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REVIEW ARTICLE

# Acupuncture Modifies Immune Cells

Takashi Takahashi<sup>1</sup>, Hiroyuki Sumino<sup>2</sup>, Tsugiyasu Kanda<sup>3</sup>, Nobuo Yamaguchi<sup>4\*</sup>

<sup>1</sup>Laboratory of Infectious Diseases, Graduate School of Infection Control Sciences, Kitasato University, Minato-ku, Tokyo, Japan

<sup>2</sup>Department of Nursing, Faculty of Nursing, Takasaki University of Health and Welfare, Takasaki, Gunma, Japan

<sup>3</sup>Department of Community Medicine, Kanazawa Medical University Himi Municipal Hospital, Himi, Toyama, Japan

<sup>4</sup>Fundamental Research for Complementary and Alternative Medicine, Kanazawa Medical University, Kahoku-gun, Ishikawa, Japan

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Acupuncture, a relief procedure originating in East Asia, has become increasingly popular as a therapy for pain and chronic diseases that are difficult to manage with conventional treatments. The attributive effects of acupuncture have been investigated in various inflammatory disorders including asthma, allergic rhinitis, inflammatory bowel disease, rheumatoid arthritis, epicondylitis, complex regional pain syndrome type 1, and vasculitis. Japan is one of the countries that has done extensive research on the various effects of acupuncture on immunological functions. Recently, we studied acupuncture's effect on leukocyte and lymphocyte subpopulations in human peripheral blood. Based on research data and other findings previously published in the literature, this article reviews the ascribed immunomodulation of acupuncture on the immune system, which includes activities of macrophages, neutrophils, natural killer cells, and lymphocytes, immunoglobulin production, and complement systems.

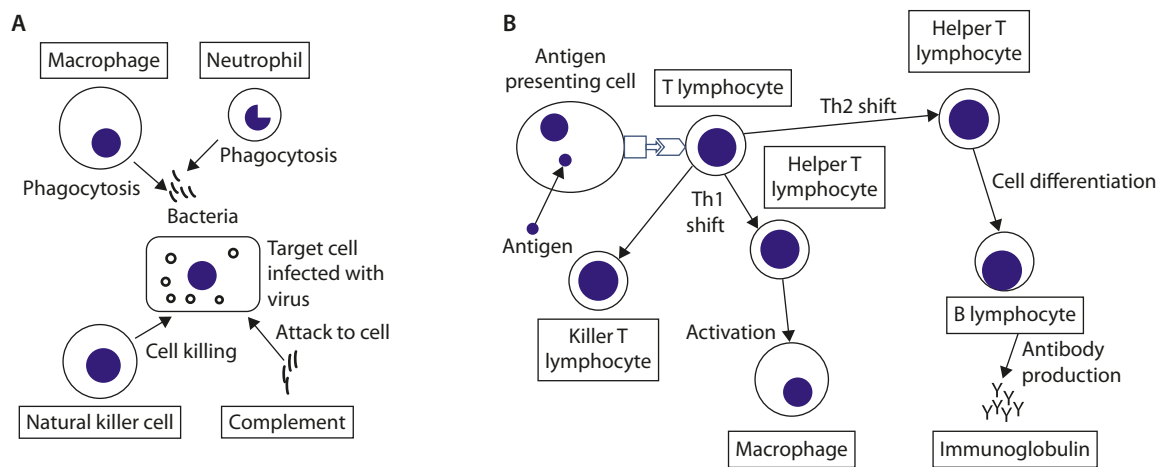
## 1. Introduction

We previously reported that hot-spring hydrotherapy or short-duration walking could regulate human immune systems.<sup>1–3</sup> Like hot-spring hydrotherapy, acupuncture treatment is traditionally used to improve disorders or complaints of ill subjects.<sup>4–7</sup> The acupuncture procedures are classified into electroacupuncture (EA) and manual acupuncture. EA is electrical stimulation through acupuncture needles with short current pulses at different frequencies and intensities (e.g., high/low frequency with low/high intensity, respectively). Interestingly, acupuncture's preventive and curative effects on the common cold have been uncovered in Japan, where there was the first report of a

multicenter randomized controlled trial.<sup>8</sup> Evidence suggests that acupuncture influences the immune system as well as the nervous system.<sup>9,10</sup> Eastern traditional medicine, including acupuncture and moxibustion, is once again being recognized in Japan and other Asian<sup>11</sup> and Western countries where complementary and alternative medicine has so far been applied. For the West, acupuncture is considered to be an alternative medicine, since it may provide effective treatment for numerous conditions from drug addiction to chronic fatigue syndrome.<sup>12,13</sup>

