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Research Article

Effect of *Lactobacillus Plantarum* IS-10506 on Paneth Cell Regeneration in the Ileum of *Sprague Dawley* Rats

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ABSTRACT

Background: Pathogenic *Escherichia coli (E. coli)* is the most common infectious agent among children in developing countries. Indigenous probiotics are not widely used to treat diarrhea and intestinal infections. This study aims to investigate the cell regeneration process of paneth cells after administration of *Lactobacillus plantarum IS-10506* due to damage caused by Lipopolysaccharide (LPS) *E. coli* O55:B5, through the expression of MATH-1 and DEFA-6. **Methods:** This study used 64 paraffin blocks from *Rattus norvegicus* strain Sprague-Dawley divided into four groups. There were three treatments, KN, KL, KP and KPR groups, The KN group represent the administration of placebo. The KL group received LPS *E. coli* O55:B5 on day one. The KP group received LPS *E. coli* O55:B5 on the first day and *Lactobacillus plantarum* IS-10506 on the second day until six-day. The KPR group were administered *Lactobacillus plantarum* IS-10506 six days prior to receiving LPS *E. coli* O55:B5, respectively. All groups, except KN, received LPS at a dose of 250 µg/kg body weight once, and *Lactobacillus plantarum* IS-10506 at a dose of $2.86x10^{10}$ CFU/day. Evaluating paneth cell regeneration, DEFA-6, and MATH-1 expression immunohistochemistry was conducted on all tissues. **Results:** The expression of DEFA-6 and MATH-1 in the KP and KPR groups on day three of observation was significantly higher from the KL group. Even though the KL group achieved significant growth, the results of this expansion were significantly smaller than KP and KPR groups. **Conclusion:** After mucosal injury caused by LPS *E. coli* O55:B5, administration of probiotic *Lactobacillus plantarum* IS-10506 may increase paneth cell regeneration through differentiation and cell number.

Key words: Lipopolysaccharide, *Escherichia coli* O55:B5, *Lactobacillus plantarum* IS-10506, Paneth cells, DEFA-6, MATH-1.

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INTRODUCTION

Paneth cells play a crucial function in infection management as producers of antimicrobial peptides and stem cell niches that aid in the regeneration of other intestinal mucosal cells.[1] Children commonly suffer from intestinal infections and diarrhea is a leading cause of morbidity and mortality, accounting for 800,000 fatalities each year globally.[2] Pathogenic *Escherichia coli* (*E. coli*) is the most prevalent infectious agent, especially among children under five in underdeveloped nations.[3] *Enteropathogenic Escherichia coli* (EPEC) can cause an increase in inflammatory cytokines and can trigger an increase in inflammatory cytokines, which lead to a decrease in tight junction proteins and loss of intestinal mucosa integrity, in turn damage the cells the intestinal epithelial mucosa forming cells, especially enterocytes, paneth cells, enteroendocrine cells, and Goblet cells.[4,5] In clinical practice, impaired paneth cell function, particularly in the small intestine, may result in necrotizing enterocolitis, an increased incidence of diarrhea, and a prolonged infectious state.[1,6,7]

A study in Zambia found that there was a relationship between the incidence of diarrhea and paneth cell damage represented by the expression of DEFA-5 and DEFA-6.[7] The treatment of intestinal infections, particularly diarrhea, has included rehydration, zinc, diet, and the administration of antibiotics. The administration of Indonesian indigenous probiotics to patients, including comparing the effect of *Lactobacillus plantarum* IS-10506 on paneth cell regeneration to the physiological regeneration process in the challenging to reducing the infection period for patients with intestinal infections or those who are susceptible to them. In this study, Lipopolysaccharide (LPS) *E. coli* O55:B5 was given to cause damage that almost resembled damage to *E. coli* infection. *Lactobacillus plantarum* IS-10506 was obtained from dadih, Indonesian traditional fermented buffalo milk of West Sumatera had been proven the probiotic properties.[8-10] Lactic acid bacteria are commonly used to preserve food due to the production of lactic acid, H2O2 and other metabolite products serve as antimicrobial agents.[11,12]

