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Research Article

Edwardsiella ictaluri Live Attenuated Vaccines Induce IgM Responses in Channel Catfish *(Ictalurus punctatus)*

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Abstract

Edwardsiella ictaluri (E. ictaluri), a Gram-negative intracellular pathogen, causes enteric septicemia of catfish (ESC). The primary role of B cells is to produce antibodies, known as immunoglobulins (Ig), that mediate humoral immune responses. Successful vaccination results in the development of primary immune responses and generation of antigen-specific memory B cells. Recently, two Live attenuated vaccines (LAV), *Ei∆evpB* and ESC-NDKL1, were developed by our research group. Followed by our previous observations on the LAV-dependent in phagocytosis and bacterial killing activities of catfish macrophages and B cells, here we evaluated the antibody titer in serum of fingerling catfish exposed to both LAV and *E. ictaluri* Wild-Type (WT) strains at 7, 14, 21, 28, and 35 d post-challenge (dpc). We showed that the two *E. ictaluri* LAVs increased the IgM levels in catfish serum significantly at 14 dpc, which remained elevated at 28 and 35 dpc. In general, the WT strain-induced antibody levels resembled the patterns induced by two LAV strains but showed significantly higher titers. These data indicate that the *Ei∆evpB* and ESC-NDKL1 strains are capable of initiating sustainable IgM production, resulting in the development of primary immune responses and possibly generation of antigen-specific memory B cells against ESC.

Keywords: Antibody response; Channel catfish; *Edwardsiella ictaluri*; Humoral immunity; Live attenuated vaccines

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Introduction

In mammals, the main function of B cells is to mediate the humoral branch of adaptive immunity by secreting antibodies of increasing affinity and maintaining an immunological memory [1]. Due to lack of bone marrow in teleost fish, B cells, as well as other blood cells, are produced in the anterior kidney (AK) [2-4]. Similar to mammals, upon activation by antigenic stimuli, mature B cells differentiate into plasma cells that are responsible for the production of antibodies [5]. Antibodies can neutralize the pathogens [5,6], induce the internalization and elimination of the opsonized pathogens by Fc receptor-mediated phagocytosis [7,8], and trigger antibody-dependent cellular Cytotoxicity (ADCC) through Fc receptor-bearing effector cells [9]. Also, antibodies activate the complement cascade that results in the internalization and degradation of complement-coated pathogens by phagocytic cells and the formation of membrane attack complex that causes lysis of pathogens [10].

Antibodies or immunoglobulins (Ig) in teleost fish show structural and functional similarities to those in mammals [11]. Three classes of Ig have been described in teleost fish and are named IgM, IgD, and IgT/Z [11,12]. IgM, the first class of antibody identified in fish, is tetrameric and the most prevalent Ig in fish serum [13]. IgD in fish is expressed in a monomeric form and may be present in two different forms, transmembrane and secreted forms [14,15]. IgT/Z is produced only by teleost fish, in rainbow trout (*Oncorhynchus mykiss*), salmonids, stickleback (*Gasterosteus aculeatus*), carp (*Cyprinus carpio*) (IgT) and zebrafish (*Danio rerio*) (IgZ) [16-20] and secreted in a monomeric form and specialized in mucosal surfaces in teleost fish, such as intestine [12,21].

Edwardsiella ictaluri (*E. ictaluri*) is a Gram-negative facultative intracellular pathogen causing enteric septicemia of catfish (ESC), one of the most severe diseases in the catfish industry [22-25]. *E. ictaluri* live attenuated vaccine (LAV) provided adequate protection in catfish fry and eyed catfish egg by immersion exposure [26-29]. Furthermore, a live attenuated *E. ictaluri* isolate (S97-773) was developed as an oral vaccine, which protected catfish fingerlings against *E. ictaluri* infection [30]. *E. ictaluri* can survive in macrophages of channel catfish [31]. *E. ictaluri* LAVs triggered both cell-mediated and humoral immunities and facilitated the bactericidal activity of macrophages [32-34].

