

## IV. 研究成果の刊行に関する一覧表

雑誌

	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年	報告書に掲載
1	Nishiya T, Matsumoto K, Maekawa S, Kajita E, Horinouchi T, Fujimuro M, Ogasawara K, Uehara T, Miwa S	Regulation of inducible nitric oxide synthase by the SPRY domain- and SOCS box-containing proteins.	J. Biol. Chem.		(in press)		
2	Honda T, Nakajima S, Egawa G, Ogasawara K, Malissen B, Miyachi Y, Kabashima K.	Compensatory role of Langerhans cells and langerin-positive dermal dendritic cells in the sensitization phase of murine contact hypersensitivity.	J Allergy Clin Immunol	125	1154-1156	2010	
3	Mori T, Ishida K, Mukumoto S, Yamada Y, Imokawa G, Kabashima K, Kobayashi M, Bito T, Nakamura M, Ogasawara K, Tokura Y.	Comparison of skin barrier function and sensory nerve electric current perception threshold between IgE-high extrinsic and IgE-normal intrinsic types of atopic dermatitis.	Br J Dermatol	162	83-90	2010	
4	Kumagai K, Hamada Y, Holmlund AB, Goto A, Nakaoka K, Arai G, Yamane S, Suzuki R	The levels of vascular endothelial growth factor in the synovial fluid correlated with the severity of arthroscopically observed synovitis and clinical outcome after temporomandibular joint irrigation in patients with chronic closed lock	Oral Surg Oral Med Oral Pathol Oral Radiol Endod	109	185-190	2010	*
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11	Yoshiki R, Kabashima K, Sakabe J-I, Sugita K, Bito T, Nakamura M, Malissen B, Tokura Y	The mandatory role of IL-10-producing and OX40L-expressing mature Langerhans cells in local UVB-induced immunosuppression.	J Immunol	184	5670-5677	2010	*
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		high-molecular-weight proteins.					
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## V. 研究成果の刊行物・別刷

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## The levels of vascular endothelial growth factor in the synovial fluid correlated with the severity of arthroscopically observed synovitis and clinical outcome after temporomandibular joint irrigation in patients with chronic closed lock

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**Objective.** This study aimed to investigate the level of vascular endothelial growth factor (VEGF) in the temporomandibular joint (TMJ) synovial fluid (SF) and the severity of arthroscopically observed synovitis before and after visually guided TMJ irrigation (VGIR) in patients with chronic closed lock (CCL). In addition, the findings were correlated with the clinical outcome.

**Study design.** Twenty-four patients with unilateral CCL, who underwent a second VGIR either as a repeated therapeutic TMJ irrigation or as a follow-up arthroscopy, were enrolled in the study. They were divided into either successful (s-group; n = 11) and unsuccessful (u-group; n = 13) groups. The VEGF level in the aspirated SF and the severity of synovitis were compared between the s- and u-groups. In each group, the same parameters were compared before and after VGIR. The correlation of the VEGF level with the severity of synovitis was also studied.

**Results.** At the first VGIR, the VEGF levels showed no significant differences when comparing s- and u-groups. At the second VGIR, the VEGF level was significantly higher in the u-group. The VEGF level significantly decreased after the first VGIR in the s-group but remained unchanged in the u-group. There was no significant correlation between the VEGF level and the severity of synovitis.

**Conclusions.** The level of VEGF in TMJ SF seems to reflect the clinical status in patients with CCL. Moreover, VEGF may be an important target molecule in future chemotherapy of TMJ CCL. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:185-190)

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Visually guided temporomandibular joint (TMJ) irrigation (VGIR) is a simple and effective treatment in patients with symptomatic internal derangement (ID) and osteoarthritis (OA).<sup>1-3</sup> The VGIR technique enables arthroscopic observation with a 1.2-mm-diameter rod-lens arthroscope and simultaneous irrigation of the superior joint compartment (SJC) under local anesthesia. It is also a valuable tool for outcome assessments,<sup>4-9</sup> and we have previously reported that VGIR may contribute to the remission of arthroscopically observed synovitis.<sup>7</sup> However, the severity of arthroscopic findings of OA, synovitis, or fibrous adhesion do not seem to be reflected by the clinical state in patients with chronic closed lock (CCL).<sup>4-9</sup>

The clinical efficiency of TMJ irrigation is thought to reduce TMJ pain by washing out various biochemical mediators in the synovial fluid (SF), such as pro-inflammatory cytokines.<sup>10-15</sup> Regarding the correlation between the levels of cytokines in the TMJ SF and clinical outcome of TMJ irrigation for ID and OA, Ishimaru et al.<sup>15</sup> reported that the concentration of matrix metalloproteinase 3 and its ratios to total protein and albumin decreased significantly after a successful

TMJ irrigation combined with postoperative medication with a cyclooxygenase-2 inhibitor. The prevalence of interleukin-10 in the SF has been considered to be a strong predictor of successful outcome after TMJ irrigation.<sup>6,16</sup> Although CCL has been recognized as an inflammatory disease,<sup>17</sup> we have not found any inflammatory mediators in the SF that strictly link to the clinical state.

