Brief Report

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Collagen-derived peptides enhance resistance to *Pseudomonas aeruginosa* infection in silkworms

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SUMMARY: Collagen-derived peptides are widely used as food ingredients and dietary supplements, but their effects on host defense against bacterial infection remain poorly understood. Here, we examined whether GFG-01, a granulated preparation of a fish-derived collagen hydrolysate produced using ginger protease, enhances resistance to *Pseudomonas aeruginosa* PAO1 infection in the silkworm (*Bombyx mori*). Oral administration of GFG-01 by mixing the preparation into the diet improved the post-infection outcome of larvae compared with vehicle-treated controls. Western blot analysis suggested that intrahemocoelic administration of GFG-01 induced accumulation of Cecropin B, an antimicrobial peptide, in the hemolymph. RNA-seq-based Gene Ontology enrichment analysis of samples collected after oral administration further showed tissue-dependent immune-related gene expression patterns: immune-related categories were enriched among downregulated genes in the fat body and among upregulated genes in hemocytes. These findings indicate that orally administered GFG-01 can improve the outcome of bacterial infection in silkworms and that GFG-01 is associated with modulation of host innate immune responses under the tested conditions.

Keywords: *Bombyx mori*, GFG-01, Cecropin B, innate immunity, RNA sequencing, functional food

1. Introduction

Collagen-derived peptides are widely used as food ingredients and dietary supplements, but their effects on host defense remain poorly defined. More broadly, food-derived molecules are increasingly recognized not only as nutrients but also as modulators of host physiology and immunity. Indeed, several food- or microbiota-derived substances have been reported to stimulate innate immune responses in invertebrates and mammals, including high-molecular-weight broccoli-derived polysaccharides, peanut triacylglycerols, and human gut-associated bacteria identified by silkworm-based screening approaches (*1-4*). However, whether collagen-derived peptides can alter infection resistance at the whole-organism level remains unclear.

Appropriate *in vivo* models are required to evaluate such host-directed effects. We and others have established the silkworm (*Bombyx mori*) as an alternative infection model for studying host-pathogen interactions and therapeutic responses *in vivo* (*5-10*). In silkworms, injection of human pathogenic microorganisms into the hemolymph causes lethal infection, and survival can be used as a quantitative readout for infection progression and therapeutic efficacy (*5,6*). This model is inexpensive, experimentally tractable, and applicable to a wide range of pathogens, including bacteria and fungi (*7-10*).

Importantly, the silkworm infection model can be used not only to detect direct antimicrobial effects but also to analyze infection resistance mediated by activation of host innate immunity. Oral administration of lactic acid bacteria has been reported to improve survival in bacterial infection models of silkworms (*11*). In addition, Gram-negative bacterial peptidoglycan and ingested bacteria can induce primed immune responses that increase resistance to subsequent systemic infection (*12,13*). More recently, pretreatment with *N*-acetylchitohexaose was shown to enhance resistance to *P. aeruginosa* infection and to induce immune effector genes at the hemocyte transcriptome level (*14*). These phenomena are commonly discussed in the context of immune priming in insects (*15*).

A key consideration in interpreting such responses is that insect immunity is organized across multiple tissues. In silkworms and other insects, the fat body is a major source of humoral immune effectors, the gut serves as a frontline barrier for orally encountered materials, and hemocytes mediate cellular defenses such as phagocytosis, nodulation, and encapsulation (*16,17*). Studies in *Drosophila* further suggest that gut-derived signals can influence systemic immunity through inter-organ communication (*18,19*). These observations raise the possibility that orally administered immunomodulators may not induce a uniform whole-body immune response, but instead provoke distinct responses in different immune-related tissues.

This possibility is supported by recent tissue-resolved studies. Comparative transcriptomic analysis in *Drosophila* has shown that hemocytes and fat body, despite being the two principal professional immune tissues, can display strikingly different responses to systemic infection (*20*). In addition, the insect fat body is a polyfunctional tissue that integrates immunity with metabolism, storage, and reproductive physiology, and constraints on this multifunctionality can give rise to reproduction-immunity trade-offs (*21*). Therefore, changes in immune gene expression in one tissue do not necessarily predict organism-level protection, and improved infection resistance may arise from differently directed responses across tissues rather than from uniform immune activation.