This research focuses on the regeneration of paneth cells by determining the amount of DEFA-6 expression represent the number of paneth cells, since DEFA-6 is particularly sensitive to paneth cell detection and DEFA-6 excretion is unaffected by bacterial activity.[13,14] MATH-1 is a basic helix-loop-helix transcription factor, deficiency of MATH-1 will reduce the number of paneth cells. Hence, MATH-1 represents a transcription factor driving the differentiation of secretory cells, including paneth cells.[15,16] It is interesting to conduct animal experiment using rodent model as an initial study to confirm the impact of probiotic *L. plantarum IS-10506* on the damaged paneth cell regeneration process due to LPS *E. coli* O55:B5.

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MATERIAL AND METHODS

Animals

Ethical clearance was obtained from The Animal Care and Use Committee of the Veterinary Medicine School, Universitas Airlangga (Surabaya, Indonesia) (No.2.KEH.014.03.2022). This is a follow up study on stem cell activation in rodent model,[17] using male Sprague-Dawley rats paraffin blocks (12 weeks old, 100-120 g; n=64) were randomly assigned to the control (KN), LPS *E. coli* O55:B5 only (KL), LPS *E. coli* O55:B5 followed by probiotic *L. plantarum IS-10506* (KP), and sequential sequential probiotic + LPS + probiotic (KPR) groups. Each group was divided into four subgroups (n=4 rats each), and the rats in each were sacrificed on day 3, 4, 6, and 7. Before beginning research, rats adjust for one week. The control (KN) rats received sterile water through a gastric tube for 14 days. On day one, LPS *E. coli* O55:B5 was administered to the KL group. LPS *E. coli* O55:B5 and *L. plantarum* IS-10506 were administered to the KP group on days 1 and 2, respectively, until being sacrificed. Before the injection of LPS, the KPR group received *L. plantarum IS-10506* for six days; then, the probiotic was administered for a day after LPS injection. The ileum of the rats was taken and cut for examination after experiment was completed. Adverse effect was recorded including morbidity and other signs of illness, such as decreased activity, irregular ejection, and reduced body weight.

Probiotic

Microencapsulated *L. plantarum IS-10506* (GenBank accession number DQ860148) was administered *via* a gastric tube once daily for up to 6 days. After LPS administration in the KP group and six days before and after LPS administration in the KPR group. The probiotic packed an aluminum foil sachet and handed to Dr. Soetomo Hospital Pharmacy Installation in Surabaya, Indonesia. A week before intervention, the viability of the probiotics was enumerated. A daily dose of $2.86x10^{10}$ CFU of the probiotic powder was administered with 1.5 mL of sterile water.

Lipopolysaccharides

A dose of 250 g/kg body weight of LPS *E. coli* O55:B5 (L2880; Sigma-Aldrich, St. Louis, MO, USA) was administered (diluted with NaCl 0.9 % in a 10:1 ratio). On the first day of the trial, LPS *E. coli* O55:B5 was delivered orally *via* a gastric tube to all groups except the KN group.

Immunohistochemistry

After cleaning and fixing the ileum in a 10% formalin buffer solution, the ileum underwent dehydration, clarifying, and embedding. Antibodies against DEFA-6 (AA31-100 Antibodies Online) and MATH-1 (sc-514145; Santa Cruz Biotechnology) were used to probe tissue sections to identify the DEFA-6 and MATH-1 proteins, respectively, on paneth cells. Alight microscope (CX21; Olympus, Tokyo, Japan) was used to examine the samples, and an ILCE6000 camera was used to take pictures of them (Sony, Tokyo, Japan). The average number of cells in 20 randomly selected fields was enumerated at a magnification of 1000 to calculate the number of immunopositive cells.

Statistical analysis

Microsoft Office Excel 2019 and IBM SPSS Statistics Version 25 was used to analyzed the data. For normally distributed data, the one-way ANOVA test was used to analyze group differences. Meanwhile, for non-normally distributed data, the Mann-Whitney U and Kruskal - Wallis tests were used to assess group differences (two and more than two groups, respectively). The number of cells expressing MATH-1 and the amount of DEFA-6 expression were assessed. A *p*-value below 0.05 was used to determine significance.

