The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adult-Onset Immunodeficiency in Thailand and Taiwan

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203 patients et contrôles de Taiwan et Thaïlande répartis en 5 groupes

Groupe 1	**Infections disséminées à mycobactéries atypiques**	**n = 52**
Groupe 2	**Infections opportunistes autres +/- mycob. Atypiques** (41/45)	**n = 45**
Groupe 3	**Tuberculose disséminée**	**n = 9**
Groupe 4	**Tuberculose pulmonaire**	**n = 49**
Groupe 5	**Contrôles sains (donneurs de sang)**	**n = 48**

- Pas d' ATCD de Kc
- Pas de ttt immunosuppresseur dans les 4 semaines
- Pas de notion de déficit immunitaire congénital
- Pas de lymphopénie T-CD4
- HIV-

Table 1. Clinical Characteristics of the 203 Participants.*

Characteristic	Group 1 (N=52)	Group 2 (N=45)	Group 3 (N=9)	Group 4 (N=49)	Group 5 (N=48)	P Value†
Age — yr						<0.001
Median	50	49	38	43	38	
Range	18–78	22–69	21–74	18–77	21–62	
Male sex — no. (%)	21 (40)	17 (38)	3 (33)	28 (57)	22 (46)	0.32
Associated conditions — no.						
Lymphatic obstruction	3	9	0	0	—	0.002
Pain or neuropathy	4	3	0	2	—	0.86
Hypercalcemia	4	3	1	1	—	0.37
Erythema nodosum	3	3	0	1	—	0.76
Exanthematous pustulosis	5	1	0	0	—	0.09
Pustular psoriasis	0	2	0	0	—	0.20
Neutrophilic dermatosis	21	19	0	0	—	<0.001

Table 2. Isolated Organisms in 97 Patients with Opportunistic Infections.

Variable	Group 1 (N=52)	Group 2 (N=45)
Organisms isolated (no./patient)		
Median	1	2
Range	1–4	1–5
Mycobacteria (no. of patients)		
Rapidly growing	36	39
Slowly growing	15	8
Nontuberculous mycobacteria, not specified	5	2
Mycobacterium tuberculosis	4*	10†
Total	60	59
Bacteria (no. of patients)		
Salmonella species		25
Burkholderia pseudomallei		4
Other		9
Fungi (no. of patients)		
Cryptococcus neoformans		10
Histoplasma capsulatum		7
Penicillium marneffei		7
Varicella–zoster virus (no. of patients)		
Disseminated		3
Local	5	10
Parasites (no. of patients)		
Strongyloides stercoralis		1

* Two patients had pulmonary tuberculosis, and two had disseminated tuberculosis.

† Three patients had pulmonary tuberculosis, and seven had disseminated tuberculosis.

- **NFS**
- **fonction rénale et hépatique**
- **dosage pondéral des Ig**
- **phénotypage lymphocytaire**

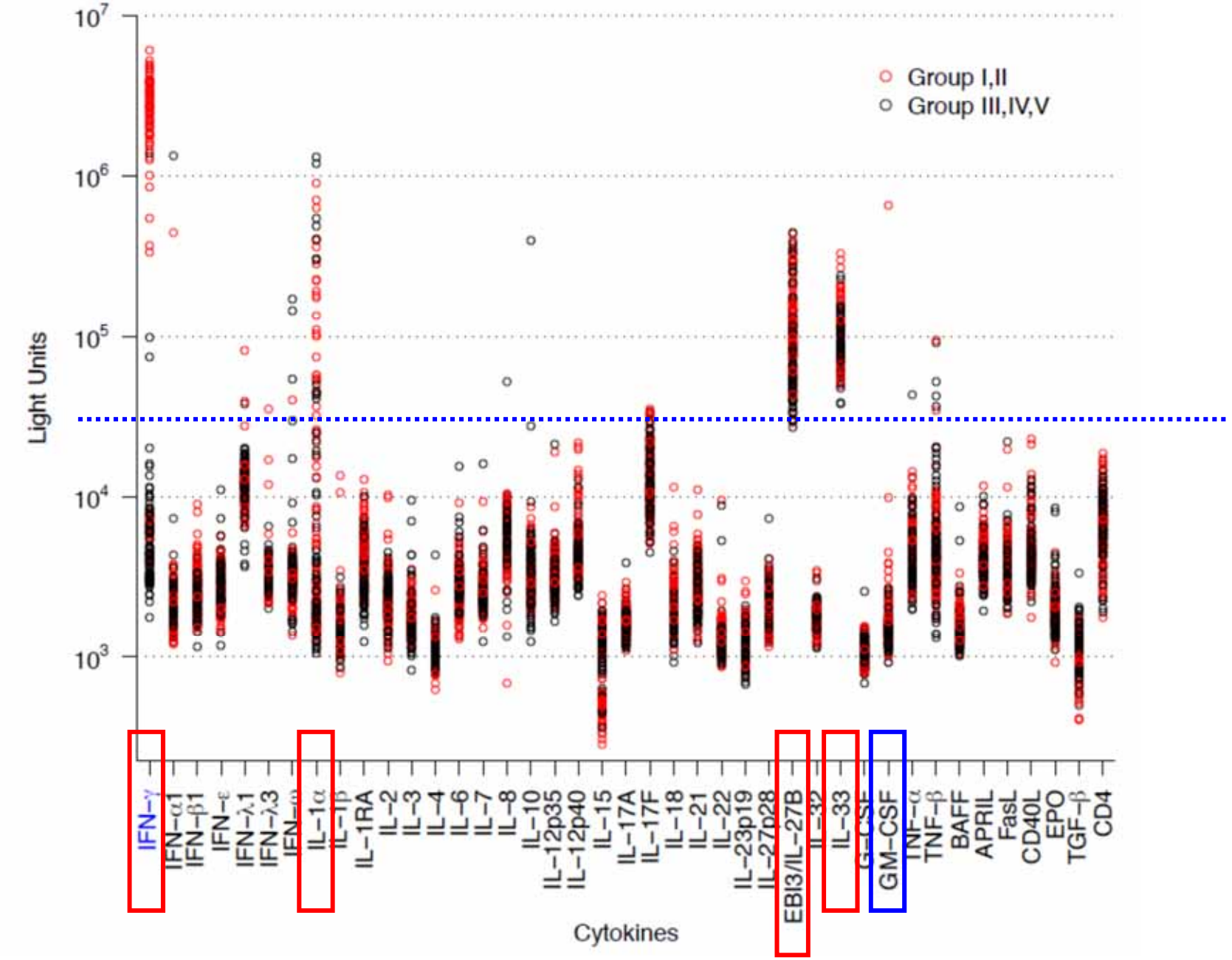
- **ANA**
- **anticorps anti-cytokines**

