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Escherichia coli-Specific Induction of Inflammatory Cytokines and Chemokines upon Infections with Periodontal Pathogens

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Abstract:

In a multifaceted interaction with interleukins (ILs), Escherichia coli (E. coli) serves both an inflammatory response initiator in the host and a transporter for therapeutically delivering modified ILs. The majority of E. coli strains that cause illness produce interleukins that promote inflammation, but naturally occurring or artificially created strains of the bacteria can either cause inflammation to decrease or be utilized to administer therapeutic interleukins. The serum concentrations of interleukin-12 (IL-12) and interleukin-17 (IL-17) were measured in micrograms per milliliter for three different infection types: implant, bacteria-implant (infections when implants are present), and bacteria only (infections where implants are not present). At the same time, the serum concentrations of IL-17 were reported as 23, 14, and 9 (pg/ml), respectively. Both the sterile and infected implants had statistically significant p-values before Bonferroni correction. There are notable distinctions between infections that occur with and without implants. For CXCL-4, the analysis of serum chemokines CXCL-4 and CCL-5 (pg/ml) revealed values of 25, 13, and 18 (pg/ml) in the Implant, Bacteria-implant, and Bacteria only infection categories, respectively. Whereas CCL-5 was found to be (81, 67, and 49 (pg/ml)) in that order. Before Bonferroni correction, there was a statistically significant difference between infected and sterile implants, as well as between infections that occurred with and without implants. In order to investigate the host's inflammatory responses systemically, including IFN-γ and granulocyte colony-stimulating factor (G-CSF), the multiplex test was expanded. Results for systemic analysis of IFN-γ and granulocyte colony-stimulating factor (G-CSF) in terms of pg/ml showed levels of 26, 14, and 7 in the Implant, Bacteria-implant, and Bacteria only infection categories, respectively, for IFN-γ. The G-CSF levels were 53, 116, and 71 pg/ml, respectively.

Keywords: Inflammatory Cytokines, Chemokines, Periodontal Pathogens, Escherichia coli

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INTRODUCTION

Humans and other warm-blooded animals are colonized by Escherichia coli (E. coli) in their intestines. One of the most significant pathogens for infections in animals, humans, and the environment is Escherichia coli, which causes food poisoning, water contamination, and hospital infections [1]. Diarrhea, UTIs, bacteremia, meningitis, septicemia, and pneumonia are just some of the clinical illnesses that E. coli can cause, and they can affect people of all ages. Breastfeeding mothers are at increased risk of contracting mastitis, an infectious condition of the mammary gland that has a significant impact on the dairy industry's bottom line. Several microbial infections, including Staphylococcus aureus (S. aureus) and Escherichia coli (E. coli), can cause this inflammation within the mammary glands [2]. Mastitis has been extensively investigated in cows, but due to high costs and management issues, testing cattle for the disease has lost some of its appeal. So, instead of using humans, researchers are turning to mice models to learn about intramammary infections [3]. Since then, researchers have applied this concept to a wide range of infections in an effort to better understand these diseases. The development of new medications and vaccines for the management of intramastitis infections is one of these topics, along with the pathophysiology and mode of action of the mastitis-causing pathogen. The mouse model of mastitis has mostly been used to study Staphylococcus aureus infections that occur within the mammary gland. On rare occasions, E. coli has been utilized as an environmental pathogen. Long ago, it was shown that coliform mastitis in mice manifests itself clinically and in general terms, including bacterial growth, PMN response, and histological alterations [4-6] in the infected mammary gland. In addition, the model has been utilized to provide light on the pathogen's pathogenicity processes and bacterial adhesion [7, 8]. Lastly, E. coli inoculation mice were also used to investigate control measures, such as antibiotic and immunomodulatory drug administration. Important details on inflammatory mediators defining the host immune response are absent from the few mouse studies that have dealt with E. coli mastitis [9–11]. The activation of the immune system in response to infections causes the secretion of cytokines that promote inflammation and the recruitment of cells that cause inflammation. The innate immune response is coordinated by IL-6, IL-β, and TNF-α, three molecules with significant functions. TNF-α is a type of pro-inflammatory cytokine mostly made by activated macrophages. It has the ability to enhance the permeability of epithelial cells and up-regulate the expression of IL-6 and IL-1β, which together accomplish the goal of eliminating intruders [2, 13]. In contrast, when an immunologic or inflammatory stimulus is activated, iNOS is able to produce the majority of NO in the body to fight against infectious pathogens that invade. Simultaneously, iNOS helps antigen-specific T cells and NK cells secrete TNF-α, IL-1β, and IL-6 to prevent pathogen invasion [14–17]. To better understand the dynamic changes that occur during an E. coli infection and to facilitate future in-depth research, it is convenient to establish a model of mouse infection.