Our research group has developed two *E. ictaluri* LAV strains (*Ei∆evpB* and ESC-NDKL1), which provided efficient protection in both catfish fry and fingerlings against ESC [35,36]. Vaccination with *Ei∆evpB* provided 100% survival in fingerlings and 80% survival in fry catfish after WT *E. ictaluri* challenge [36]. In addition, vaccination of catfish fingerlings with ESC-NDKL1 resulted in similar survival rates with the *Ei∆evpB* LAV strain, however vaccination of fry with ESC-NKDL1 showed moderately elevated 3-4% mortality rates [35]. We reported that two LAVs enhanced the phagocytic and bacterial killing abilities of catfish peritoneal macrophages and AK B cells [34,37,38]. We also demonstrated the effects of both LAVs on the

initiation of innate and adaptive immune responses in lymphoid organs of catfish [39]. However, the role of *Ei∆evpB* and ESC-NDKL1 on the IgM production in the serum of channel catfish is still unexplored. The purpose of this study was to assess the IgM levels in channel catfish sera after exposure to *E. ictaluri* LAVs and WT strains. The elevated levels of IgM will indicate the successful role of LAVs in the initiation of humoral-mediated responses in adaptive immunity against ESC.

Materials and Methods

Animals

All fish experiments were conducted based on a protocol approved by the Mississippi State University Institutional Animal Care and Use Committee (IACUC). Six months old specific pathogen-free (SPF) channel catfish fingerlings were obtained from the fish hatchery at the College of Veterinary Medicine, Mississippi State University, which raises catfish from disinfected catfish eggs indoors under strict biosecurity protocols and maintained at 25-28°C. Tricaine methanesulfonate (MS-222, Western, Cehemical, Inc.) was used (400 mg/L) to euthanize the catfish.

Bacterial strains

E. ictaluri 93-146 Wild-Type (WT) and two LAVs (*Ei∆evpB*, and ESC-NDKL1) were cultured in brain heart infusion (BHI) agar or broth (Difco, Sparks, MD, United States) at 30°C for overnight. Media were supplemented with colistin sulfate (Col: 12.5 mg/ml, Sigma–Aldrich, St. Louis, MN) when it is needed.

Fish vaccination and serum collection

Two hundred forty SPF catfish fingerlings (6-month-old) with fully developed innate and adaptive immune systems were stocked into four 40 L tanks (60 fish per tank) that were supplied with continuous water flow and aeration. The fish were fed twice daily and acclimated for one week. Then, tanks were assigned randomly to *Ei∆evpB*, ESC-NDKL1, WT (positive control), and BHI (negative control) groups, and fish in each tank were exposed to their respective treatment by immersion as described previously [34,40]. Briefly, 100 ml of overnight culture for each treatment were added to 10 L water yielding an infection dose of approximately 3.67 x 10^7 CFU/ml of water. Following vaccination, blood was collected from the caudal vein of 10 catfish per group at 7, 14, 21, 28, and 35 d post-challenge (dpc), and placed at 4°C overnight for clot formation. Then, serum from 10 fish was pulled and obtained by centrifugation at 2,000 rpm for 10 min. All serum was kept at -20°C for 45 d, then used for enzyme-linked immunosorbent assay (ELISA).