Screeening par immunoprécipitation avec évaluation de 41 cibles (!!):

IFNγ, α1, β1, ε, λ1, λ3, ω; IL-1α et 1β, IL-1Ra, IL-2, 3, 4, 6, 7, 8, 10, 12p35, 12p40, 15, 17A, 17F, 18, 21, 22, 23p19, 27p28, 27b, 32, 33; G-CSF, GM-CSF, TNF-α, TNF-β, BAFF, APRIL, FasL, CD40L, EPO, TGFβ, CD4R.

Laboratories	Dissem. NTM (N=52) Group I Mean (95%CI)	Other CF +/- NTM (N=45) Group II Mean (95%CI)	Dissem MTB (N=9) Group III Mean (95%CI)	Pulm MTB (N=49) Group IV Mean (95%CI)	P-Value
Hemoglobin (mg/dL)	12.5 (11.9,13.1)	11.2 (10.6,11.8)	13.5 (12,15.2)	12.8 (12.2,13.5)	< 0.001
WBC ($x10^3/\mu l$)	9.19 (8.22,10.3)	10.6 (9.42,12)	6.92 (5.31,9.01)	7.47 (6.67,8.36)	< 0.001
Neutrophils abs ($x10^3/\mu l$)	5237 (4469,6136)	6186 (5216,7336)	3676 (2521,5361)	4118 (3504,4841)	0.003
Neutrophils (%)	61.9 (57.9,65.8)	63.8 (59.6,68.1)	58.8 (49.4,68.2)	60.9 (56.9,64.9)	0.69
Lymphocytes abs ($x10^3/\mu l$)	2022 (1778,2299)	2118 (1845,2433)	1578 (1162,2143)	1739 (1525,1982)	0.10
Lymphocytes (%)	25.9 (22.8,29)	24.7 (21.3,28)	27.8 (20.5,35.1)	27.2 (24,30.3)	0.71
Monocytes abs ($x10^3/\mu l$)	413 (279,611)	256 (168,390)	214 (84.3,543)	386 (259,576)	0.26
Monocytes (%)	5.85 (5.1,6.59)	4.5 (3.7,5.31)	6.98 (5.2,8.76)	6.89 (6.13,7.65)	< 0.001
Platelets ($x10^3/\mu l$)	270 (243,300)	276 (246,309)	212 (166,272)	252 (227,281)	0.23
Alanine transferase (units/L)	20.6 (16.2,26.1)	24.5 (18.9,31.7)	24.9 (14.1,44.1)	23.1 (18.1,29.4)	0.77
Aspartate transferase (units/L)	25.4 (22.3,28.8)	28 (24.4,32.1)	27.6 (20.4,37.3)	24.1 (21.1,27.4)	0.43
Alkaline phosphatase (units/L)	44.3 (34.7,56.7)	35.7 (27.4,46.5)	50.3 (28,90.2)	53.8 (41.9,69.1)	0.17
Total bilirubin (mg/dL)	0.98 (0.88,1.08)	1.02 (0.92,1.14)	1.02 (0.8,1.3)	0.99 (0.89,1.1)	0.93
Antinuclear antibody # (%) positive	14 (28.0%)	15 (35.7%)	3 (33.3%)	24 (49.0%)	0.19
IgG (mg/dL)	1652 (1493,1828)	1860 (1675,2065)	1657 (1283,2141)	1793 (1627,1975)	0.41
IgA (mg/dL)	274 (242,311)	296 (260,337)	272 (198,374)	326 (290,368)	0.24