MATERIALS AND METHODS

Inoculation and bacterial strains

Throughout this experiment, the pathogenic E. coli that was isolated from a human patient was utilized. After being incubated overnight at 37℃, bacterial strains were scattered onto trypticase soy agar from stock cultures at a temperature of −80℃. When the optical density (OD600) reached 1.0, 3 ml of PBS was injected with a loopful of culture. For a single intragastric injection of mice (n=10–13 mice per group), bacterial suspensions were diluted twofold in PBS and 0.2 ml (1×10–8 CFU) was administered orally. The inoculum was confirmed by plating diluted bacterial colonies on MacConkey agar.

Animals

The ASF-defined microbiota is present in male and female mice between the ages of 12 and 15 weeks. A sterile cabinet was used for all inoculation and handling processes. The mice were subjected to a 12-hour light-dark cycle while being given an irradiated meal and water that had been autoclaved. The animals' weights were measured once a week, and they were checked for diarrhea and behavioral changes every day. The experiment concluded with the intake of carbon dioxide to put an end to the mice.

Mouse model of infections and subcutaneous implants

The female mice used in the study were bred at Central Animal Facility and were 8-1.2 weeks old. They were fed and watered regularly and housed in individual cages with good ventilation. There were three distinct species utilized. Intraperitoneal injections of xylazine (10 mg/kg) and ketamine (4 mg/kg) put the animals to sleep. The insertion sites were cleaned using a 70/ethanol solution after the fur was removed using a hair trimmer. We used tissue forceps and surgical shears to make three incisions, each 1 cm in diameter. On these incisions, subcutaneous pouches were created. In order to close the incisions, simple interrupted sutures were used. Regardless of whether implantation was done or not, 5 _L of bacterial suspension was inoculated within 30 minutes of the surgical site being closed. Animals were routinely monitored after blood samples were taken three weeks following implantation.

Cytokine Quantification in Blood

Three weeks following implantation, the mice were given a strong anesthetic and blood samples were taken from their hearts without the use of coagulant. Before being centrifuged at 1500 g for 10 minutes at 4 o C, blood samples were incubated at room temperature by keeping them motionless and letting them incubate for 30 minutes. The serum was centrifuged to separate it and then kept at approximately 80 degrees Celsius until it was ready for further processing. The serum cytokine concentrations were measured with the help of the Bio-Plex Pro Mouse Cytokine Assay.

Evaluation using statistical methods

We used GraphPad Prism version 6 to analyze all the data. A number of variables were compared, including the degree of colonization in fecal and intestinal samples, the amount of cytokines released from colonic biopsies, the mean body weight changes, the inflammation in the intestines of ASF mice, and the success of the experiment overall. Histopathology scores were compared using the Kruskal-Wallis test, and the fraction of tissues positive for lesions was compared using Fisher's exact test (two-tailed). Significant results were defined as p-values<0.05.