ELISA for serum antibody response

Antibody titers were assessed by the ELISA as described previously with some minor modifications [41]. Briefly, heat-killed *E. ictaluri* WT strain was resuspended in 0.9X Hank's Balanced Salt Solution (HBSS, Sigma) with 100X Sodium Azide, and high binding 96-well Immulon plates (Nunclon ™ Delta Surface, Thermo Scientific) were coated with the heat-killed bacteria (10^8 CFU/ml) by centrifugation at 2,000 rpm for 5 min. To fix the bacteria, 0.5% Glutaraldehyde solution was added to each well and incubated at room temperature (RT) for 15 min, followed by washing twice in phosphate-buffered saline (PBS). Then, 100 mM glycine conjugated with bovine serum albumin (BSA) was added to each well for blocking unreacted aldehydes. Followed by incubation at RT for 30 min, the wells were washed twice in PBS and distilled water and dried at 37° C for overnight. Subsequently, wells were blocked with 5% non-fat dry milk in PBS for 2h at RT and washed three times in PBS. The serum samples collected at 14 dpc were tested for the presence of specific antibodies at the following dilutions, 1:10, 1:100, 1:1000. Significant increases in the antibody responses were found in all diluted sera of catfish challenged with *E. ictaluri* LAV and WT strains compared to the non-vaccinated control group. However, the most profound differences in the antibody response between LAVs and WT strains were documented by using 1:10 serum dilution. Diluted serum (1:10) samples were added to each well (100 µl /well), incubated at RT for 1 h and washed three times in PBS containing 0.1% tween 20 (PBS-T) and followed by washing three times in PBS. Then, monoclonal antibody 9E1 (anti-catfish Ig) [42,43] was diluted in 1:4 ratio and added to each well. Following 1h incubation at RT, wells were washed in PBS-T, and 1:1500 dilution of goat anti-mouse Ig (H+L) AP (SouthernBiotech) conjugated antibody was added to each well and incubated at RT for 1 h. After washing, the *p*-nitrophenyl phosphatase substrate (Sigma 104 phosphatase substrate) was dissolved in 10% diethanolamine buffer and added to per well. Finally, the plates were incubated at RT for 40 min, and absorbance at 405 nm was measured by an ELISA Microplate Reader (SpectraMax M5, CA, USA). The negative control group included serum from non-vaccinated fish, and control wells containing PBS, instead of serum, were prepared in the same manner. All samples (7, 14, 21, 28, and 35 dpc) were processed and analyzed on the same day by the same people, also multichannel pipet (Eppendorf) was used to eliminate technical and/or human related error.

Statistical analysis

Linear models with PROC MIXED in SAS for Windows 9.4 were applied for the absorbance. The fixed effects of ELISA assay were treatment, days, and their interaction. When there is significant interaction, the differences in least squares means between 7, 14, 21, 28 and 35 d for each of the treatments and also between treatments for each day were calculated by using an LSMESTIMATE statement. Also, the simulate adjustment for multiple comparisons was used in the case of the significant terms.

The level of significance for all tests was set at $P < 0.05$. The distribution of the residuals was evaluated for each model to make sure the assumptions of normality and homoscedasticity for the statistical method had been met.

Results and Discussion

The IgM isotype is the main Ig in channel catfish (*Ictalurus punctatus*) as it is present in both catfish serum and mucosal tissues [11]. In this study, we determined the IgM response in the sera of catfish fingerlings challenged with *E. ictaluri* LAVs (Figure 1). In parallel, the antibody levels in the sera of fish challenged with the WT strain and non-vaccinated catfish sera were used as positive and negative controls, respectively. Significant increases in the IgM titers were detected in the sera of catfish in all LAV- and WT-challenged groups compared to the non-vaccinated control group at 7 dpc (Figure 1A). Furthermore, the antibody responses in the sera of catfish exposed to the *Ei∆evpB* and WT strains were significantly higher than those found in the serum of catfish challenged with the ESC-NDKL1 strain at 7 dpc while there were no significant differences in the IgM levels between the *Ei∆evpB* and WT-challenged fish. Both LAV strains induced significant increases in the IgM response in catfish