Parameter	Dissem. NTM (N=26) Group I	Other OI +/- NTM (N=25) Group II	Dissem. MTB (N=6) Group III	Pulm. MTB (N=19) Group IV	Healthy Control (N=47) Group V	P-value*
CD3	1328 (1099,1606)	1359 (1120,1649)	1175 (792,1744)	1214 (973,1516)	1519 (1319,1749)	0.43
CD3 %	57.2* (52.8,61.6)	58.6* (54.1,63.1)	68.4 (59.1,77.6)	61.8 (56.6,66.9)	66.7 (63.4,70)	0.004
CD3/CD4	651 (523,809)	588 (450,768)	345 (179,663)	731 (571,936)	797 (696,912)	0.05
CD3/CD4 %	28.9* (25.2,32.6)	27.4* (22.8,31.9)	40.3 (29.1,51.4)	35 (30.8,39.3)	35.4 (33.1,37.7)	0.003
CD3/CD8	500 (392,637)	650 (483,875)	223 (108,462)	431 (328,568)	533 (459,619)	0.06
CD3/CD8 %	22.3 (19.1,25.6)	28.4 (24.4,32.3)	26.4 (16.7,36.1)	21.2 (17.5,24.9)	24.1 (22.1,26.1)	0.10
T4/T8 Ratio	1.82 (1.59,2.09)	1.47* (1.24,1.74)	2.05 (1.35,3.09)	2.21 (1.89,2.59)	2.02 (1.86,2.2)	0.007
CD3+/CD4-/CD8-	83.1 (58.6,118)	98.3 (64.1,151)	36.4 (12.8,104)	107 (71.2,162)	139 (112,173)	0.03
CD3+/CD4-/CD8- %	5.14 (3.18,7.1)	4.83 (2.43,7.22)	5.5 (-0.37,11.4)	5.96 (3.66,8.26)	6.84 (5.63,8.05)	0.49
CD4/CD45RO	376 (298,475)	402 (302,535)	136* (67.4,273)	336 (258,438)	353 (304,409)	0.09
CD4/CD45RO %	16.7 (14.1,19.4)	18.4 (15.2,21.7)	16.4 (8.4,24.4)	16.5 (13.5,19.6)	16.1 (14.4,17.8)	0.81
CD4/CD45RA	77.7* (49.9,121)	37.3* (21.6,64.2)	126 (33.2,477)	191 (116,316)	201 (152,267)	< 0.001
CD4/CD45RA %	5.02* (2.79,7.25)	4.12* (1.4,6.85)	14.6 (7.87,21.2)	10.6 (8.05,13.1)	9.8 (8.37,11.2)	< 0.001
CD3/HLA-DR	409 (313,534)	483 (369,634)	223 (128,388)	276 (202,377)	363 (298,443)	0.03
CD3/HLA-DR %	20.8 (16.6,25)	24.2* (19.9,28.5)	16.1 (7.31,24.9)	15.6 (10.7,20.6)	17 (13.8,20.1)	0.04
CD19	217 (163,288)	215 (161,287)	176 (97,318)	261 (187,364)	315 (254,389)	0.10
CD19 %	11* (8.9,13.1)	10.6* (8.42,12.7)	12.3 (7.95,16.7)	14.1 (11.7,16.6)	14.4 (12.8,15.9)	0.02
CD19/CD27	49.8* (36.5,68.1)	48.3* (35.2,66.4)	38.8* (20.3,74.3)	50.8* (35.3,73.1)	107 (84.3,136)	< 0.001
CD19/CD27 %	2.65* (2.06,3.24)	2.31* (1.71,2.91)	3.05* (1.82,4.28)	2.78* (2.09,3.47)	4.92 (4.47,5.38)	< 0.001
NK	677* (534,858)	661* (519,841)	307 (188,504)	438 (332,578)	400 (336,478)	< 0.001
NK %	31.8* (27.2,36.4)	30.8* (26.2,35.5)	19.3 (9.76,28.9)	24.1 (18.8,29.5)	18.9 (15.5,22.3)	< 0.001
NKT	33.5 (23.1,48.4)	38.3 (26.2,55.8)	31.9 (14.8,68.9)	29.3 (19,45.1)	42.7 (32.4,56.2)	0.62
NKT %	1.93 (1.22,2.63)	2.07 (1.35,2.79)	2.3 (0.83,3.77)	2.18 (1.35,3.01)	2.29 (1.76,2.81)	0.95
$IFN_{\gamma}RI$ GMC#	186 (162,214)	168* (145,195)	153 (115,204)	171 (143,203)	217 (196,240)	0.02



Seuls les anti-IFNγ distinguent groupes 1/2 des goupes 3/4/5 (p<0.001)