Collagen-derived peptides are plausible candidates for such orally active host modulators precisely because their reported biological behavior is compatible with non-uniform, tissue-dependent immunoregulation. After oral ingestion of collagen hydrolysates, multiple hydroxyproline-containing oligopeptides are detected in human blood, indicating that orally administered collagen peptides are systemically bioavailable in peptide form (*22*). Moreover, some collagen-derived peptides can reach peripheral tissues after ingestion (*23*). Importantly, the reported immunological effects of collagen-derived peptides are context- and cell type-dependent rather than uniformly stimulatory (*24,25*).

Among insect innate immune effectors, antimicrobial peptides are major defense factors. Cecropins are evolutionarily conserved antimicrobial peptides induced by microbial challenge, and cecropin genes have been characterized in silkworms (*26,27*). Induction of such peptides is therefore an important indicator when evaluating whether collagen-derived peptides modify infection resistance through host responses.

Based on these considerations, we investigated whether orally administered GFG-01, a granulated preparation of a fish-derived collagen hydrolysate produced using ginger protease, improves the outcome of *P. aeruginosa* infection in silkworms. In separate experiments, we examined whether intrahemocoelic GFG-01 administration induced Cecropin B accumulation in the hemolymph and whether oral administration produced tissue-dependent immune-related gene expression.

2. Materials and Methods

2.1. Silkworms

Silkworm (*Bombyx mori*) larvae were reared as described previously (*5,6*). Unless otherwise stated, fifth-instar larvae were used. After sample pretreatment, larvae were maintained at 27°C before infection challenge and at 37°C after infection challenge.

2.2. Bacterial strain

Pseudomonas aeruginosa PAO1 was used as the infectious strain. A full-growth culture was diluted 10^{-6} in saline, and 50 μL was injected into the hemolymph as described for the silkworm infection model (*5,6*). The viable count of the undiluted culture was 2×10^9 CFU/mL, corresponding to an inoculum of 100 CFU/larva after dilution and injection.

2.3. GFG-01 preparation

GFG-01 was supplied by Nippi, Inc. (Tokyo, Japan). According to the manufacturer, GFG-01 is a granulated preparation of GFF-01, a fish-derived collagen hydrolysate prepared using ginger protease. GFF-01 and the preparation of ginger-protease-degraded collagen hydrolysates have been described previously (*28,29*). GFG-01 was mixed into the diet for oral administration or dissolved in saline for intrahemocoelic administration.

2.4. Oral administration and infection challenge

GFG-01 (1.018 g) was mixed with 6 g of artificial diet and administered orally to a group of five day-1 fifth-instar larvae at 27°C for 15 h. This amount was selected based on preliminary dose-ranging experiments. The amount consumed was estimated from the difference between the initial and remaining diet weights, corresponding to an estimated intake of 99 mg GFG-01/larva. Vehicle-treated controls received diet prepared under the same conditions without GFG-01. After feeding, each larva was challenged intrahemocoelically with 50 μL of a 10^{-6} dilution of a full-growth *P. aeruginosa* PAO1 culture. Larvae were maintained at 37°C, and survival was assessed 24 h after infection.

2.5. Western blotting

GFG-01 (500 μg/larva in 50 μL saline) or 50 μL saline was injected into the hemolymph of fifth-instar larvae. After incubation at 27°C for 6 h, hemolymph was collected from six larvae in each group and pooled in

pairs to generate three samples per group. Proteins were precipitated, separated by SDS-PAGE, and transferred to PVDF membranes. Cecropin B was detected using a rabbit anti-Cecropin B antibody (Abcam, ab27571; 1:1,000) and horseradish peroxidase-conjugated goat anti-rabbit IgG (SouthernBiotech, 4030-05; 1:4,000), followed by chemiluminescent detection.