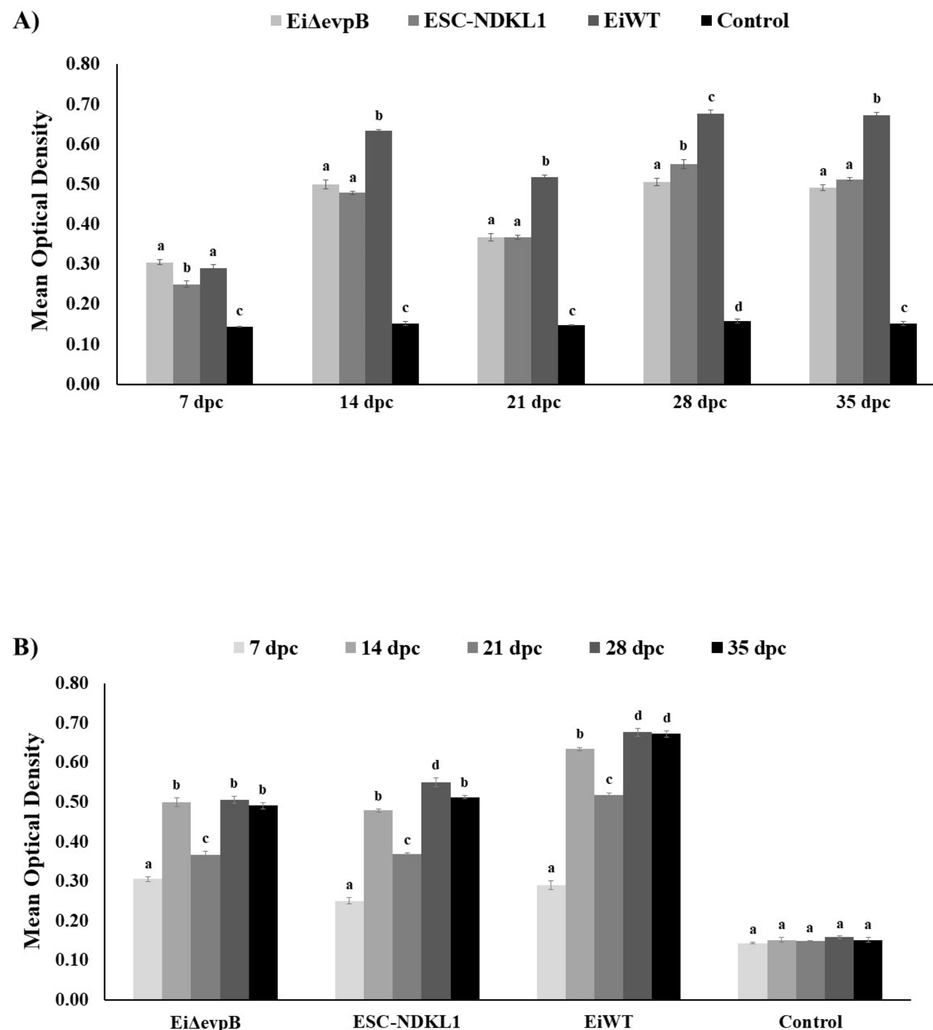

Figure 1: Antibody response in the serum of channel catfish challenged with E. ictaluri LAV and WT strains. Letters (a, b, c, and d) show significant differences between the treatments at any given time point (A) and also indicate significant differences between time points for each treatment (B) ($P < 0.05$). The data represent optical densities at 405 nm for the mean of ten fish±SD in each experimental group.

sera compared to the non-vaccinated control group at 14 dpc (Figure 1A). Moreover, significantly elevated antibody responses were found in sera of catfish challenged with both LAVs and WT strain at 21 dpc compared to the non-vaccinated control fish (Figure 1A). No significant changes were documented in the antibody titer between the *EiΔevpB* and ESC-NDKL1 strains at 21 dpc (Figure 1A). These data suggest that the *EiΔevpB* and ESC-NDKL1 strains can initiate the IgM production during the development of primary immune responses in channel catfish. A recent study reported that an attenuated *Flavobacterium psychrophilum* vaccine showed an elevation of IgM titer in the serum of rainbow trout [44]. Also, the IgM titer increased 100-fold in the serum of rainbow trout immunized with *Streptococcus iniae* [45]. Similar to teleost fish, a single dose of LAV containing measles, rubella, mumps, and varicella increased the antibody titer in humans [46].

In addition, significant increases in the antibody responses were found in sera of catfish with *E. ictaluri* LAV and WT strains compared to the non-vaccinated control group. In contrast, the ESC-NDKL1 strain significantly elevated the antibody levels in catfish serum compared to the *EiΔevpB*-counterparts at 28 dpc (Figure 1A). The patterns of antibody responses in catfish sera at 35 dpc resembled the patterns induced at 14 and 21 dpc (Figure 1A). Two LAV strains significantly increased the antibody responses in catfish sera compared to the non-vaccinated control group at 35 dpc (Figure 1A). These results suggest possible generation of memory B cells for long term immunity against ESC. These findings agree with our earlier reports indicating that immersion vaccination of catfish fry and fingerlings with ESC-NDKL1 and *EiΔevpB* provided significant safety and protection [35,36]. Another study reported that vaccination of channel catfish with *Ichthyophthirius multifiliis* resulted in a high titer of serum IgM

for five weeks and followed by the formation of memory B cells [47]. Furthermore, live attenuated *Vibrio anguillarum* vaccine candidate strain elevated specific antibody response in zebrafish during 28 d post-vaccination [48].