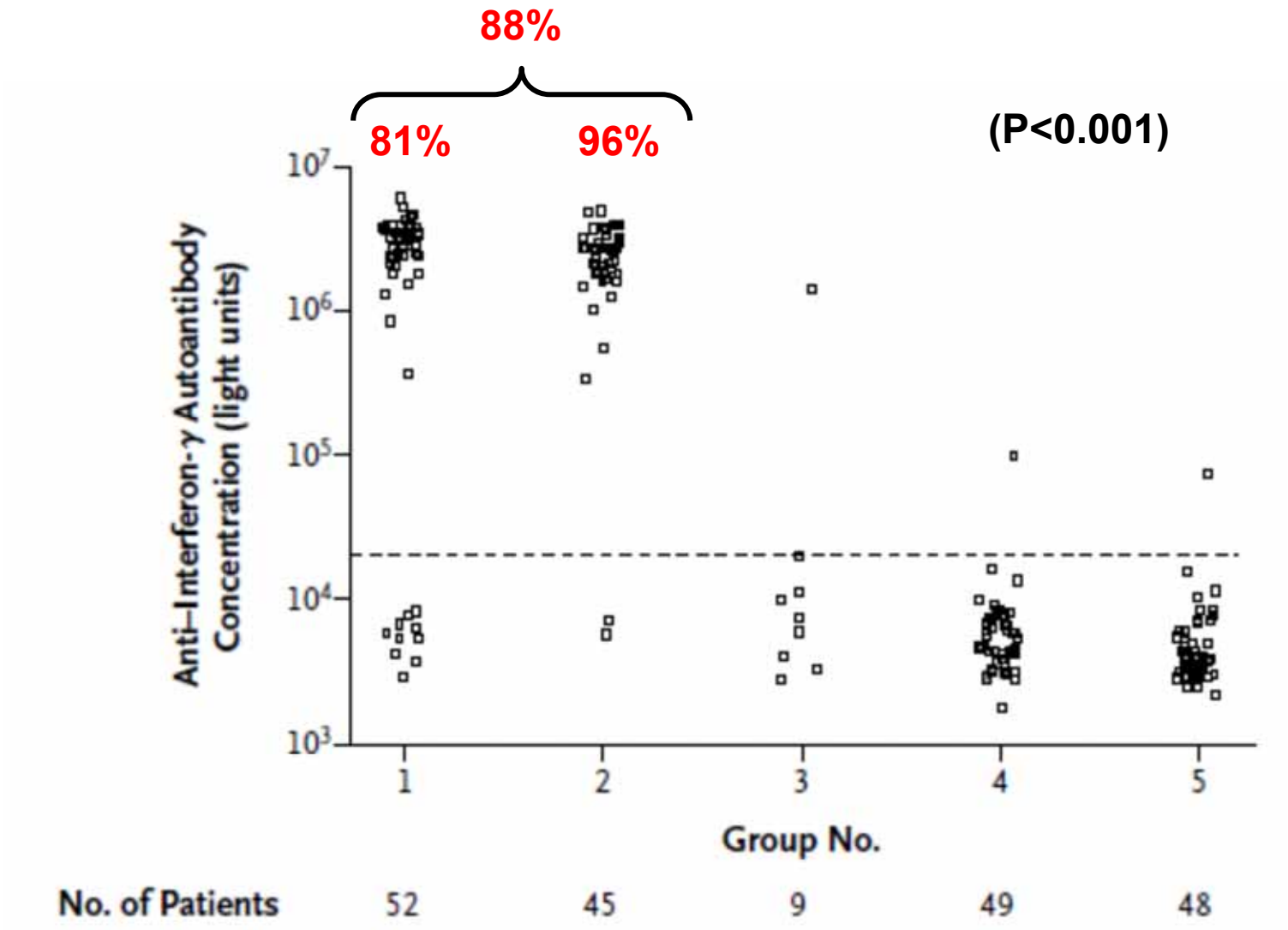
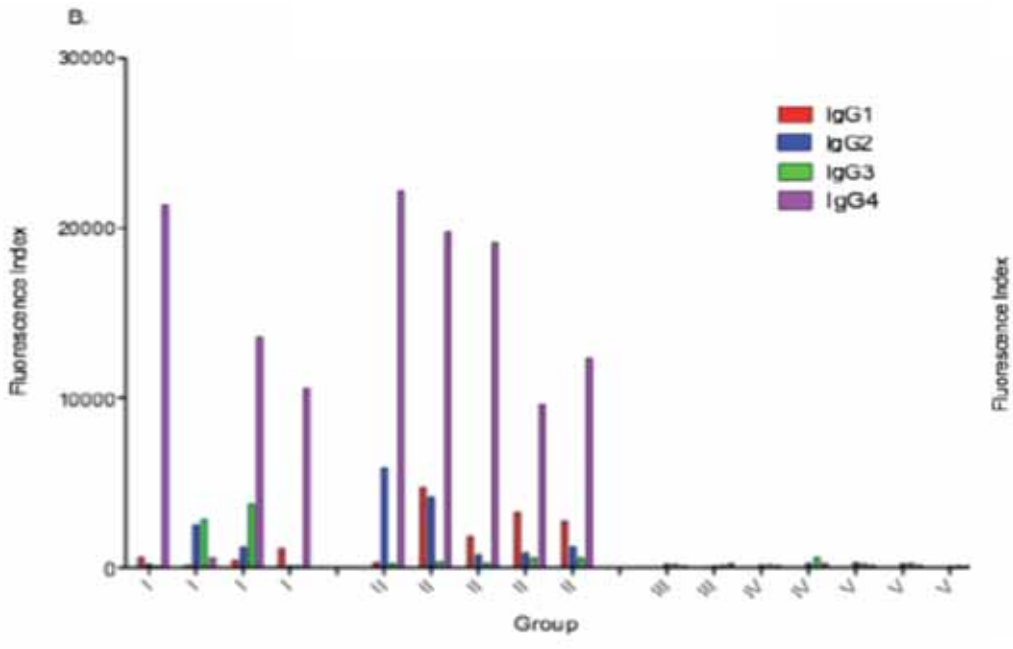
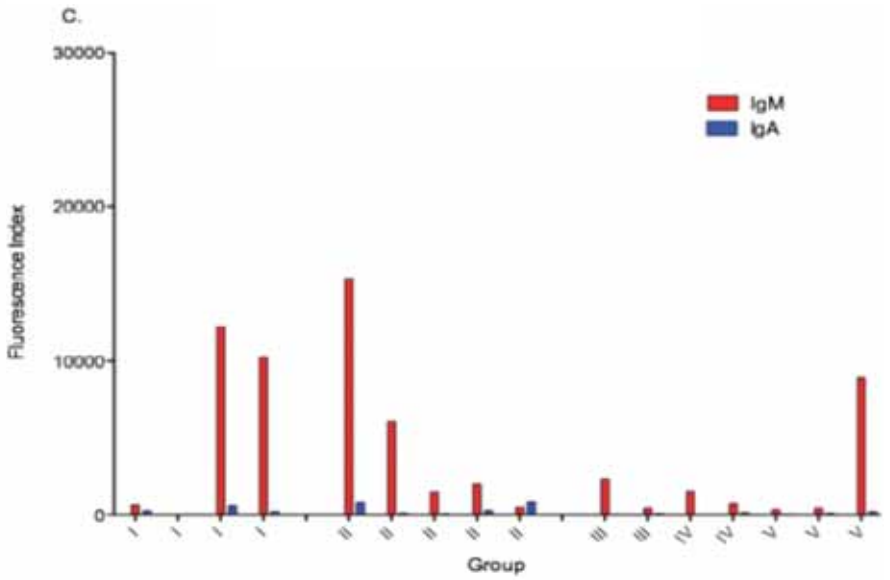


Figure 2. Anti–Interferon-γ Autoantibody Concentrations in 203 Participants, According to Study Group.