2.6. RNA-seq and GO enrichment

Fat body and hemocyte samples were collected from fifth-instar larvae 15 h after oral administration of GFG-01 at an estimated intake of 76 mg/larva or control diet. One larva was used for each biological replicate, and three biological replicates were analyzed per condition for each tissue. Fat bodies were dissected, collected with forceps, and homogenized before RNA extraction. Hemolymph was collected into tubes containing phenylthiourea to prevent melanization, and hemocytes were recovered by centrifugation. Total RNA was extracted using the Direct-zol RNA MiniPrep Kit (Zymo Research, R2050), and RNA concentration was measured using the Qubit RNA HS Assay Kit (Thermo Fisher Scientific, Q32852). Library preparation and mRNA sequencing on an Illumina NovaSeq X Plus platform, generating approximately 6 Gb per sample, were performed as described by Mikami *et al.* (*14*), with modifications. Transcript abundance was quantified using Salmon version 1.10.3 and imported with tximport. Genes with counts of at least 10 in three or more samples were retained for analysis. Differential expression analysis was performed using DESeq2 version 1.43.1 in R version 4.5.0. Differentially expressed genes were defined by an adjusted P value < 0.05 and an absolute $\log_2$ fold change ≥ 1. Genes were annotated using SilkDB3.0 annotation files. GO enrichment analysis was performed using the enricher function of clusterProfiler version 4.16.0 with Benjamini-Hochberg correction. The feeding conditions were the same in the infection and RNA-seq experiments; the different estimated intakes reflect differences in actual diet consumption.

2.7. Statistical analysis

Survival at the 24-h endpoint was compared using a two-sided Fisher's exact test. For RNA-seq, differential expression and enrichment significance were evaluated as described above. A P value < 0.05 was considered statistically significant.

3. Results

3.1. Oral administration of GFG-01 improves post-infection larval condition

We first asked whether GFG-01 could affect the course of bacterial infection when administered through a physiologically relevant oral route. GFG-01 was mixed into the diet and administered for 15 h before intrahemocoelic challenge with *P. aeruginosa* PAO1. This design allowed us to test whether prior oral exposure to GFG-01 could alter the subsequent course of systemic bacterial infection. At the estimated intake of 99 mg/larva shown in Figure 1, all vehicle-treated infected larvae died within 24 h (0/5 survived), whereas all GFG-01-treated larvae survived and remained visibly healthier (5/5; two-sided Fisher's exact test, P = 0.0079). These observations indicate that oral administration of GFG-01 can improve the outcome of *P. aeruginosa* infection in silkworms.

3.2. Intrahemocoelic GFG-01 administration induces Cecropin B accumulation in the hemolymph

We next examined whether GFG-01 could induce an antimicrobial peptide response independently of gastrointestinal processing. GFG-01 was administered intrahemocoelically, and hemolymph was collected 6 h later for western blot analysis using an antibody against Cecropin B. This assay was used because Cecropin B is a representative antimicrobial peptide involved in insect humoral innate immunity. Western blot analysis showed a Cecropin B-positive band in GFG-01-treated larvae, whereas saline-treated controls showed a weak or absent corresponding signal under the same processing conditions (Figure 2). These results suggest that intrahemocoelic administration of GFG-01 induces the accumulation of Cecropin B, an antimicrobial peptide, in the hemolymph.

3.3. GFG-01 treatment is associated with tissue-dependent immune-related transcriptional patterns

Because insect immune responses are distributed across multiple tissues, we then asked whether orally administered GFG-01 produced similar or distinct transcriptional responses in major immune-related tissues. Fat body and hemocyte samples were collected 15 h after administration of GFG-01 at an estimated intake of 76 mg/larva or control diet and analyzed by RNA-seq. Differentially expressed genes were then subjected to Gene Ontology (GO) enrichment analysis. GO enrichment analysis revealed different immune-related expression patterns between the fat body and hemocytes (Figure 3). In the fat body, downregulated genes were enriched for terms including innate immune response and defense response to bacterium. In contrast, upregulated genes in hemocytes were enriched for similar immune-related categories. Thus, at 15 h after oral administration, the transcriptomic response to GFG-01 was not uniform across tissues.

4. Discussion

These findings support three main conclusions.