RESULTS

There were no adverse effects or complications observed which included critical clinical signs such as abnormal breathing patterns, shock, anaphylaxis, bleeding, diarrhea, vomiting, nervous system disorders, paralysis, blindness, and seizures. Furthermore, the pieces of ileum were kept using paraffin blocks, and 64 rats *Rattus norvegicus* strain Sprague Dawley were used.

Lactobacillus plantarum IS-10506 administration promotes the regeneration of paneth cells by expression of DEFA-6

The LPS without *L. plantarum* IS-10506 treatment group (KL group), showed the lowest score, but it was not significantly different from the control group (KN group), at day 3, KL group showed a significant improvement of DEFA-6 expression as compared to day 7 (p=0.033). Means that LPS was not significantly damage paneth cells and the KL group was still undergoing a physiological regeneration process. Following LPS administration with probiotic *L. plantarum* IS-10506 (KP group), there was a significant increase of DEFA-6 expression from day 3 to day 7 (p=<0.001), and the highest was observed on day 6 (p =<0.001) (Table 1). The KPR group had the highest number after three days, even though the increase was not significant (p=0.172).

A significant of DEFA-6 expressing cells from day three until up to the end of the experiment was observed in rats pre-treated and treated with *L. plantarum* IS- 10506. Hence, probiotics *L. plantarum* IS-10506 promoted the regeneration of paneth cells (Figure 1). KL group increased up to day 7 while KP group showed stable DEFA-6 expression at day 7, likewise with the KPR group.

Lactobacillus plantarum IS-10506 administration promotes the differentiation of Paneth cells by expression of MATH-1

In the KL group, there was a significant increase in MATH-1 expression from day 3 to day 7 (p=0.019). The KP group showed a significant increased (p=0.002) from day 3 to day 6, and stable at day 7. The KPR group showed higher number of MATH-1 expressions but did not increase significantly by the time (p=0.172).

Table 2 shows significant differences between each group. The KN and KL groups only differed significantly on day 3. There was significant difference of MATH-1 expression between the KN, KL and KP and KPR groups from day 3 to day 7 and no significant different of MATH-1 expression between KP and KPR from day 3 to day 7.

Administration of *L. plantarum* IS-10506 showed significant increase of MATH-1 expression (Figure 2). *L. plantarum* IS -10506 administration of as well as treatment significantly increased the MATH-1 expression cells. Figure 3 illustrate the DEFA-6 and MATH-1 expression at 400 times magnification on the four groups.

DISCUSSION

Damaged paneth cells regenerate through the secretory cells differentiation process after administration of *L. plantarum* IS-10506 as shown by the activity of the Interleukin 10 (IL-10), WNT, and *epidermal growth factor receptor* (EGFR) pathways, resulting in increased stem cell proliferation. The knowledge of paneth cell regeneration *via* the MATH-1 pathway by this study.[16] MATH-1 is a transcription factor produced by DEFA-6 secretory precursor cells as a specific biomarker of paneth cells. MATH-1 expression can occur up to the villi, but DEFA-6 expression in paneth cells is predominantly at the base of the crypts.

Several studies have shown that LPS *E. coli* damaged the intestinal cell mucosa, causing intestinal villi edema, capillary congestion, lymph

Table 1: DEFA-6 expression in each treatment group.

Groups	Days of Observation (day)				p
	3	4	6	7	
KN	6 ± 0.81	5 ± 0.81	5.5 ± 1.29	6 ± 0.81	0.426
KL	3.50 ± 1.29	3.75 ± 1.70	5.75 ± 2.21	7.25 ± 1,70	0.033*[a]
KP	8.75 ± 1.70	10.5 ± 1.29	12.75 ± 1.25	13.00 ± 1,82	0.006*[b]
KPR	9.75 ± 1.70	12.00 ± 1.41	12.25 ± 1.70	12.00 ± 1,82	0.172
p	<0.001*[c]	<0.001*[d]	<0.001*[e]	<0.001*[f]	