Anti-IFNγ IgG subclass



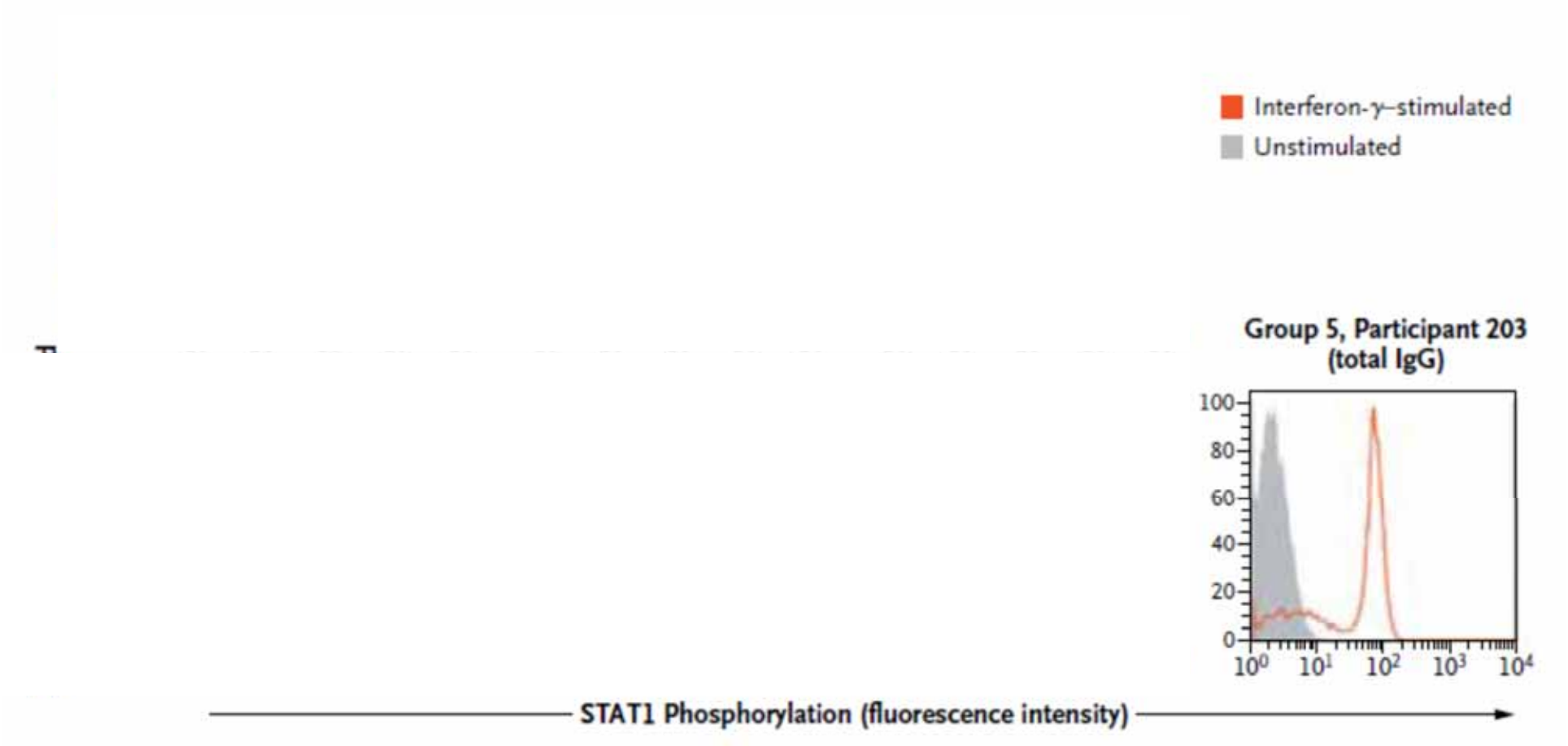
Anti-IFNγ IgM and IgA



(mais non neutralisants)