As expected, the antibody levels significantly elevated in the sera of catfish challenged with two LAVs and WT strain at 14 dpc compared to 7dpc (Figure 1B). Antibody responses in the sera of catfish exposed to both LAVs and WT strain at 21 dpc, significantly decreased compared to the responses at 14 dpc, however were still significantly higher than at 7 dpc (Figure 1B). These data agree with our previous observation that the expression of T and B cell-specific genes, in particular IgM was significantly elevated in the spleen of catfish challenged with *E. ictaluri* LAV and WT strains at 14 dpc, but decreased at 21 dpc. Importantly, the activity of these genes was only moderately elevated at 21 dpc in the anterior kidney [49]. We speculate that the drops in the antibody response to bacterial strains at 21 dpc could be explained by the gradual replacement of short-lived antibody-producing B cells with long-lived plasma cells and possible memory B cells migrating from the spleen to periphery. Surprisingly, both LAV and WT strains induced significant increases in antibody responses of catfish sera at 28 dpc compared to 21 dpc (Figure 1B). No significant changes in the antibody titer were detected in sera of catfish with the *EiΔevpB* and WT strains at 35 dpc compared to 28 dpc (Figure 1B). However, the ESC-NDKL1 strain induced significant decreases in the antibody responses in catfish serum at 35 dpc compared to 28 dpc (Figure 1B). Furthermore, no significant differences in IgM levels were detected in serum of the non-vaccinated fish group at all time points (Figure 1B).

Interestingly, the antibody levels in the serum of catfish challenged with WT strain significantly increased at 14, 21, 28, and 35 dpc compared to the LAV-challenged and non-vaccinated counterparts (Figure 1A). Channel catfish fingerlings that survived for five weeks post WT strain challenge showed significantly higher levels of the IgM titer in serum compared to their two LAV-counterparts, which could be explained by the differential framework of initiation of humoral immune responses in adaptive immunity between the LAVs and WT strains. In the agreement with this result, our previous research demonstrated that the WT strain induced significant increases in the activities of innate and adaptive immune-related genes in lymphoid organs of catfish compared to the *EiΔevpB* and ESC-NDKL1 strains [39].

Specific antibodies bind their molecular targets with exquisite sensitivity and specificity, providing protection against a variety of pathogens. Polyreactive antibodies as a major component of the natural antibody repertoire bind to broad unrelated structures and protect hosts with functional components to rapidly recognize and protect against different pathogens [50-52]. In our study, the antibody response to the LAV and WT strains of *E. ictaluri* showed kinetics of adaptive immunity suggesting possible generation of memory B cells for long term protection against ESC. We cannot rule out the possibility that innate polyreactive antibodies might be induced by the bacterial challenges, however based on the IgM kinetics in the serum of catfish challenged with the LAV and WT strains and our previous research, their effect was not significant.

In conclusion, successful vaccination establishes a balance between efficacy and safety. Also, successful vaccination requires both the development of primary immune responses and generation of highly antigen-specific memory cells [53]. These results showed that *EiΔevpB* and ESC-NDKL1 strains were able to initiate humoral immune responses in catfish against ESC. These two LAVs developed the effective primary immune responses and generated antigen-specific B cells during *E. ictaluri* infection.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Institutional Review Board Statement

All fish experiments were conducted based on a protocol approved by the Mississippi State University Institutional Animal Care and Use Committee (IACUC #17-288).

Author's Contribution

Conceptualization LMP, and AOK; Investigation LMP and AK; Project administration LMP, Methodology, AOK. and HA; Formal Analysis, AOK; Supervision LMP; Writing – Original Draft Preparation AOK; Writing-Review & Editing LMP, AK, and HA, All authors were involved in critical interpretation of the data, manuscript revision, and final version approval.

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