*Significant at p<0.005. ANOVA test was used in the analysis. The unit of the table is shown as cells Analysis using *Post Hoc Multiple comparisons*:
[a]Significant increase in KL group on day 3 with day 7
[b]Significant increase in KP group on day 3 with day 6
[c]Significant difference in amount between KN and KPR, KL with KP and KPR,
[d]Significant differences in numbers between KN with KP and KPR, KL with KP and KPR,
[e]Significant differences in numbers between KN with KP and KPR, KL with KP and KPR,
[f]Significant differences in numbers between KN with KP and KPR, KL with KP and KPR.
KN: the control group; KL: LPS *E. coli* O55:B5 only; KP: LPS *E. coli* O55:B5 followed by probiotic *L. plantarum* IS-10506; and KPR: sequential probiotic + LPS + probiotic

Table 2: MATH-1 expression in each treatment group.

Groups	Day of Observations (day)				p
	3	4	6	7	
KN	5.25 ± 1.29	5.75 ± 2.21	6 ± 1.41	5.25 ± 1.25	0.919
KL	2.75 ± 1.25	3.50 ± 1.29	5.75 ± 1.70	6.50 ± 2.08	0.019*[a]
KP	9.50 ± 1.29	10.50 ± 1.29	14 ± 1.41	14 ± 2.16	0.002*[b]
KPR	12.50 ± 1.29	13.25 ± 0.95	14.50 ± 1.29	14.75 ± 2.21	0.172
p	<0.001*[c]	<0.001*[d]	<0.001*[e]	<0.001*[f]	

*Significant if *p*<0.005. ANOVA test was used in the analysis. The unit of the table is shown as cells Analysis using *Post Hoc Multiple comparisons*:
[a]A significant increase in KL group on day 3 to day 7
[b]Significant increase in cell expression of the KP group on day 3 to 6
[c]Significant difference was found between KN and KL; KP and KPR; KL with KP and KPR; KP and KPR
[d]Significant differences were found between KN with KP and KPR; KL with KP and KPR
[e]Significant differences were found between KN with KP and KPR; KL with KP and KPR
[f]Significant differences in numbers between KN with KP and KPR, KL with KP and KPR
KN: the control group; KL: LPS *E. coli* O55:B5 only; KP: LPS *E. coli* O55:B5 followed by probiotic *L. plantarum* IS-10506; and KPR: sequential probiotic + LPS + probiotic