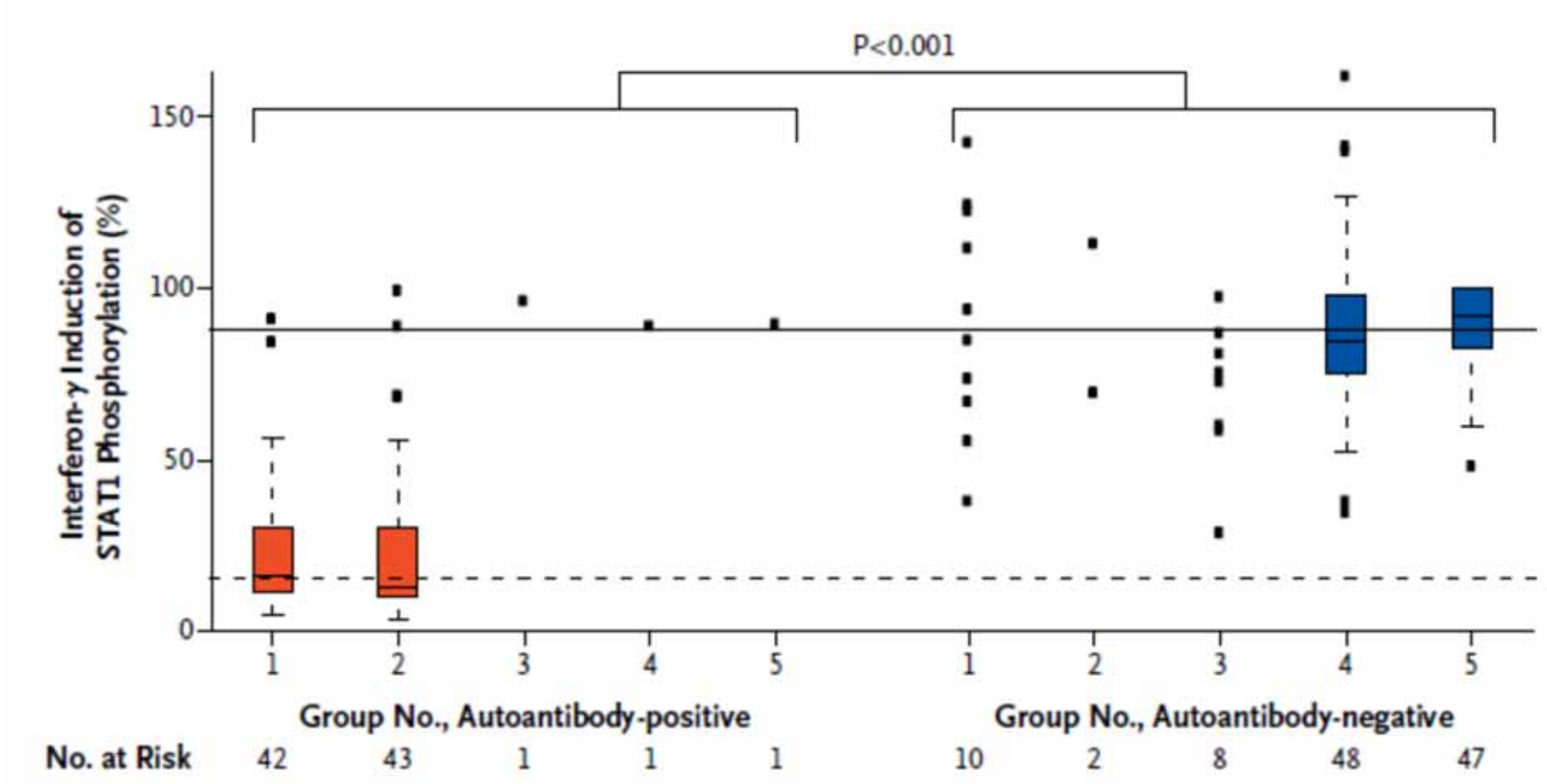
Activité neutralisante des Ac anti-IFNγ

PBMC témoins + 10% sérum patient + IFNγ → **Quantif. phospho-STAT1**



Activité neutralisante des Ac anti-IFNγ

PBMC + IFNγ + 10% sérum patient → **Quantification phospho-STAT1**



Patients sans Ac anti-IFNγ

Groupe 1 (n=10):

- **6 formes purement ganglionnaires**
- **3 formes purement osseuses**
- **5/10 ont pu être traitées avant inclusion**

Groupe 2 (n=2):

- **1/2 avait des Ac neutralisant anti-GM-CSF**

(cryptococcose + tuberculose pulmonaire)

CONCLUSION

Neutralizing anti–IFNγ autoantibodies were detected in 88% of Asian adults with multiple opportunistic infections and were associated with an adult-onset immunodeficiency akin to that of advanced HIV infection.

- ➔ **Infections opportunistes à germes intra-cellulaires**
- ➔ **Surtout mycobactéries atypiques (96%)**
- ➔ **Début à l'âge adulte**
- ➔ **Pas de cluster familial**

Blood. 2013 Feb 21;121(8):1357-66

Anti–IFN-γ autoantibodies in adults with disseminated nontuberculous mycobacterial infections are associated with HLA-DRB1*16:02 and HLA-DQB1*05:02 and the reactivation of latent varicella-zoster virus infection

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- **17 adultes + infection disséminée à mycobactéries atypiques**

- **17 / 17 ont des Ac anti-IFNγ**

- **Association salmonella (35%) , VZV (71%)** + autres

- **Association DRB1*16:02 + DQB1*05:02 (82%)**

Anti-cytokine autoantibodies are associated with opportunistic infection in patients with thymic neoplasia

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Patients with thymic malignancy have high rates of autoimmunity leading to a variety of autoimmune diseases, most commonly myasthenia gravis caused by anti-acetylcholine receptor autoantibodies. High rates of autoantibodies to cytokines have also been described, although prevalence, spectrum, and functionality of these anti-cytokine autoantibodies are poorly defined. To better understand the presence and function of anti-cytokine autoantibodies, we created a luciferase immunoprecipitation system panel to search for autoantibodies against 39 different cytokines and examined plasma from controls ($n = 30$) and patients with thymic neoplasia ($n = 17$). In this screen, our patients showed statistically elevated, but highly heterogeneous immunoreactivity against 16 of the 39 cytokines. Some patients showed autoantibodies to multiple cytokines. Functional testing proved that autoantibodies directed against interferon-α, interferon-β, interleukin-1α (IL-1α), IL-12p35, IL-12p40, and IL-17A had biologic blocking activity in vitro. All patients with opportunistic infection showed *multiple anti-cytokine autoantibodies* (range 3-11), suggesting that anti-cytokine autoantibodies may be important in the pathogenesis of opportunistic infections in patients with thymic malignancy. This study was registered at http://clinicaltrials.gov as NCT00001355. (*Blood*. 2010; 116(23):4848-4858)

Recurrent Staphylococcal Cellulitis and Subcutaneous Abscesses in a Child with Autoantibodies against IL-6[1]

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We investigated an otherwise healthy patient presenting two episodes of staphylococcal cellulitis and abscesses, accompanied by high fever and biological signs of inflammation but, paradoxically, with no detectable increase in serum levels of C-reactive protein (CRP), an IL-6-responsive protein synthesized in the liver. Following in vitro activation of whole blood cells from the patient with multiple cytokines, TLR agonists, heat-killed bacteria, and mitogens, we observed a profound and specific impairment of IL-6 secretion. However, the patient's PBMCs, activated in the same conditions but in the absence of the patient's plasma, secreted IL-6 normally. The patient's serum contained high titers of IgG1 autoantibodies against IL-6, which specifically neutralized IL-6 production by control PBMCs as well as IL-6 responses in the human hepatocellular carcinoma cell line Hep3B. These anti-IL-6 autoantibodies were detected over a period of 4 years, in the absence of any other autoantibodies. Our results indicate that these Abs probably prevented an increase in CRP concentration during infection and that impaired IL-6-mediated immunity may have contributed to staphylococcal disease. Patients with severe bacterial infections and low serum CRP concentrations should be tested for anti-IL-6 autoantibodies, especially in the presence of other clinical and biological signs of inflammation. *The Journal of Immunology,* 2008, 180: 647–654.

Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I

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J. Exp. Med. 2010 Vol. 207 No. 2 291-297

Most patients with autoimmune polyendocrine syndrome type I (APS-I) display chronic mucocutaneous candidiasis (CMC). We hypothesized that this CMC might result from autoimmunity to interleukin (IL)-17 cytokines. We found high titers of autoantibodies (auto-Abs) against IL-17A, IL-17F, and/or IL-22 in the sera of all 33 patients tested, as detected by multiplex particle-based flow cytometry. The auto-Abs against IL-17A, IL-17F, and IL-22 were specific in the five patients tested, as shown by Western blotting. The auto-Abs against IL-17A were neutralizing in the only patient tested, as shown by bioassays of IL-17A activity. None of the 37 healthy controls and none of the 103 patients with other autoimmune disorders tested had such auto-Abs. None of the patients with APS-I had auto-Abs against cytokines previously shown to cause other well-defined clinical syndromes in other patients (IL-6, interferon [IFN]-γ, or granulocyte/macrophage colony-stimulating factor) or against other cytokines (IL-1β, IL-10, IL-12, IL-18, IL-21, IL-23, IL-26, IFN-β, tumor necrosis factor [α], or transforming growth factor β). These findings suggest that auto-Abs against IL-17A, IL-17F, and IL-22 may cause CMC in patients with APS-I.

