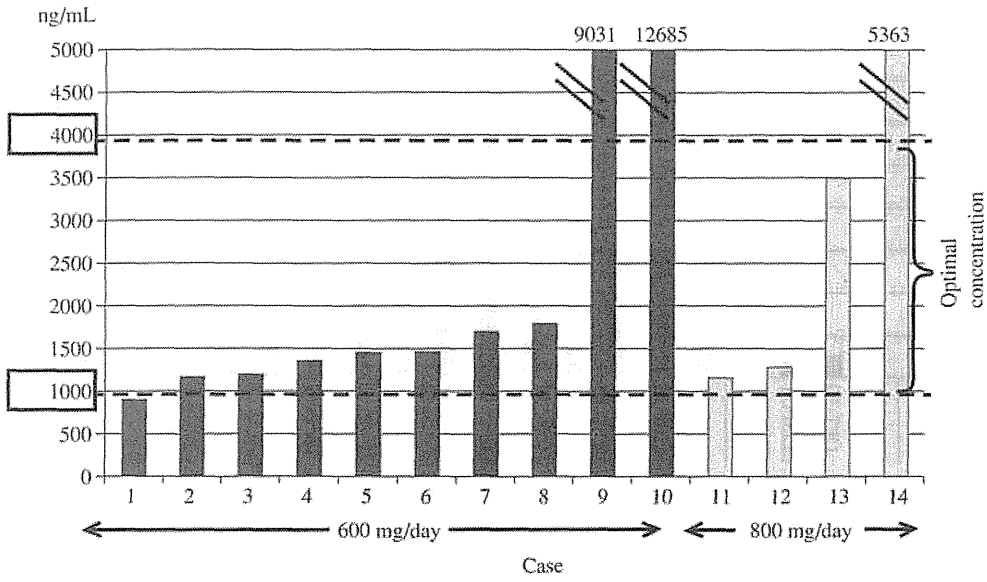


**Fig. 4** Plasma concentration (trough) of efavirenz

above the target concentration of 1,000 ng/mL at 14 hours after administration (Fig. 4). Several patients exhibited extremely high plasma EFV concentration, and the dose was actually lowered to reach the optimal concentration. The patient who received RAL (1,600 mg/day) exhibited a trough plasma concentration of 26.6 ng/mL, well above RAL's IC95 of 14.5 ng/mL.

In general, RFP lowers the plasma concentration of anti-HIV drugs by inducing CYP3A4, but there are differences in this reaction across individuals. While EFV is mainly metabolized in the liver by CYP2B6, the gene has three genotypes (G/G, G/T, T/T). The T/T genotype is known to metabolize EFV slowly, which increases serum EFV concentration. However, none of the patients at our hospital had the T/T genotype.

Moreover, the neuropsychiatric symptoms that appear as a side effect of EFV are known to be dependent on plasma concentration. Thus, plasma concentration levels must be monitored to maintain the continuous administration that sustains the anti-HIV effect and suppresses side effects.

## Conclusion

The author has researched HIV/TB since 1992. While HIV/TB cases are concentrated in large cities, it is doubtful that Japan's situation will lead to an immediate decline in the number of cases, prompting continued research to reduce HIV/TB incidence and improve prognosis.

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# 感染症のバイオマーカー：結核

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## Summary

結核におけるバイオマーカーの研究は長年つづけられており，活動性結核の診断と治癒の判定，潜在性結核感染症（LTBI）の診断と発病の判定，BCGなどのワクチンによる予防免疫などの分野がおもな研究領域である．いずれの分野でもだれもが満足するような成果はいまのところ得られていないが，すでに臨床応用されているものもある．インターフェロン-γ遊離測定法（IGRA）は代表的なバイオマーカー測定法であり，広く使用されているが，最近，連続検査における変動と再現性の不安定さが指摘されるようになった．上記の領域のバイオマーカーの開発が待たれるが，途上国での結核対策を考慮すれば，測定に複雑な手技を要しコストがかかるようなバイオマーカーでは結核対策としては役に立たない．

## Key Words

インターフェロン-γ遊離測定法（IGRA），クォンティフェロン® TBゴールド，T-スポット®.TB，インターフェロン-γ（INF-γ），IP-10

## はじめに

世界保健機関（WHO）によれば2013年の世界における新規結核患者数は900万人であり，結核による死亡者数は150万人であった．新規多剤耐性結核患者数は48万人であり，21万人が死亡している．結核は途上国を中心に多数の感染者と発病者を生み，国の発展の障害となっている．結核を撲滅するには，発病者の早期発見と確実な治療の完遂が必要であり，それにより新たな感染者を減らすことができる．また，感染しているが発病していない人〔潜在性結核感染症（latent tuberculosis infection：LTBI）〕をみつけ，治療をおこなって発病を減らすことも，もう一つの重要な戦略である．

結核対策に必要なバイオマーカーの研究は長年つづけられており，活動性結核の診断と治癒の判定，LTBIの診断と発病の判定，BCGなどのワクチンによる予防免疫などの分野がおもな研究領域である．しかしながら，途上国での結核対策を考慮すれば，測定に複雑な手技を要しコストがかかるようなバイオマーカーでは結核対策と

しては役に立たない．いずれの分野でもだれもが満足するような成果はいまのところ得られていないが，すでに臨床応用されているものもある．ここではとくに結核感染の診断について述べたい．