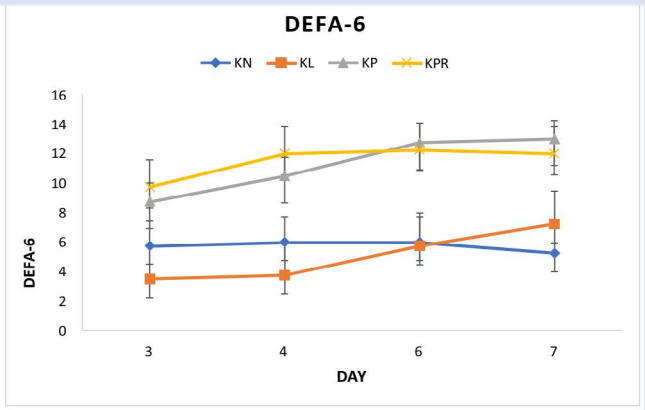

Figure 1: DEFA-6 expression of the 4 groups at day 3,4,6 and 7

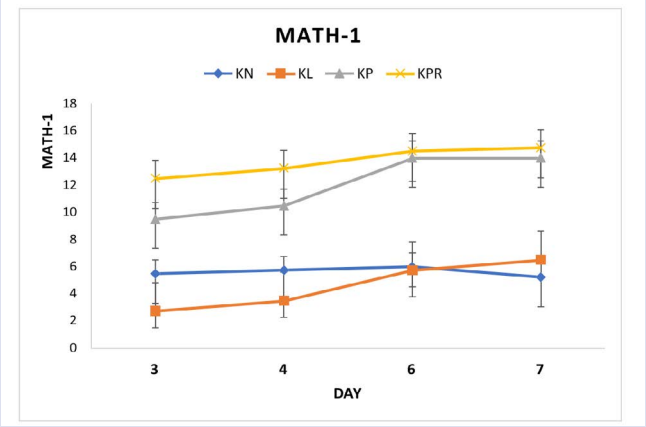

Figure 2: MATH-1 expression of the 4 groups at day 3,4,6 and 7

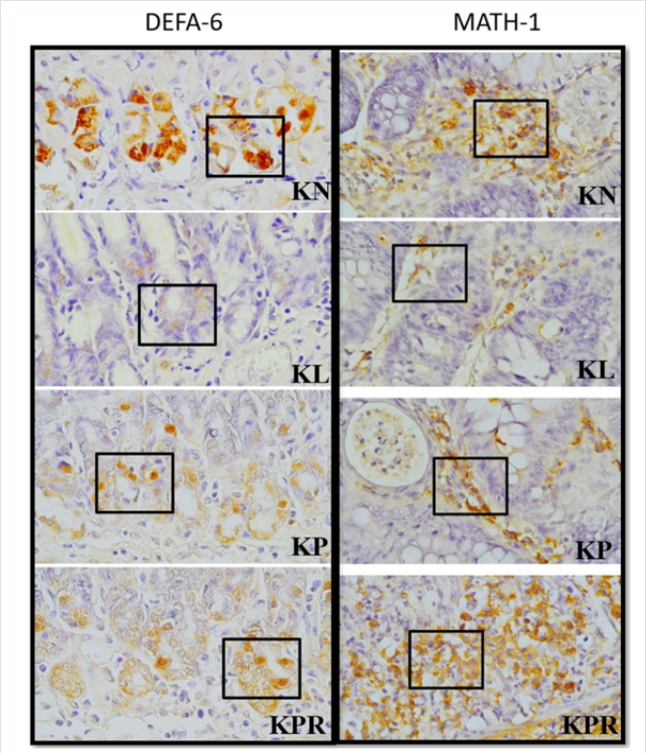

Figure 3: Immunohistochemical on the DEFA-6 expression and MATH-1 expression at 400 times magnification. DEFA-6 expression occurs at the base where Paneth cells are located. MATH-1 expression occurs up to the villi. DEFA-6 and MATH-1 expression I n the KL group looked paler than in the KN, KP, and KPR groups

channel extension, polymorphonuclear (PMN) infiltration in the intestinal cavity, which may give effect on variations in goblet cell proliferative activity and loss of goblet cells.[5,17,18] However, this study showed that the KL group had a lower amount of DEFA-6 expression than the KN group but this was not significant because the LPS exposure was brief and not strong enough to achieve severe damage to Paneth cells. Studies show that to achieve severe paneth cell damage requires intact live bacteria and prolonged exposure, this is demonstrated by *Staphylococcus aureus* and *Salmonella typhimurium* infections which cause leakage of cytoplasmic contents and fragmentation of paneth cells,[19] chronic exposure to arsenic-contaminated water for five weeks

will cause a significant decrease in the number of paneth cells,[16] whereas *Toxoplasma gondii* the number of paneth cells was significantly lower after five days of the infection process.[20]

DEFA-6 expression in the KP and KPR groups was significantly higher from the KL and KN groups. This was proven since the supplementation of *L. plantarum* IS-10506 increased the number of paneth cells significantly higher and faster than the number of the KN group and for 3 days after exposure to LPS. This is following studies showing that paneth cells will experience regeneration in number that exceeds normal and will return a week after dithizone injection,[21] so that administration of *L. plantarum* IS-10506 orally is potential to enhance the potency of antimicrobial peptides. Hence, it is potential in lowering the dose of drugs and antibiotics treatment. The expression of DEFA-6 in the KP group was not significantly different as compared to KPR group throughout the observation period. This indicated that the administration of *L. plantarum* IS-10506 for paneth cell regeneration was not significantly different when administered preventively or only after the damage occurred.

In MATH-1 marker, it was found that there was a significant difference in the number of cells between KN and KL, this is in accordance with a study showing LPS *E. coli* can damage the mucosa of intestinal cells by electron microscopy.[5] In contrast to the DEFA-6 marker, which did not significantly differ between the KL and KN groups, MATH-1 is located close to the villi, making it susceptible to damage from LPS *E. coli*.