RESULTS AND DISCUSSION

An important part of the body's defense mechanism against various microbes is the immune system. Even non-self cells can be identified by it. The article also discussed innate immunity and specialized immunity. To prevent the infiltration of harmful substances, the immune system employs a network of interrelated processes [18]. Innate and acquired immunity work together to combat infections. The immune system primarily consists of immunoglobulins, helper T-cells, polymorphonuclear, cytotoxic T-cells, and dendritic cells. When bacteria infect a cell, the antigen on MHC class II stimulates CD4 T cells, while the antigen on MHC class I stimulates CD8 T cells. After CD4 cells are activated, they produce more IFN-gamma, which in turn stimulate macrophages. Macrophages then secrete more nitrous oxide, which kills germs. As an added bonus, CD8 cells are highly effective at protecting against infections through cytotoxicity, namely the killing of infected macrophages. Many bacterial infections that occur within cells also rely on CD8 T cells. In the early stages of an Escherichia coli infection, CD8 cells emerged, although CD4 cells did not manifest until much later [19–23]. Interleukin-12 and interleukin-17 serum concentration expression (pg/ml) There were [571, 335, and 254 (pg/ml)] serum concentrations of IL-12 for implant, bacteria-implant, and bacteria-only infections, respectively. There was a simultaneous measurement of IL-17 serum concentrations of 23, 14, and 9 pg/ml, respectively. Both the sterile and infected implants had statistically significant p-values before Bonferroni correction. There are notable distinctions between infections that occur with and without implants. The levels of CXCL-4 and CCL-5 in serum were found to be 25, 13, and 18 pg/ml, respectively, in three different infection types: implant, bacteria-implant, and bacteria only. In contrast, CCL-5 was found to be [81, 67, and 49 (pg/ml)] in various samples. Both the sterile and infected implants had statistically significant p-values before Bonferroni correction. There are notable distinctions between infections that occur with and without implants. In order to investigate the host's inflammatory responses systemically, including IFN-γ and granulocyte colony-stimulating factor (G-CSF), the multiplex test was expanded. In the Implant group, there were 26 pg/ml of IFN-γ and 14 pg/ml of granulocyte colony-stimulating factor (G-CSF) in systemic analysis. In the Bacteria-implant group, there were infections with implants, and in the Bacteria only group, there were infections without implants. However, for G-CSF, the values were 53, 116, and 71 (pg/ml) independently.