従来，LTBIの診断はツベルクリン反応検査（ツ反）によっておこなわれてきた．この方法はBCG未接種者においては感度，特異度ともに高く基本的にはすぐれた方法である．しかし，BCG接種を受けていると特異度は97%から59%に低下する．ツ反にはほかにも「ブースター効果が認められる」，「非結核性抗酸菌との交差反応がある」，「判定のための再受診が必要」，「ツ反の接種技術や判定技術の差が指摘されている」など多数の問題がある．

そこにBCG接種の影響を受けない新しい結核診断法が登場した．特異的抗原刺激に対するリンパ球のインターフェロン（IFN）-γ産生能を測定することによって結核感染の診断をおこなう方法である〔インターフェロン-γ遊離測定法（interferon-gamma release assay：IGRA）〕．IFN-γは結核感染の代表的バイオマーカーである．

## 1．IGRA

結核菌特異的抗原の探索のなかで，結核菌培養ろ液中の蛋白としてearly secreted antigen target 6 kDa（ESAT-6）と10 kDa culture filtrate protein（CFP-10）が得られた．これらはBCGや多くの非結核性抗酸菌などの結核菌近縁菌種に含まれないこと，かつ，結核感染マウスでメモリーT細胞を刺激しIFN-γ産生誘導することから有力な抗原物質と考えられIGRAが開発された．現在では，クォンティフェロン® TBゴールド（第3世代であり，以下QFT-3 Gとする）とT-スポット®.TB（以下T-SPOT）が使用されており，ツ反にかわって結核感染の診断に用いられるようになった．

### 1）QFT-3 G

QFT-3 Gは全血を用いる検査法であり，採血管のなかにすでに刺激抗原が含まれており，採血後ただちに抗原刺激がはじまる．使用される結核菌由来の特異抗原はESAT-6，CFP-10，TB7.7の3種類である．産生されたIFN-γをELISA法で測定し，感度は93.7%，特異度は93.8%である．採血した施設で処理がすめば長期保存が可能となるので，検査会社へ依頼する時間的余裕ができることは大きな利点である．ただし，全血を用いるためリンパ球数が低下しているような免疫不全状態では感度が低下する可能性がある．

### 2）T-SPOT

T-SPOTではヘパリン採血した血液を用い，32時間以内に検査を開始すればよい．末梢血単核球を洗浄し細胞数をそろえ，ESAT-6およびCFP-10を添加して培養する．ELISPOT法（Enzyme-Linked ImmunoSpot）によりIFN-γ産生細胞の存在した場所をスポットとして可視化し，その個数を計測し結核感染を診断する．感度は97.5%，特異度は99.1%である．T-SPOTは細胞数をそろえるので細胞数の多寡によって結果が変動しない利点がある．免疫機能低下患者でも健常人と同様の感度を示すという報告が多い．

### 3）IGRAの諸問題

最近，IGRAで問題となっているのが，連続検査における変動と再現性の不安定さである．

連続検査における変動とは，医療従事者などに一定間隔で経時的にIGRAをくり返すと陽転化や陰転化して結果が一定しないことを指す[1]．それは基準値をやや超えたあたりの値であることが多く，偽陽性と考えられている．

再現性の不安定さとは連続検査における変動にも影響を及ぼしていると考えられるが，検体の扱いによって検査結果が変動することや，同じ検体を異なる検査室で検査したときの変動などである[2)3)4)]．

これらの問題点は，IGRAが生きた細胞を扱う検査であることに起因し，検体の慎重な扱いと検査の精度管理の重要性を示している．

IGRAは結核菌の感染を示しているが，活動性結核とLTBIの鑑別はできないし，LTBIの治療効果判定にも利用できない[5]．

## 2. 結核感染診断の他のバイオマーカー

結核感染診断のバイオマーカーとしては，IFN-γ以外のサイトカインやケモカインについての研究がつづけられている．

IFN-γ-inducible protein 10（IP-10）は結核感染の有望な指標となり得るケモカインとして注目を浴びてきた[6]．QFT-3Gで抗原刺激後の血漿中のIP-10を測定した報告では，活動性結核についてはIFN-γと同様の反応を示した[7][8][9]．しかし，LTBIでも同様の反応を示し，LTBIと活動性結核との鑑別には用いることはできないという．小児ではQFT-3Gの感度が低下するが，QFT-3GとIP-10を併用することにより，小児では感度が上昇したという報告もあり，用い方によっては有用である[10]．

末梢単核球に対するESAT-6およびCFP-10による抗原刺激後に上昇し，結核感染を示す他のサイトカインとしては，腫瘍壊死因子（tumour necrosis factor：TNF)-α[11]，IL-2[12]，IL-10[12]，IL-13[12]などが報告されている．

活動性結核とLTBIの鑑別に2種類のサイトカインを組み合わせると有用であるという報告がある．Kimら[12]はQFT-3G抗原刺激後の血漿中IL-2/IFN-γの比をとり，LTBIと活動性結核で比較したところ，前者で有意に高く（p＝0.014），とくに塗抹陽性結核患者とは有意差（p＝0.047）があったと報告している．Wangら[13]も同様の方法でIL-2/IFN-γの比をみているが，LTBIと活動性結核の鑑別において感度77.2%，特異度87.2%であった．

上記のように種々の研究はあるが，結核感染の診断および治療効果を明確に示すバイオマーカーは現時点では存在しない．

## おわりに

結核感染の診断はツ反にかわってIGRAが登場したことにより，きわめて容易になったが，経験を積むにつれ種々の問題点も浮き彫りになってきた．活動性結核とLTBIの鑑別が明確にできるバイオマーカー，結核の治癒判定のできるバイオマーカー，結核の予防免疫を示すバイオマーカーなどの開発が待たれる．

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