The immune system is designed to not only fight against pathogens, but also respond to cytokine and immunocompetent cells. It has been reported that its function is closely related to the brain and endocrine

\*Corresponding author. Department of Fundamental Research for Complementary and Alternative Medicine, Kanazawa Medical University, 1-1 Daigaku, Uchinada-machi, Kahoku-gun, Ishikawa, 920-0293, Japan.  
E-mail: serumaya@kanazawa-med.ac.jp



**Figure 1** Schematic illustration showing the roles of immune cells in the human immune system: (A) innate immunity; (B) adaptive immunity.

system.<sup>14</sup> Recently, we demonstrated the effects of acupuncture on leukocyte and lymphocyte subpopulations in human peripheral blood.<sup>15</sup> Based on our research data and previously published findings, this article reviews the ascribed immunomodulation of acupuncture on the immune system (Figure 1), including activities of the immune cells (e.g., macrophages, neutrophils, natural killer cells, lymphocytes), immunoglobulin production, and complement system. In September 2009, the data sources were systematically selected through entering the key words of acupuncture and the above immune systems into PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>).

## 2. Macrophages

Aoki and colleagues recently investigated whether EA could affect lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF)- $\alpha$  production by macrophages.<sup>16</sup> When EA intervention was immediately performed following injection of the *Streptococcus pyogenes* preparation OK-432, a significant decrease was observed in TNF- $\alpha$  production by the peritoneal macrophages induced by LPS. In addition, naloxone, an antagonist of opioid receptors, to some extent inhibited the suppression of TNF- $\alpha$  induced by EA. In another report, treatment with EA is described to have reduced LPS-stimulated induction of cyclooxygenase-2 mRNA in macrophages from the murine model of type II collagen-induced arthritis.<sup>17</sup>

Experimental evidence suggests that electrical stimulation of the vagus nerve inhibits macrophage activation and production of TNF, interleukin (IL)-1 $\beta$ , IL-6, IL-18, and other proinflammatory cytokines.<sup>18</sup> The activated macrophages appear to be important target cells of EA's immunosuppressive effects. On the other hand, the activation by acupuncture for macrophage

function is shown in rat models of immunodepression.<sup>19</sup> After 6 days of acupuncture on the Zusani (ST36) point, the phagocytic percentage and index of peritoneal macrophages from the immunosuppressant rats significantly increased, suggesting that acupuncture increases macrophage function. Monocyte phagocytosis in patients suffering from various painful disorders was elevated in 45% of subjects 30 minutes post-acupuncture treatment on the ST36 and Hegu (LI4) points, and in 100% after 24 hours.<sup>20</sup>

In our investigation, the CD11b+ cell counts, which are closely associated with macrophage activity, did not significantly increase in 17 healthy volunteers receiving single acupuncture treatment on the Ganshu (BL18), Pishu (BL20), Shenshu (BL23), and ST36 points. However, the expression levels of IL-1 $\beta$  in blood cells showing macrophage activity significantly increased on days 2 and 8 post-acupuncture. The abovementioned findings are summarized in Table 1.<sup>15–20</sup> Further clinical research is required to clarify the role of the immunomodulator, acupuncture, on macrophage activity in a pathological or healthy setting.

## 3. Neutrophils

The effects of acupuncture treatment on rats with sepsis by cecal ligation and puncture have been investigated.<sup>21</sup> Results demonstrated that acupuncture intervention enhanced survival and reversed neutrophil impairment migration toward the peritoneal cavity, suggesting that acupuncture can be applied for treatment of experimental infectious disease. Interestingly, there is a manuscript regarding acupuncture's effect on neutrophil respiratory burst in a placebo-controlled single-blinded clinical study.<sup>22</sup> For 11 volunteers, acupuncture on the LI11 point was performed for 30 minutes twice a week for 4 weeks (8 times in all); the

**Table 1** Effects of acupuncture on macrophage activity

Procedure	Function or cell count	Research type	Reference
Electroacupuncture	Suppressed	Animal	16
Electroacupuncture	Suppressed	Animal	17
Electroacupuncture	Not significant	Animal	18
Acupuncture	Activated	Animal	19
Acupuncture	Activated	Human	20
Acupuncture	Activated	Human	15

**Table 2** Effects of acupuncture on neutrophil activity

Procedure	Function or cell count	Research type	Reference
Acupuncture	Activated	Animal	21
Acupuncture	Activated	Human	22
Acupuncture	Not significant	Human	23
Acupuncture	Increased	Human	24
Acupuncture	Modulated	Human	15

respiratory burst of neutrophils was shown to be significantly activated after a course of several acupuncture treatments. However, a single acupuncture intervention had no immediate treatment effect on the neutrophil respiratory burst in similar clinical investigations.<sup>23</sup>