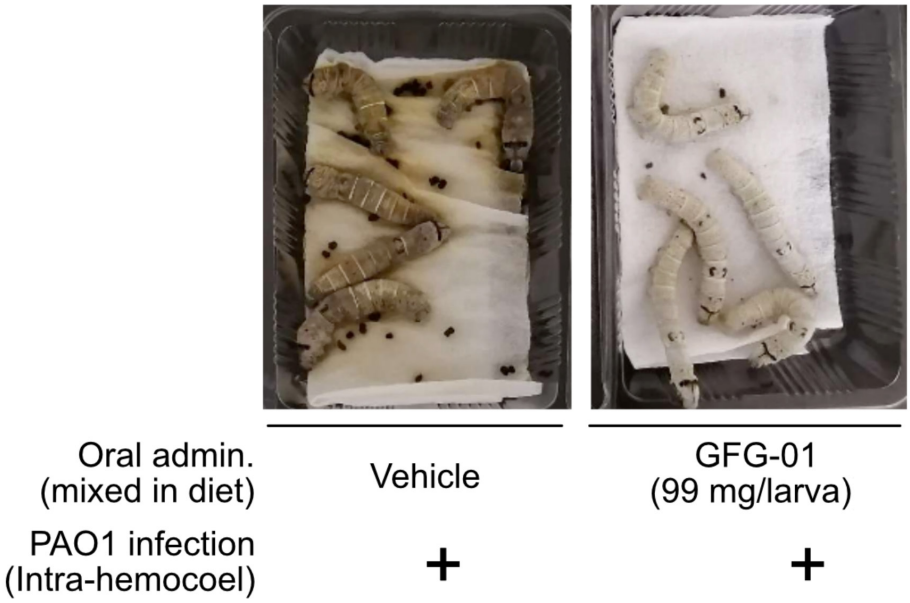


Figure 1. Oral administration of GFG-01 improves post-infection larval condition. GFG-01 was mixed into the diet and administered orally for 15 h at 27°C before intrahemocoelic infection with *P. aeruginosa* PAO1. Five larvae were examined per group. The estimated GFG-01 intake was 99 mg/larva. At 24 h after infection, none of the vehicle-treated larvae survived (0/5), whereas all GFG-01-treated larvae survived and remained visibly healthier (5/5; two-sided Fisher's exact test, $P = 0.0079$).

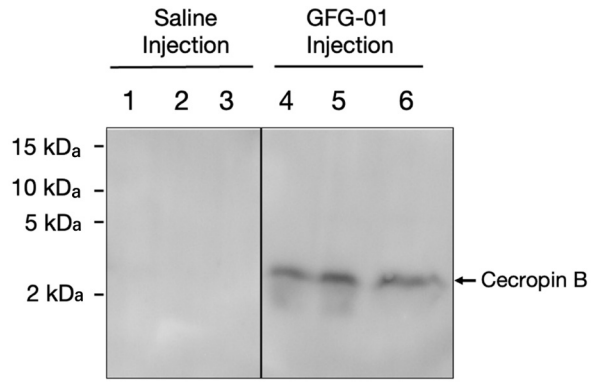


Figure 2. Intrahemocoelic GFG-01 administration induces Cecropin B accumulation in the hemolymph. Western blot of hemolymph collected from six larvae in each group 6 h after intrahemocoelic administration of saline or GFG-01 (500 µg/larva). Hemolymph from two larvae was pooled for each lane. Lanes 1-3, saline-treated samples; lanes 4-6, GFG-01-treated samples. A band in the expected Cecropin B region is observed in the GFG-01-treated lanes.

First, oral administration of GFG-01 improves the outcome of *P. aeruginosa* infection in silkworms under defined conditions. Second, intrahemocoelic GFG-01 administration induces Cecropin B accumulation in the hemolymph. Third, oral GFG-01 administration produces immune-related transcriptional responses that differ between the fat body and hemocytes rather than showing a uniform systemic pattern.

The transcriptomic data further support the view that the protective state is not explained by a single uniform immune program. At 15 h after oral administration, the fat body and hemocytes showed opposite trends in immune-related gene categories. Because these tissues play different roles in insect immunity, such non-parallel behavior is biologically plausible (*16-21*). Additional time-course analysis will be useful to determine whether these tissue responses represent different regulatory directions or different phases of a shared dynamic process.

The fat body findings require particularly cautious interpretation. Reduced expression of immune-related gene sets in the fat body might appear inconsistent with improved infection outcome. However, the fat body is a multifunctional tissue integrating immunity with metabolic and physiological functions (*16,21*). Reduced immune-related transcription at a single time point may reflect temporal resolution of earlier responses, tissue resource balancing, or selective pathway usage.