In this study, MATH-1 in the KL group increased significantly from day 3 to day 7 and the KP group increased significantly with more cells, while the KN and KPR groups did not increase significantly. This shows that there is still an increase in MATH-1 physiologically, but the supplementation of *L. plantarum* IS-10506 MATH-1 produces more cells, this is significantly different from the group without *L. plantarum* IS-10506 administration. This demonstrates that *L. plantarum* IS-10506 does not lead in mutant MATH-1 and does not have the possibility of resulting in tumors when administered for seven days.

L. plantarum IS-10506 administration (Group KP and KPR) showed significant increase of MATH-1 expression, as compared to the group without probiotics (Group KN and KL), as a result, it may be concluded that *L. plantarum* IS-10506 has been proven to increase the activity of the secretory cell differentiation pathway. This finding is in contrast with other study reported that administration of *E. coli* K-12 and *E. coli* Nissle 1917 decreased MATH-1 expression.[22] Another study reported that *Lactobacillus acidophilus* LA85 significantly increased the expression of MATH-1.[23] The high level of MATH-1 expression represents an increase in stem cell activity, which in turn may lead to an increase of the secretory precursor.[17]

CONCLUSION

Lactobacillus plantarum IS-10506 significantly accelerated and increased paneth cell regeneration as shown by the amount of DEFA-6 and significantly increased the activity of secretory precursors MATH-1 expression in the ileum of mice induced by LPS. *Lactobacillus plantarum* IS-10506 is potential to prevent post-infection, particularly in activating paneth cell regeneration.

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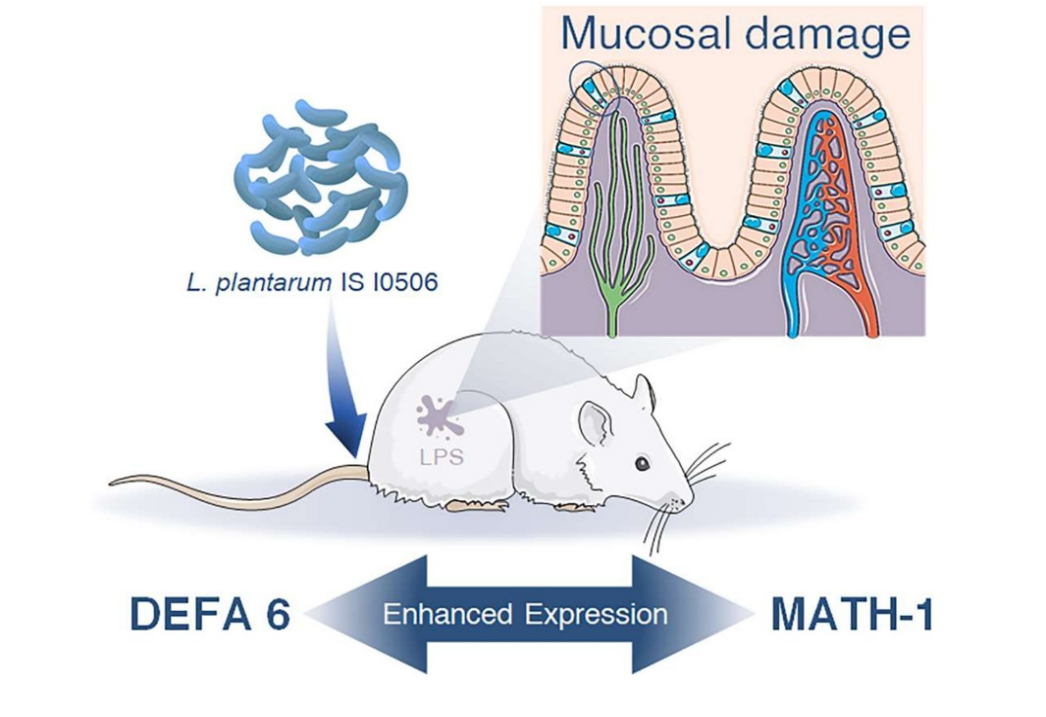
GRAPHICAL ABSTRACT



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