Idiopathic Pulmonary Alveolar Proteinosis as an Autoimmune Disease with Neutralizing Antibody against Granulocyte/Macrophage Colony-Stimulating Factor

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Summary

Idiopathic pulmonary alveolar proteinosis (I-PAP) is a rare disease of unknown etiology in which the alveoli fill with lipoproteinaceous material. We report here that I-PAP is an autoimmune disease with neutralizing antibody of immunoglobulin G isotype against granulocyte/macrophage colony-stimulating factor (GM-CSF). The antibody was found to be present in all specimens of bronchoalveolar lavage fluid obtained from 11 I-PAP patients but not in samples from 2 secondary PAP patients, 53 normal subjects, and 14 patients with other lung diseases. It specifically bound GM-CSF and neutralized bioactivity of the cytokine in vitro. The antibody was also found in sera from all I-PAP patients examined but not in sera from a secondary PAP patient or normal subjects, indicating that it exists systemically in I-PAP patients. As lack of GM-CSF signaling causes PAP in congenital cases and PAP-like disease in murine models, our findings strongly suggest that neutralization of GM-CSF bioactivity by the antibody causes dysfunction of alveolar macrophages, which results in reduced surfactant clearance.

J. Exp. Med. 1999, Vol. 190 No. 6 p 875-880

Arthritis Rheum. 2002 Sep;46(9):2384-91

Autoantibodies Against Granulocyte Colony-Stimulating Factor in Felty's Syndrome and Neutropenic Systemic Lupus Erythematosus

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Objective. Cytokines and growth factors can be a target of autoantibodies in systemic inflammatory diseases. We examined whether patients with neutropenia and either Felty's syndrome (FS) or systemic lupus erythematosus (SLE) have autoantibodies against granulocyte colony-stimulating factor (G-CSF) and whether these autoantibodies are functionally relevant.

Methods. Fifteen patients with neutropenia due to FS were matched for age, sex, and disease activity with 16 normocytic rheumatoid arthritis (RA) control patients. Sixteen patients with SLE and neutropenia were matched with 16 normocytic SLE control patients. Antibodies against G-CSF were measured by enzyme-linked immunosorbent assay and Western blotting. Antibody specificity was verified by competitive inhibition using recombinant human G-CSF. The effect of anti–G-CSF antibodies on the functional activity of their target molecule was measured in a bioassay using G-CSF–sensitive murine 32D cells.

Results. IgG anti–G-CSF was found in 11 FS patients, 6 SLE patients with neutropenia, 6 SLE control patients, and none of the RA control patients. IgM anti–G-CSF was found in 6 neutropenic and 3 normocytic SLE patients. Anti–G-CSF antibodies were associated with an exaggerated serum level of G-CSF and a low neutrophil count. A neutralizing effect of anti–G-CSF antibodies on its target molecule was found in 3 of the 9 patients tested. Irrespective of the presence or absence of anti–G-CSF antibodies, neutropenic patients with FS and SLE had exaggerated serum levels of G-CSF.

Conclusion. Anti–G-CSF autoantibodies are common in neutropenia due to FS and SLE. In individual patients, these autoantibodies have a neutralizing capacity. In patients without neutralizing antibodies, hyposensitivity of the myeloid cells to G-CSF appears to be central to the pathogenesis of the neutropenia in FS and SLE.

BRIEF REPORT: AUTOANTIBODIES AGAINST ERYTHROPOIETIN IN A PATIENT WITH PURE RED-CELL APLASIA

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AUTOIMMUNITY is often implicated in pure red-cell aplasia. Approximately 10 to 15 percent of patients with pure red-cell aplasia have thymomas,[1] and remission of the anemia occurs in 25 to 30 percent of these patients after the thymoma is removed.[2] In other patients there are immunologic abnormalities, such as hypogammaglobulinemia,[3] monoclonal immunoglobulins,[4] antithyroid antibodies,[5] antinuclear antibodies,[6,7] and autoimmune hemolytic anemia.[3,8] Immunosuppressive therapy is successful in many patients,[2,9-12] and a good response to plasmapheresis has been reported in two patients.[13,14]

N Engl J Med. 1996 Mar 7;334(10):630-3

Anticorps anti-cytokines et lupus

J Interferon Cytokine Res. 2003 Mar;23(3):143-7.

Incidence of autoantibodies against type I and type II interferons in a cohort of systemic lupus erythematosus patients in Slovakia.

Slavikova M, Schmeisser H, Kontsekova E, Mateicka F, Borecky L, Kontsek P.

Autoantibodies against interferon (IFN) can be found in patients with systemic lupus erythematosus (SLE). However, detailed information about the occurrence of type-specific antihuman IFN antibodies is not available. In this study, we investigated the incidence of autoantibodies specifically recognizing various type I IFNs (alpha1, alpha2, beta, omega) and type II IFN (gamma). Sera from 100 SLE patients were screened for the presence of IFN-binding antibodies by ELISA, using various types of recombinant IFNs as antigen. On the whole, autoantibodies against type I or type II or both IFNs were detected in 45% (45 of 100) of the serum samples investigated. More than half (56%) of the positive samples (25 of 45) contained antibodies specific only for type I IFNs, and 36% of positive sera (16 of 45) had autoantibodies only against type II IFN. Antibodies against both type I and type II IFNs were detected in 8% (4 of 45) of the positive samples. Among autoantibodies to type I IFNs, the most abundant were those against the type IFN-omega (15%) and the subtype IFN-alpha2 (11%). Autoantibodies binding subtype IFN-alpha1 and type IFN-beta were detected at a relatively lower incidence of about 3%-4%. The highest occurrence (20%) showed autoantibodies to the proinflammatory cytokine, IFN-gamma. We did not find any correlation between the production of autoantibodies against particular IFN species and an antibody response to other IFN species. We further observed that 84% (38 of 45) of the positive sera bound only one IFN species, and 13% (6 of 45) of positive samples contained antibodies against two IFN species of five different combinations (alpha1/beta, alpha1/omega, alpha2/omega, alpha2/gamma, omega/gamma). One sample uniquely showed reactivity with three IFN species (alpha2/omega/gamma). Our findings suggest that formation of autoantibodies could reflect humoral immune responses to increased spontaneous production of the respective IFN species in SLE patients.