The accumulation of Cecropin B in the hemolymph after intrahemocoelic GFG-01 administration is consistent with previous studies linking cecropin induction to immune priming and enhanced infection resistance in silkworms (*12,13*). When considered together with the RNA-seq results, these findings raise the possibility that GFG-01 does not simply increase overall immune activity but instead alters the balance of immune responses among tissues. Increased defense-related transcription in hemocytes could contribute to infection resistance even when immune-related transcription in the fat body is reduced. However, Cecropin B was examined after intrahemocoelic administration, whereas RNA-seq was performed after oral administration; therefore, these findings cannot yet be placed within a single mechanistic sequence. Whether oral GFG-01 also induces Cecropin B remains to be

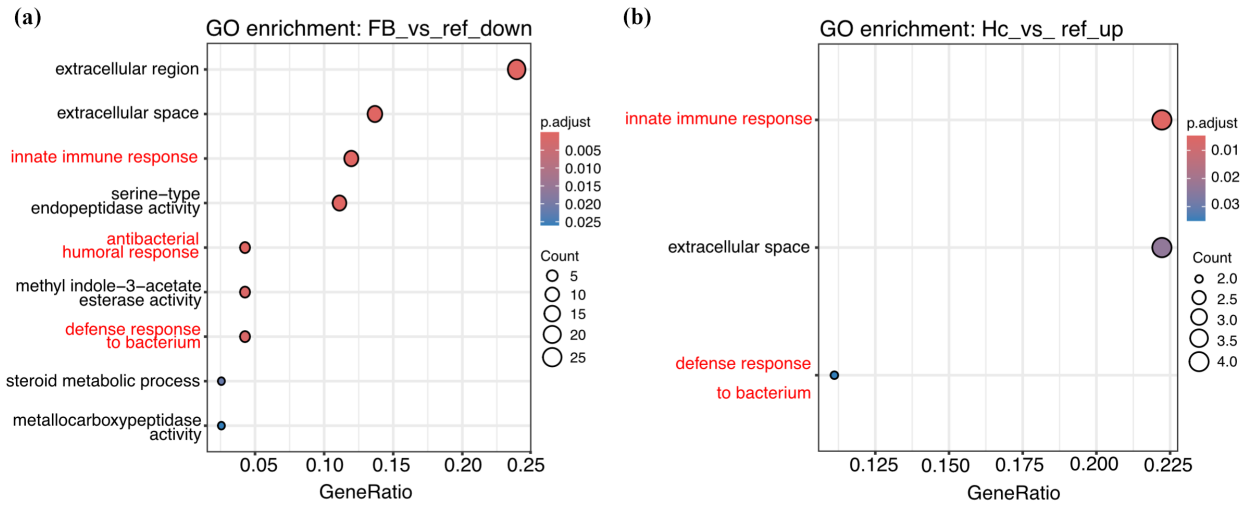


Figure 3. Tissue-dependent GO enrichment patterns are observed after oral GFG-01 administration. Fat body and hemocytes were collected 15 h after oral GFG-01 (76 mg/larva) or control diet (n = 3 larvae per condition and tissue; one larva per replicate). (**a**) GO enrichment of downregulated fat-body genes (FB_vs_ref_down). (**b**) GO enrichment of upregulated hemocyte genes (Hc_vs_ref_up). Immune-related terms are highlighted.

determined.

Further work will be needed to identify the active molecular species in GFG-01 and clarify the mechanisms underlying the enhanced infection resistance observed after oral administration. Nevertheless, the present results demonstrate that GFG-01 can improve the outcome of bacterial infection in an invertebrate host and support the use of silkworms as a tractable model for analyzing food-derived modulators of host defense *in vivo*.

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Conflict of Interest: Kazuhisa Sekimizu was an advisor to Genome Pharmaceuticals Institute Co., Ltd. Kumiko Kuwaba, Kazunori Mizuno, Yuki Taga, and Masashi Kusubata were employees of Nippi, Inc. The other authors declare no competing interests.

Data Availability: The processed RNA-seq gene expression datasets and sample metadata generated and analysed during the current study are publicly available in the Zenodo repository (*30*) at https://doi.org/10.5281/zenodo.21799087. Additional data supporting the findings of this study are available from the corresponding author upon reasonable request.

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