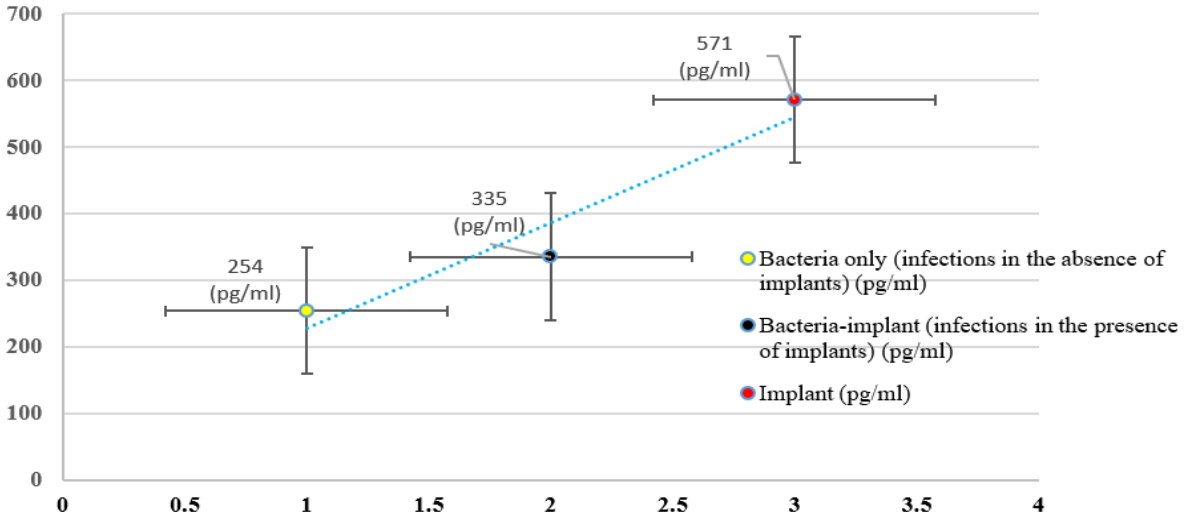

Figure 1. Inflammatory cytokine IL-12 upon infections with periodontal pathogens *Escherichia coli* specific induction

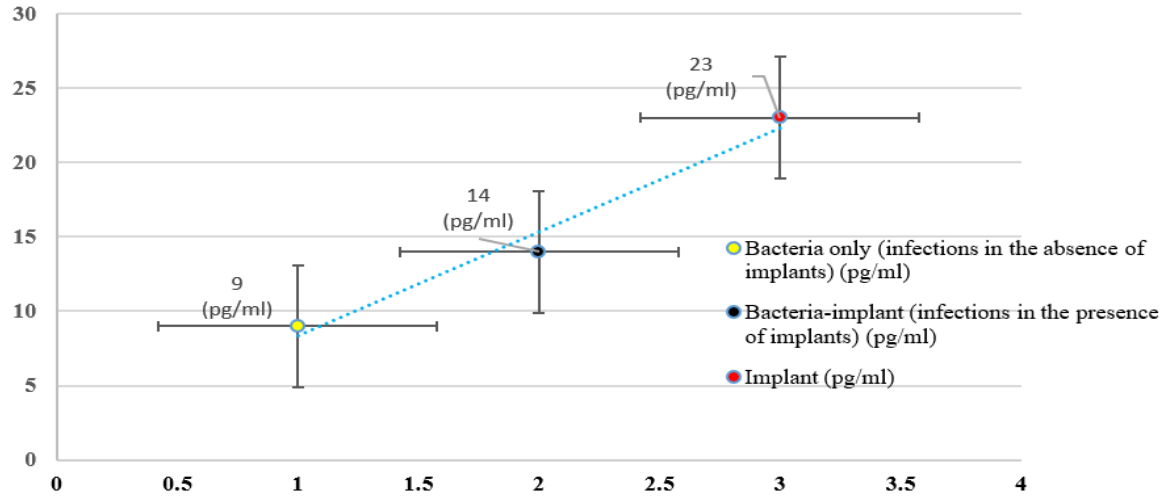

Figure 1. Inflammatory cytokine IL-17 upon infections with periodontal pathogens *Escherichia coli* specific induction