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Association of Endogenous Anti–Interferon-α Autoantibodies With Decreased Interferon-Pathway and Disease Activity in Patients With Systemic Lupus Erythematosus

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Objective. Numerous observations implicate interferon-α (IFNα) in the pathophysiology of systemic lupus erythematosus (SLE); however, the potential impact of endogenous anti-IFNα autoantibodies (AIAAs) on IFN-pathway and disease activity is unclear. The aim of this study was to characterize IFN-pathway activity and the serologic and clinical profiles of AIAA-positive patients with SLE.

Methods. Sera obtained from patients with SLE (n = 49), patients with rheumatoid arthritis (n = 25), and healthy control subjects (n = 25) were examined for the presence of AIAAs, using a biosensor immunoassay. Serum type I IFN bioactivity and the ability of AIAA-positive sera to neutralize IFNα activity were determined using U937 cells. Levels of IFN-regulated gene expression in peripheral blood were determined by microarray, and serum levels of BAFF, IFN-inducible chemokines, and other autoantibodies were measured using immunoassays.

Results. AIAAs were detected in 27% of the serum samples from patients with SLE, using a biosensor immunoassay. Unsupervised hierarchical clustering analysis identified 2 subgroups of patients, IFN^{low} and IFN^{high}, that differed in the levels of serum type I IFN bioactivity, IFN-regulated gene expression, BAFF, anti–ribosomal P, and anti-chromatin autoantibodies, and in AIAA status. The majority of AIAA-positive patients had significantly lower levels of serum type I IFN bioactivity, reduced downstream IFN-pathway activity, and lower disease activity compared with the IFN^{high} patients. AIAA-positive sera were able to effectively neutralize type I IFN activity in vitro.

Conclusion. Patients with SLE commonly harbor AIAAs. AIAA-positive patients have lower levels of serum type I IFN bioactivity and evidence for reduced downstream IFN-pathway and disease activity. AIAAs may influence the clinical course in SLE by blunting the effects produced by IFNα.

Table 1
The possible pathogenic potential of high levels of neutralizing autoantibodies against cytokines and related bio-modifiers.

Cytokine autoantibodies	Disease groups	Pathology confirmed experimentally	References
Interferon alpha	Infection with viruses	Yes [161,162]	Mogensen et al. [22], Antonelli et al. [14]
Interferon alpha	Cancer	Yes [163,164]	Trown et al. [17,19]
Interferon alpha	Systemic lupus erythromatosus	No	Suit et al. [18], Panem et al. [21], Prümmer et al. [165]
Interferon gamma	Infection with mycobacteria and virus	Yes [126,166]	Hoflich et al. [57], Kampmann et al. [58], Patel et al. [59], Caruso et al. [39]
IL-1α + IL-1β	Rheumatoid arthritis	No	Suzuki et al. [76–78]
IL-1α	Renal failure	No	Sunder-Plassmann et al. [79,80]
IL-2	HIV	No	Monti et al. [167], Bost et al. [40]
IL-3	Felty's syndrome and healthy subjects		Hellmich et al. [168], Watanabe et al. [169]
IL-6	Systemic sclerosis	No	Takemura et al. [75]
IL-6	Type 2 diabetes	Yes [130]	Steensberg et al. [131]
IL-6	Bacterial infections	Yes [170]	Hohman et al. [147], Puel et al. [52]
IL-8	Rheumatoid arthritis	No	Peichl et al. [32,81]
IL-8	Acute lung injury. Respiratory distress syndrome	Yes [53]	Fudala et al. [171], Stankowska et al. [172], Allen et al. [51], Krupa et al. [49], Kurdowska et al. [47], Takasaki et al. [46]
IL-8	Rheumatoid arthritis	No	Peichl et al. [32]
IL-12	Infections with mycobacteria and other microbes	Yes [120]	Shiono et al. [61], Zhang et al. [60], Meager et al. [43,44]
TNF alpha	Bacterial infections	Yes [173,174]	Fomsgaard et al. [30]
TNF alpha, IFN gamma, IL-4, IL-10	Multiple sclerosis, meningitis, stroke	Yes [175]	Elkarim et al. [72]
GM-CSF	Alveolar proteinosis	Yes [62]	Bonfield et al. [63], Lin et al. [176], Uchida et al. [54,64]
GM-CSF	Granulocyte defects	Yes [54]	Uchida et al. [54]
G-CSF	Granulocytopenia	Yes [177]	Revoltella et al. [178], Hellmich et al. [179]
VIP	Asthma	No	Paul et al. [20]
EPO	Pure red cell aplasia	Yes [180,181]	Sipsas et al. [182], Marmont et al. [183]

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Anti-cytokine autoantibodies are ubiquitous in healthy individuals

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Abstract Anti-cytokine autoantibodies in healthy individuals have been widely reported but the occurrence is variable and inconstant. We hypothesized that cytokine-binding in vivo may explain their variable and infrequent detection. Therefore, we focused on the detection of the cytokine-autoantibody complexes and found that anti-cytokine autoantibody to IL-2, IL-8, tumor necrosis factor-α, vascular endothelial growth factor and granulocyte- colony stimulating factor were present in all 15 individuals evaluated, while those to IL-3, osteopontin and macrophage-colony stimulating factor were not detected in anyone. Autoantibodies against IL-4, IL-6, IL-10, and interferon-gamma were variously detected. Thus, we discovered that anti-cytokine autoantibodies to multiple cytokines are ubiquitous in healthy individuals.