Vascular endothelial growth factor (VEGF), known to participate in angiogenesis and vascular permeability, has been detected in the serum and SF in patients with rheumatoid arthritis (RA) and OA and is suggested to be an indicator of RA disease activity.<sup>18</sup> It has also been detected in TMJ SF. Moreover, in TMJs with CCL, synovitis with growth of small new blood vessels has been frequently observed during arthroscopic examination,<sup>19-23</sup> and the number of vessels significantly correlated with the degree of arthroscopically diagnosed synovitis.<sup>21,23</sup>

With this background, we hypothesized that VEGF in the TMJ SF is involved in the pathogenesis of synovitis and may influence the clinical outcome after treatment of CCL. We therefore studied the level of VEGF in the TMJ SF and the severity of arthroscopically observed synovitis before and after VGIR in patients with CCL. Moreover, these findings were correlated with the clinical outcome after VGIR.

## MATERIAL AND METHODS

### Patients and clinical assessments

The inclusion criteria for the study were a clinical diagnosis of unilateral CCL, defined as a persistent restricted mouth opening with functional TMJ pain for more than 3 months, and MRI findings of nonreduced disc displacement with or without signs of OA in the affected TMJ. The exclusion criteria were previous severe jaw trauma, previous TMJ surgeries, or other TMJ diseases.

Forty-five patients (13 men, 32 women) were enrolled in the study and underwent a first VGIR. All of them had unconscious bruxism which was proved by attrition, oppressive pain or discomfort of masticatory muscles, and awareness of their clenching habit. Moreover, 36 of the 45 patients had OA signs on the MRI. Before VGIR, they had all received nonsurgical treatment comprising medication, physiotherapy, and/or nocturnal bite splint therapy for more than 1 month, without success. Any nonsteroidal antiinflammatory drugs (NSAIDs), muscle relaxants, or minor tranquilizers were interrupted at least 2 weeks before VGIR to prevent any influence on the parameters being studied.

The VGIR technique was performed under local anesthesia, according to previously described procedures.<sup>4,5,8,9,16</sup> Briefly, the VGIR involved a simple ir-

**Table I.** Severity of arthroscopically observed synovitis

Synovial lining score	
0	Within normal
1	Hypervascularity (hyperemia) and/or synovial hyperplasia, or both, limited to the posterior attachment
2	More extensive hypervascularity (hyperemia) and/or synovial hyperplasia

**Table II.** Clinical success criteria for visually guided temporomandibular joint (TMJ) irrigation

1	Postoperative painless range of mandibular motion (P-ROM; interincisor distance, mm) has increased.
2	Postoperative P-ROM is $\geq 38$ mm.
3	Postoperative self-evaluated TMJ pain (visual analog scale, range 0-100) is $< 20$ and $< 60\%$ of preoperative level.

For success, all of these criteria must be fulfilled.

rigation of the SJC with  $> 150$  mL physiologic saline solution under arthroscopic observation using a 1.2-mm-diameter rod-lens arthroscope. During VGIR, we did not perform any surgical treatment, such as lysis of fibrous adhesions or lateral release of the joint capsule. No agents, such as sodium hyaluronate or corticosteroids, were injected into the TMJ during VGIR. After VGIR, antibiotics and NSAIDs were prescribed for 3 days. Mandibular motion exercises consisting of mouth opening, protrusion, and lateral movements (2 or 3 sessions per day, with 5 repeats of each movement per session) were begun 3 days after VGIR, and a nocturnal bite splint therapy was continued in those patients needing it. These postoperative therapies were continued until the patients were symptom free. Moreover, patients were told to regularly perform relaxation of masticatory muscles when noticing clenching to avoid continuous excessive compression force to the TMJ, even in symptom-free patients.

All VGIR procedures in this study were performed by one of authors (Y.H.). The severity of arthroscopically observed synovitis were assessed intraoperatively by 3 oral surgeons (Y.H., K.N., and G.A.) without discussion, according to the criteria of synovial lining (SL) score (Table I).<sup>7</sup> All of their assessments were the same. Moreover, the SL scores were reassessed in the digital videotapes to confirm the intrainvestigator variation. The reassessed SL scores completely accorded with the data during VGIR.