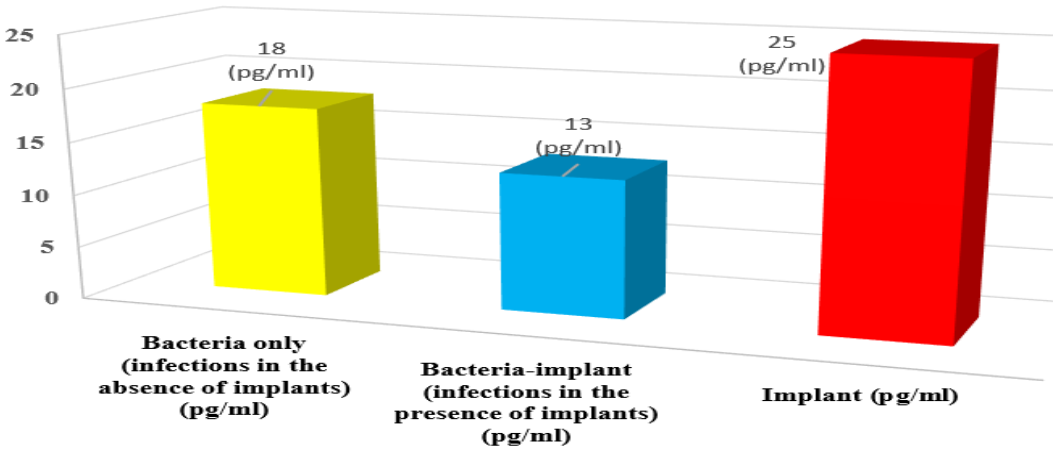

Figure 3. Escherichia coli-Specific Induction of Chemokines CXCL-4

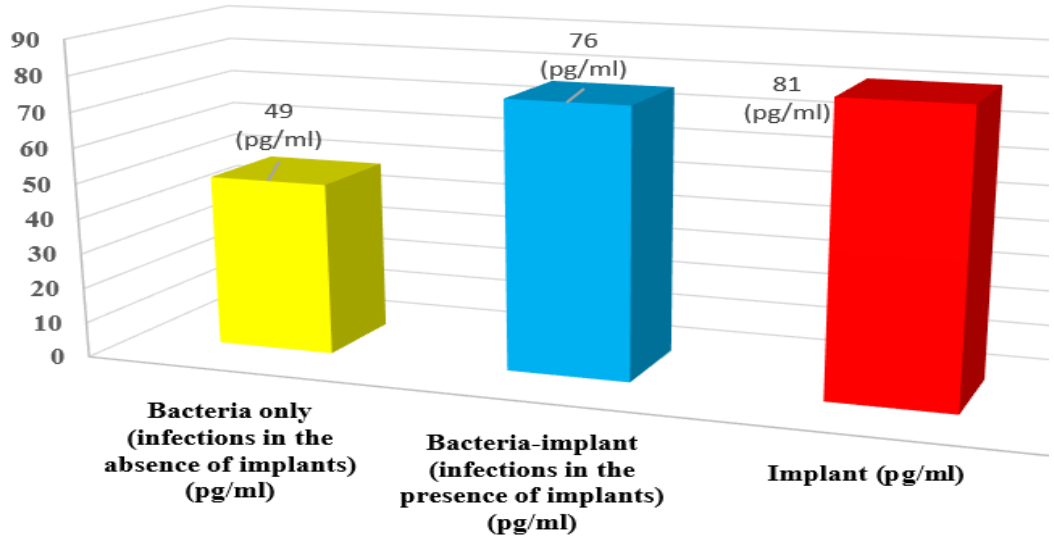

Figure 4. Escherichia coli-Specific Induction of Chemokines CXCL-5

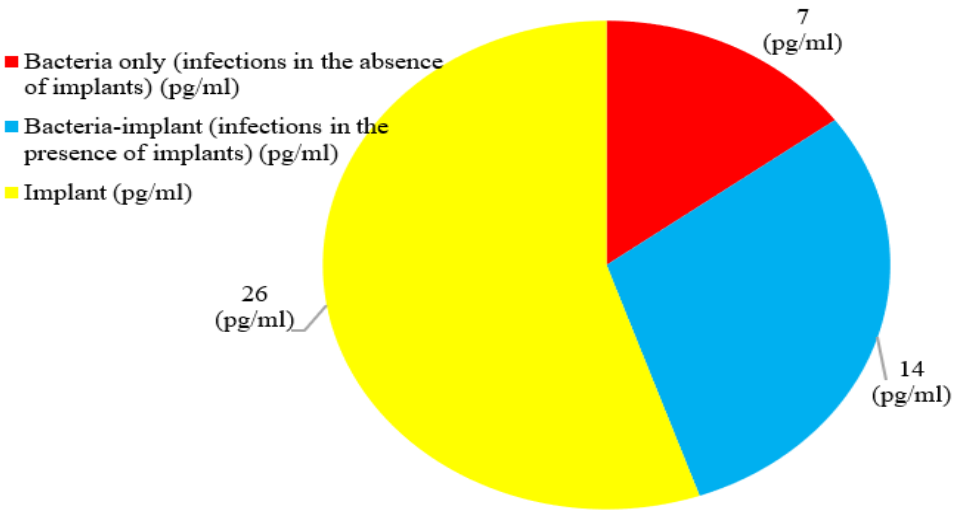

Figure 5. Systemic investigation of host inflammatory responses of [IFN-γ]