In our research, the granulocyte counts, including that of neutrophils, decreased the day after acupuncture; meanwhile, lymphocyte numbers increased on day 8 after acupuncture in granulocyte-dominant volunteers (comprising over 70%).<sup>15</sup> Nevertheless, lymphocyte counts decreased on days 1 and 2 after acupuncture, accompanied by an increase in granulocyte numbers on day 2 after acupuncture in lymphocyte-dominant individuals (comprising over 40%).<sup>15</sup> Recently, in patients with gynecologic malignancies, acupuncture's effects on chemotherapy-induced neutropenia have been reported in a pilot randomized, sham-controlled clinical trial.<sup>24</sup> The abovementioned findings are summarized in Table 2.<sup>15,21–24</sup> Research suggests that acupuncture treatment induces immunomodulation of neutrophil functions and counts.

#### 4. Natural Killer Cells

Yu et al previously demonstrated that once-a-day EA stimulation on the bilateral ST36 point for 3 successive days enhanced splenic natural killer (NK) cell activity via augmented endogenous levels of interferon- $\gamma$  in BALB/c mice<sup>25</sup> or Fischer 344 rats.<sup>26</sup> After starting acupuncture on the BL23 points for 20 days, the ratio of NK cells to T lymphocytes (CD3-negative, NK-positive) is described as increasing in the spleen of mice after day 7.<sup>27</sup> EA treatment also affected the modulation of splenic NK cell activity through the anterior<sup>28</sup> or lateral<sup>29</sup> hypothalamic area of rats. The beneficial

effects of acupuncture stimulation on NK cell activity are shown in peripheral blood obtained from subjects with various painful disorders,<sup>20</sup> patients with malignant tumors,<sup>30</sup> or individuals with rheumatoid arthritis.<sup>31</sup> Of note, however, is that patients receiving chemotherapy experienced no significant changes post-EA treatment in NK activity, T cell subpopulations, humoral immunity, and leukocyte count as compared to those before treatment.<sup>32</sup>

In our study, CD16+ and CD56+ cell counts, which are closely associated with the activity of NK cells, also gradually increased by statistically significant levels in healthy volunteers; especially remarkable were the variations in CD56+ cell numbers on day 8 after single acupuncture intervention.<sup>15</sup> Interestingly, the identification of genes (e.g., PTK, CD94, SHP-1) altering their expression in the EA-induced upregulation of NK cell activity has recently been described using high-throughput screening by cDNA microarray technique.<sup>33</sup> These findings are summarized in Table 3.<sup>15,20,25–33</sup>

#### 5. Lymphocytes

After starting acupuncture on the BL23 points for 20 days, the ratio of CD4+/CD8+ and T lymphocyte surface antigens is shown to be significantly reduced on days 3 and 7 as compared to the controls, while the activated T cells increased by day 7.<sup>27</sup> In subjects with various painful disorders, 80% of treated patients showed a significant increase in CD3+ and CD4+ values 30 minutes after acupuncture on the ST36 and LI4 points, and additionally demonstrated an increase in CD8+ count 24 hours post-stimulation.<sup>20</sup>

In our research, the CD2+, CD4+ and CD8+ cell counts, which are closely associated with T cell activity,

**Table 3** Effects of acupuncture on natural killer cell activity

Procedure	Function or cell count	Research type	Reference
Electroacupuncture	Activated	Animal	25, 26
Acupuncture	Increased	Animal	27
Electroacupuncture	Activated	Animal	28, 29
Acupuncture	Activated	Human	20, 30, 31
Electroacupuncture	Not significant	Human	32
Electroacupuncture	Activated	Animal	33
Acupuncture	Increased	Human	15

**Table 4** Effects of acupuncture on lymphocyte activity

Procedure	Function or cell count	Research type	Reference
Acupuncture	Increased	Animal	27
Acupuncture	Increased	Human	20
Electroacupuncture	Suppressed	Animal	34
Acupuncture	Suppressed	Human	35
Electroacupuncture	Suppressed	Animal	36
Electroacupuncture	Activated	Animal	37
Acupuncture	Increased	Human	15