The 45 patients were divided into successful (s-) and unsuccessful (u-) groups according to the clinical success criteria (Table II). Thirty-two of the 45 patients fulfilled the success criteria within median 8 months (range 2-23 months) after the first VGIR. Twenty-one

**Table III.** Clinical data of the s- and u-groups at the first and second visually guided temporomandibular joint irrigations (VGIRs)

	Age (yrs)	Positive signs of OA	P-ROM (mm)		VAS	
			1st VGIR	2nd VGIR	1st VGIR	2nd VGIR
s-group (n = 11)	41 (24-65)	9	32 (23-43)	44 (38-48)	50 (4-65)	0 (0-10)
u-group (n = 13)	32 (27-56)	10	30 (22-37)	32 (28-37)	50 (35-67)	48 (7-90)
P value	.643	.585	.385	<.001*	.235	<.001*

Values are median (range). Mann-Whitney *U* test or Fisher exact probability test.  
 OA, Osteoarthritis; VAS, visual analog scale; ROM, painless range of mandibular motion.  
 \**P* < .001.

patients in the s-group declined a second VGIR as a follow-up arthroscopy, and the remaining 11 patients underwent a second VGIR median 14 months (range 4-23 months) after the successful first VGIR. On the other hand, 13 of the 45 patients did not fulfill the success criteria. They all underwent a therapeutic second VGIR median 5 months (range 2-13 months) after the first VGIR. After the second therapeutic VGIR, 5 of the 13 patients fulfilled the success criteria, 5 underwent a successful open TMJ surgery, and the remaining 3 patients declined further TMJ surgery. In summary, 24 patients (s-group: n = 11; u-group: n = 13) were enrolled in the final analyses. The clinical data of these 24 patients at the first and second VGIR are shown in Table III.

The study was approved by the Research Ethical Committee of Tsurumi University, and informed consent for this study was obtained from each of the subject patients.

**Preparation of aspirated SF sample**

Synovial fluid samples were collected by one of the authors (Y.H.) immediately before each VGIR. After local anesthesia, 2 mL physiologic saline solution was injected into the SJC using a 21-gauge needle and 5-mL disposable syringe. The mixture of SF and saline solution was aspirated and reinjected 10 times. The last aspirated SF sample with saline solution (A-SF) was then collected. The samples were centrifuged (440g for 10 minutes at 4°C) to remove cells and stored at -80°C until the assay was performed.

**Measurement of the concentration of VEGF and total protein in the A-SF**

The concentration of VEGF in the A-SF was measured by the first author. The concentration of VEGF in the samples were assayed using human VEGF-A Quantikine ELISA kit (R&D Systems, Minneapolis, MN) according to the manufacturer's instructions. The assay sensitivity of VEGF was 3.25 pg/mL. Concentrations of VEGF less than minimal sensitivity were calculated as 0.

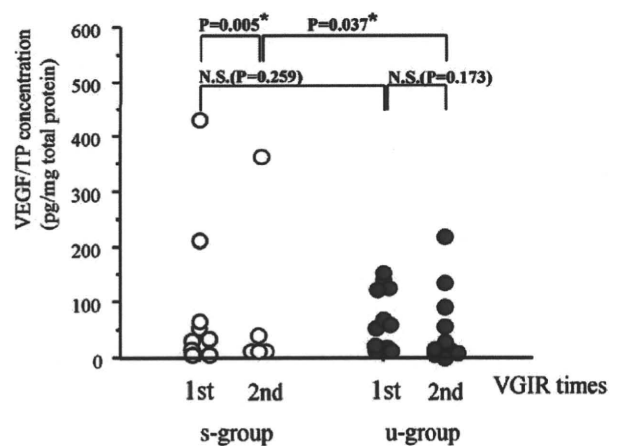


Fig. 1. Vascular endothelial growth factor (VEGF) level in the synovial fluid (SL) of s- and u-groups at the first and second visually guided temporomandibular joint irrigation (VGIR).  
 TP, Total protein.  
 \**P* < .05.

Protein was assayed using the Bradford Reagent (Sigma-Aldrich, St. Louis, MO) according to the manufacturer's technical instructions for the Bradford method. The level of VEGF was defined as its concentration per milligram of total protein in the A-SF. This procedure can replace the use of an internal standard, such as vitamin B12.<sup>24</sup>

**Statistical analysis**

At the first and second VGIR, the levels of VEGF in the A-SF and the SL score were compared between the s- and u-groups. In each group, the same parameters were also compared between the first and second VGIR. Moreover, the correlation of the VEGF level in the A-SF with the SL score was studied. Fisher exact probability test, Mann-Whitney *U* test, or Wilcoxon signed ranks test was used for statistical analyses. A probability value (*P* value) of <.05 was considered to be significant. The software used for the statistics was the Stat View J-5.0 (SAS Institute, Cary, NC).