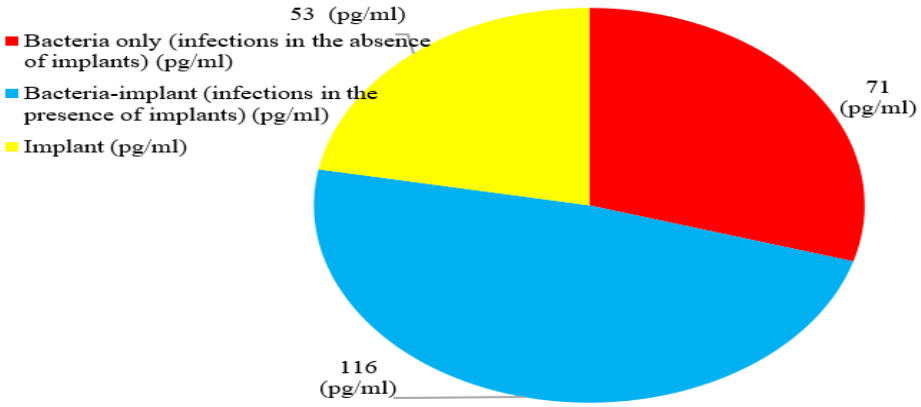

Figure 6. Systemic investigation of host inflammatory responses granulocyte colony-stimulating factor (G-CSF)

Innate immune recognition is well-known to cause inflammatory phagocytosis of harmful microbes and non-inflammatory phagocytosis of apoptotic. One way to measure the body's immune response is by looking at the levels of inflammatory factors in mice. One effective cell pro-inflammatory factor among them is IL-1β. The immune system's response to an infection or injury can help the body fight the infection or injury, but it can also make chronic conditions worse and cause more harm to wounded tissues. [24-27] By referring to the value generated by IL-1β, clinicians can determine which treatments to target, for example, by blocking the production of caspase-1 to prevent the release of IL-1β, so reducing harm to the body. The primary function of IL-6 is to regulate homeostasis inside living organisms. By stimulating the immune response, IL-6 aids the host in resisting emergency stress when homeostasis is disrupted by infection or tissue damage [28-31]. However, the body will create a harmful reaction when acute systemic inflammatory response syndrome and chronic immune-mediated disorders manifest, due to the excessive and persistent synthesis of IL-6. Some recent research has pointed to IL-6 as a potential marker for the early detection of sepsis. One cytokine that promotes inflammation is TNF-α. In healthy individuals, it was typically undetectable. Nevertheless, when there is infection or inflammation, the levels of tumor necrosis factor-α (TNF-α) in the blood and tissues will rise, leading to inflammation. This inflammation can eliminate irritants and speed up the healing process of tissues, but it can also damage tissues and, in extreme circumstances, cause organ failure and death. Furthermore, iNOS concentration is somewhat indicative of the body's oxidative stress level in response to stimulating stimuli. The majority of bacterial infections manifest with inflammatory infiltration of organs, which is typically detected through blood tests and tissue biopsies used to diagnosis clinical bacterial infections. While some studies have found a statistically significant difference between individuals with and without bacterial infections, others have shown that interleukin (IL)-9, IL-12, and IL-13 are better indicators of sepsis in bacterial infections. Prominent indicators of inflammatory reactions linked to implants include elevated levels of inflammatory cytokines, such as [IL-9, IL-12, and IL-13]. The implants themselves, bacterial communication, and other infections are among the many potential causes of this dysregulation of inflammatory cytokine expressions. Further study using mice models including infected implants put in the bones of the mouth is needed, according to the results of this subcutaneous model, regarding the use of inflammatory cytokines [32, 33].