had significantly increased by day 8 post-acupuncture intervention, and CD19+ cell counts, which are related to B cell activity, elevated on day 8 post-acupuncture.<sup>15</sup> The production of the Th2-specific cytokines IL-4 and IL-13 in anti-CD3 monoclonal antibody-activated splenocytes was significantly suppressed in ST36 EA mice as compared to non-acupunctured mice immunized intraperitoneally with 2,4-dinitrophenylated key-hole limpet protein (DNP-KLH).<sup>34</sup> For individuals with chronic allergic rhinitis, a significant decrease in plasma levels of IL-10, Th2-specific cytokine, was discovered after a specific acupuncture treatment as compared to the controls.<sup>35</sup> The inhibitory effects of EA on ST36 and Lanwei (Extra 33) points on thymocyte apoptosis are demonstrated in morphine-induced immunosuppressed mice.<sup>36</sup> In the traumatized rats, EA stimulation on ST36 and Extra 33 points could enhance the activity of tyrosine protein kinase in subcellular fractions during the early stages of T lymphocyte activation, indicating that EA could prevent the inhibition of tyrosine protein kinase induced by traumatic stress, thus contributing to transmembrane signal transduction of T cells.<sup>37</sup> These findings are summarized in Table 4.<sup>15,20,27,34-37</sup>

## 6. Immunoglobulin Production and Complement System

Using mice immunized with DNP-KLH, the effects of EA stimulation on the ST36 point on production

of immunoglobulin (Ig) E were determined.<sup>34</sup> Serum levels of antigen-specific IgE and total IgE were reported to be significantly reduced compared to the non-acupunctured controls. In a clinical investigation of 46 subjects with Behcet's disease, the recurrence rate in the acupuncture treatment group was significantly lower than that in the control group, with very significant differences in the serum level of the light-chain (kappa) of IgM of the treatment group before and post-acupuncture.<sup>38</sup> For 39 women who had had chronic pelvic inflammatory disease for at least 2 years (and who had been previously treated pharmacologically with no effect), a 4-week therapeutic protocol consisting of acupuncture treatments thrice a week resulted in a significant decrease in serum IgM levels.<sup>39</sup> In addition, exercise-induced decreases in salivary secretory IgA were inhibited by acupuncture stimulation, which was applied 4 hours post-game every night during the exercise period at the LI4 and ST36 points for 20 minutes, and the Kyosya (ST6) and Ko-sai (LU6) points for 15 minutes.<sup>40</sup> In contrast, for cases of major abdominal surgery, acupuncture intervention did not induce significant changes in serum immunoglobulin (IgA, IgG, IgM) concentration either during or post-surgery.<sup>41</sup> Another investigation of 30 inpatients with schizophrenia revealed that IgG, IgA and IgM levels in sera did not significantly change pre- and post-acupuncture intervention on the ST36 point thrice a week for 8 weeks, although it had preventive effects with regard to hospital infections.<sup>42</sup> The serum from acupuncture-stimulated rats had more

**Table 5** Effects of acupuncture on immunoglobulin production and complement systems

Procedure	Function or amount	Research type	Reference
Electroacupuncture	Decreased	Animal	34
Acupuncture	Decreased	Human	38
Acupuncture	Decreased	Human	39
Acupuncture	Increased	Human	40
Acupuncture	Not significant	Human	41
Acupuncture	Not significant	Human	42
Acupuncture	Activated	Animal	43

potent complement activity than that from the control rats, suggesting that it might activate the complement system.<sup>43</sup> The abovementioned findings are summarized in Table 5.<sup>34,38–43</sup> Basic or clinical studies still need to be performed to clarify acupuncture's role in Ig production and complement system.

## 7. Discussion

Regarding the mechanisms of acupuncture action, Abo and Kumagai<sup>44</sup> reported that granulocytes increased as a result of excitation of the sympathetic nervous system, as did lymphocytes by excitation of the parasympathetic nervous system. Subjects dominated by the sympathetic nervous components could release stress, whereas those in subjects dominated by the parasympathetic nervous system were excited by acupuncture. In this way, cell counts return to appropriate levels post-acupuncture. In addition, the endogenous opioid-mediated mechanisms of EA are well-understood.

Another article about the role of acupuncture on immune function<sup>45</sup> reported the following considerations: (1) the Zusanli (ST36) point might be one of the specific points modulating immune activity; (2) this immune modulation system might share a common nervous pathway with the acupuncture analgesia-producing system; (3) acupuncture treatment might modify NK cell activity through unknown heat-stable humoral factors and the nervous system; and (4) acupuncture might activate the complement system. In future studies, we should determine whether or not acupuncture treatment can be used more often to treat disorders including acquired immunodeficiency syndrome and swine-origin novel influenza (H1N1).

In conclusion, it seems that acupuncture treatment is able to modulate immunosuppressed or immunoactivated conditions through various immune functions, including the activities of macrophages, neutrophils, NK cells and lymphocytes, immunoglobulin production, and complement systems. Further basic or clinical studies are required to clarify acupuncture's effect on immune system function in various clinical settings.

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