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LETTER

# Response to 'Fragment of tegument protein pp65 of human cytomegalovirus induces autoantibodies in BALB/c mice'

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See related research by Hsieh *et al.*, http://arthritis-research.com/content/13/5/R162

We read with interest the recent paper by Hsieh and colleagues [1] asserting that cytomegalovirus (CMV) induces systemic lupus erythematosus (SLE) in genetically susceptible individuals. This assertion is based on the idea that SLE-associated autoantibodies that had been induced by a certain fragment of CMV were found in rodents. However, our previous studies have reported that autoantibodies detected in SLE and viral infection are different, especially with regard to the anti-microtubule organizing center with microtubule (anti-MTOC-MT) [2-4]. We conducted a retrospective study comparing autoantibodies in three groups: anti-CMV IgM-positive SLE patients (SLE-CMV group); anti-CMV IgM-positive patients without SLE (CMV group); and anti-CMV IgM-negative SLE patients (SLE group). This study was approved by the institutional review board of Hanyang University Medical Center.

Autoantibodies from 245 patients were analyzed from January 2005 to March 2012 by the autoimmune target (AIT) test, which was developed to overcome the limitations of the antinuclear antibody test using the human macrophage cell line (IT-1) as a substrate [2].

What is noteworthy is that anti-MOTC-MT was highly detected in the CMV group, while it was not detected in all SLE patients regardless of CMV infection. Moreover, if CMV is a cause of SLE, detected autoantibodies between the SLE-CMV and CMV groups should overlap, but they show a clear distinction (Table 1).

CMV becomes latent in multiple organs and can later be reactivated during severe dysregulation of the immune system. In our study, over 90% of patients in the three groups were anti-CMV IgG-positive. Detection of anti-CMV IgG implies the presence of latent virus, but anti-CMV IgG does not protect the individual from reactivation of the latent virus. In contrast, anti-CMV IgM responses are often seen during reactivation of CMV, so it seems that CMV infection in the SLE-CMV group was not caused by primary infection but by reactivation of CMV. MTOC, cytokines and T cells are closely coordinated to maintain the immune system [5] and anti-MTOC-MT is not found in SLE patients owing to impairment of the immune system. In conclusion, we postulate that CMV is not sufficiently intense to cause SLE, but is reactivated in some SLE patients as an innocent bystander.

**Abbreviations**

AIT, autoimmune target; CMV, cytomegalovirus; MTOC-MT, microtubule organizing center with microtubule; SLE, systemic lupus erythematosus.

**Competing interests**

Think-You Kim holds patents relating to the IT-1 cell line.

Published: 10 September 2012

**References**

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doi:10.1186/ar4023
**Cite this article as**: Kim G, Kim T-Y: Response to 'Fragment of tegument protein pp65 of human cytomegalovirus induces autoantibodies in BALB/c mice'. *Arthritis Research & Therapy* 2012, **14:**404.

**Table 1. Immunofluorescence patterns and titers of AIT test in SLE-CMV, SLE and CMV groups**

| | Titer | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Patterns from AIT test** | **≤1:20** | **1:40** | **1:80** | **1:160** | **1:320** | **1:640** | **1:1280** | **≥1:2560** | **Total** |
| SLE-CMV group[a] | | | | | | | | | |
| Homogeneous | | | | | | 2 | | 9 | 11 |
| Homogeneous + speckled | | | | | | 4 | | 13 | 17 |
| Homogeneous + cytoplasmic | | | | | | | | 1 | 1 |
| Homogeneous + diffuse granular | | | | | | | | 4 | 4 |
| Homogeneous + speckled + cytoplasmic | | | | | | | | 3 | 3 |
| Speckled | | | | | | | 1 | 8 | 9 |
| Speckled + cytoplasmic | | | | 1 | | | | 1 | 2 |
| Diffuse granular + cytoplasmic | | | | | | | | 1 | 1 |
| Diffuse cytoplasmic + speckled | | | | | | | | 3 | 3 |
| Diffuse cytoplasmic + diffuse granular | | | | | | | | 2 | 2 |
| Total | 0 | 0 | 0 | 1 | 0 | 6 | 1 | 45 | 53 |
| SLE group[b] | | | | | | | | | |
| Homogeneous | | | | | | 1 | 2 | 15 | 18 |
| Homogeneous + speckled | | | | | 2 | | 3 | 33 | 38 |
| Homogeneous + cytoplasmic | | | | | | | | 2 | 2 |
| Homogeneous + diffuse granular | | | | | | | 1 | 12 | 13 |
| Homogeneous + speckled + cytoplasmic | | | | | 2 | | 1 | 4 | 7 |
| Speckled | | | | | 5 | 3 | 5 | 34 | 47 |
| Speckled + cytoplasmic | | | | | 1 | 3 | 3 | 3 | 10 |
| Diffuse granular + cytoplasmic | | | | | 2 | | 1 | 5 | 8 |
| Diffuse granular | | | | | | 1 | 5 | 7 | 13 |
| Diffuse cytoplasmic + speckled | | | | | | | | 9 | 9 |
| Diffuse cytoplasmic + diffuse granular | | | | | | 1 | 1 | | 2 |
| Diffuse cytoplasmic + nucleolar | | | | | | 1 | | 2 | 3 |
| Total | 0 | 0 | 0 | 0 | 12 | 10 | 22 | 126 | 170 |
| CMV group[c] | | | | | | | | | |
| MTOC-MT | | | 4 | 4 | 1 | 1 | 1 | | 11 |
| MTOC-MT + IF + speckled | | 1 | 1 | 2 | | | 1 | | 5 |
| Speckled | | | 2 | | | | | | 2 |
| Negative | 4 | | | | | | | | 4 |
| Total | 4 | 1 | 7 | 6 | 1 | 1 | 2 | 0 | 22 |

[a]SLE-CMV group, anti-CMV IgM-positive SLE patients; [b]SLE group, anti-CMV IgM-negative SLE patients; [c]CMV group, anti-CMV IgM-positive patients without SLE. The AIT test was performed using an indirect immunofluorescent test kit (IT-AIT™; ImmunoThink Co., Seoul, Republic of Korea). In the CMV group, anti-MTOC-MT-positive patients accounted for 72.7% of the total patients in the CMV group and 88.9% of autoantibody-positive patients, but in the SLE-CMV group, anti-MTOC-MT was not detected at all ($P < 0.001$). Patients in the SLE-CMV group showed high titers of over 1:640 except for one who received steroid pulse therapy just before the test, but the proportion of patients in the CMV group with a titer over 1:640 was not more than 13.6% ($P < 0.001$). In addition, most of the autoantibody frequently found in the SLE-CMV group was not found in the CMV group. AIT, autoimmune target; CMV, cytomegalovirus; IF, intermediate filament; MTOC-MT, microtubule organizing center with microtubule; SLE, systemic lupus erythematosus.