There is a rich diversity of microbes in the mammalian gastrointestinal (GI) tract, which can prevent disease colonization. In humans, Escherichia coli is a lifelong resident of the typical gut microbiota and one of the first members to colonize babies. Certain strains of E. coli can cause sickness, however there are other non-pathogenic bacteria that provide benefits to the host, like vitamin K and B 12 (Blount, 2015). Humans can contract enterohemorrhagic E. coli (EHEC) if they have moderate to severe bloody diarrhea, which can lead to hemolytic uremic syndrome. The EHEC strain carries the Shiga toxin and LEE genes, which include the type III secretion system and intimin, a key adhesion factor. The serotype of E. hepatitis C virus most commonly infected humans in the United States is O157:H7. Direct contact with infected ruminants or consumption of feces-contaminated food or water are the most common ways for people to contract O157 EHEC, which mostly lives in ruminants like cattle [34–38]. Following ingestion, EHEC invades the colonic epithelial cells and transports inflammatory stimulators and suppressors, such as endotoxin, flagellin, and Shiga toxin. Within a week or two of ingesting O157 EHEC, the colonization process begins and symptoms of the disease manifest. Severe illness is more common in children less than 5 years old after contracting EHEC. Some research have found that O157 EHEC shedding in children can extend for more than 100 days, but the majority of investigations have found a mean duration of 1 month. Even while adults can get sick from EHEC, some people, such those who work on cattle farms or in processing plants, have reported being asymptomatic after colonizing with the virus. The establishment of intestinal colonization is a challenge in animal models used to research E. coli. There is a high demand for veterinary care, human resources, and financial resources when using large animal models like pigs, monkeys, baboons, and greyhounds. Because of their small size, short generation period, and well-characterized genetics, mice are an appealing model organism. However, it is not uncommon for adult CONV mice to have a built-in resistance to E. coli colonization [39]. The use of streptomycin to inhibit facultative anaerobic bacteria has enabled streptomycin-resistant Escherichia coli to colonize, thus circumventing resistance. Streptomycin-treated mice have a diverse microbiota and need the creation of mutant strains of E. coli that are resistant to streptomycin. This process can influence the expression of virulence factors that bacteria express. When studying E. coli colonization, several researchers have utilized germ-free mice models. However, these

animals do not have a microbiota, so their immune systems are not fully matured, and their intestinal architecture is different [40, 41].

It is believed that invading E. coli strains are inhibited in their proliferation by the facultative anaerobes found in CONV mice. In order to overcome the colonization resistance in mice, E. coli is often treated with streptomycin to decrease facultative anaerobes. Although the precise process by which streptomycin reduces colonization resistance remains unknown, it has been proposed that streptomycin-induced inflammation and the removal of microbe-microbe contacts contribute to the proliferation of E. coli through nitrate respiration. The use of spontaneous streptomycin-resistant E. coli strains has certain limitations, one of which is the possibility that these strains exhibit reduced levels of colonization factors, which could impact the interactions between hosts and pathogens. Also, the intestine becomes more sensitive after a single course of streptomycin therapy, which causes a small rise in histological alterations. Although germ-free mouse models have been utilized in the past (Goswami et al., 2015; Taguchi et al., 2002), these animals do not possess fully developed mucosal immune systems and cannot be used to evaluate interactions between microbes [42]. To evaluate inflammatory changes without introducing a confounding antibiotic treatment, ASF mice can be utilized as an alternative to germ-free and streptomycin-treated models. When fighting against infections, inflammation in the gastrointestinal tract is essential. During an EHEC infection, bacterial components like endotoxin, flagellin, and Shiga toxin can trigger an inflammatory response [43, 44].

In the colon supernatants of EHEC-inoculated mice, there were numerically higher quantities of common proinflammatory indicators compared to uninfected mice, but no significant differences were observed. These markers include IL-1β, IL-12, IFNγ, and TNFα. Intestinal inflammation found in this system may be due to other reasons, according to these studies. The levels of IL-12 in the supernatants of CONV mice injected with MG1655 were considerably greater ($P<0.05$) than those in uninfected mice. Dendritic cells and macrophages initiate the production of IL-12 when Toll-like receptors bind to microbial products. Furthermore, a method for evaluating mucosal inflammation was employed, which involved injecting an imaging agent that becomes active when inflammation-associated proteases such cathepsin B, K, L, and S are present. Here, MG1655-colonized ASF mice had lower levels of mucosal inflammation in the cecum than 278F2-colonized mice. This finding is in line with gene expression data that shows higher expression of chemokines, such as Ccl20, which could attract macrophages to the mucosa. While EHEC was present in significant concentrations in both the cecum and the colon, prior research in mice has shown that EHEC forms strong associations with the cecal epithelium rather than the colon. This could explain why the cecum was the only area where a substantial variation was found. Although cathepsin B release could be demonstrated in human monocytes infected with EHEC, it was not possible to do so in mice monocytes. This provides more evidence that the mouse may secrete several cathepsins or that different cell types secrete cathepsin B during EHEC infection. Therefore, there are hazards to human health during both the acute infection phase and the chronic effects of inflammatory bowel disease. Effector proteins are released by EHEC to combat inflammation. In a manner dependent on the type III secretion system, EHEC strains suppress NF-κB activation. Before, it was discovered that a number of effector proteins that are not LEEs could disrupt signaling pathways in the innate immune system. Therefore, EHEC employs tactics to evade host cell recognition of microbial factors and activation of inflammatory pathways in order to persist in the inflammatory gut, while the host cells attempt to eradicate the pathogen. E. coli-colonization mice models have shown a spectrum of illness severity, from no change at all to death [45-47]. There were no fatalities in the present investigation, and the histopathological findings included minor abnormalities such elongation of the glands and increased inflammatory cells. Other mice models of EHEC infection have also shown colonoscopies, with the germ-free model providing the most detailed description of these lesions. While prior research using EHEC mouse models has shown weight loss, the present investigation found just a small initial drop for ASF mice infected with MG1655 and 278F2 [48, 49]. Furthermore, aside from the seventh day after injection, both the ASF and CONV groups of mice that received the 278F2 vaccine increased weight. Metabolic process modulation during chronic colonization with 278F2 may explain the weight increase, according to changes in inflammatory-related genes (such as adiponectin, leptin, and thrombopoietin) that are also involved with metabolism.

CONCLUSION

Inflammation and oxidative stress can be induced by Escherichia coli in mice, leading to varying degrees of damage to the kidney, spleen, and lung tissues. This finding lends theoretical credence to the idea that Escherichia coli infections in humans can produce similar alterations. In inflammatory disorders and infectious disorders, harmful bacteria are associated with elevated serum interleukin (IL) levels during systemic evaluation. As ILs, especially IL-12 and IL-17, tend to be raised during bacterial infections, they could be used as biomarkers for sepsis and other illnesses. The production of ILs triggers the immune response in response to the presence or abundance of certain bacteria. Using a persistently inflamed mouse model of the implant site, this work comprehensively investigated inflammatory cytokines [CXCL-4 and CCL-5] and growth factors after inoculating mice with four distinct periodontal infections. A test tube experiment would not be able to adequately study the intricate interplay between bacteria and the tissues. Inflammatory cytokine expression regulation was implant-dependent, infection-specific, and systemic. Systemic treatment of inflammatory cytokines adds another layer of difficulty to interventions involving biomaterial-related illnesses. Our results also lend credence to the idea that future research using animals to represent biomaterial-related diseases should incorporate studies involving multiple species.

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