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FXR/TGR5 mediates inflammasome activation and host resistance to bacterial infection

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ABSTRACT

Bacterial infections are a major cause of chronic infections and mortality. Innate immune control is crucial for protection against bacterial pathogens. Bile acids facilitate intestinal absorption of lipid-soluble nutrients and modulate various metabolic pathways through the farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5). Here, we identified a new role of FXR and TGR5 in promoting inflammasome activation during bacterial infection. Caspase-1/11 activation and release of cleaved interleukin (IL)-1β in FXR- and TGR5-deficient mouse bone marrow-derived macrophages upon *Listeria monocytogenes* or *Escherichia coli* infection was significantly reduced. In contrast, FXR- or TGR5-deficiency did not affect the transcription of caspase-1/11 and IL-1β. Inflammasome activation is critical for host immune defense against bacterial infections. Consistent with this, the deletion of FXR or TGR5 impaired effective clearance of *L. monocytogenes* or *E. coli in vitro* and *in vivo*, which was associated with greater mortality and bacterial burden than that of wild-type mice. Pretreatment with an FXR agonist decreased bacterial burden *in vitro* and increased survival *in vivo*. Thus, FXR and TGR5 promote inflammasome-mediated antimicrobial responses and may represent novel antibacterial therapeutic targets.

1. Introduction

Bacterial infections are a major cause of chronic infections and mortality that continues to threaten public health worldwide. The innate immune system is responsible for the first-line of defense against bacterial infections [1]. It detects the presence of bacteria and activates mechanisms to eliminate potential pathogens. The innate immune system utilizes various pattern recognition receptors (PRRs), including Toll-like receptors, nucleotide-binding oligomerization domain-like receptors (NOD-like receptors, NLRs), and retinoic acid-inducible gene-I (RIG)-like receptors (RLRs) to identify pathogens [2]. These are essential for the detection of various pathogen-associated molecular patterns (PAMPs), and their activation triggers the formation of multiprotein complexes called inflammasomes [3].

The inflammasome is critical for host immune defenses against bacterial infections [4–6]. Both extracellular and intracellular bacterial infections trigger different types of inflammasome activation via distinct inflammasome sensors [7]. Inflammasome activation requires two signals. First, innate immune cells are primed by recognizing PAMPs expressed on the pathogen through PRRs, resulting in the expression of critical components of the inflammasome. These include the NOD-, LRR-and pyrin-containing domain 3 (NLRP3) and pro-interleukin-1 (pro-IL-1). Second, the inflammasome is assembled in PAMP-primed cells upon further stimulation by damage-associated molecular patterns (DAMPs), such as ATP, which recruits apoptosis-associated speck-like protein containing CARD (ASC) adaptor protein. Pro-caspase-1 is activated by the inflammasome to produce active caspase-1, which further converts pro-IL-1 into the mature IL-1 [8]. In addition to this canonical inflammasome activation, a noncanonical activation targets caspase-11 [9]. In contrast to gram-positive bacteria, gram-negative bacteria can induce the expression of pro-caspase-11, and activated caspase-11 directly mediates the activation of caspase-1 to induce pro-IL-1β maturation.

Bile acids (BAs) are generated by hepatocytes and are essential for dietary lipid absorption and cholesterol homeostasis [10]. BAs may serve as signaling molecules in the regulation of systemic endocrine functions [11]. BAs specifically bind with different affinities to nuclear and membrane receptors, including the farnesoid X receptor (FXR, gene symbol NR1H4) [12] and G protein-coupled BA receptor 1 (TGR5, gene symbol GPBAR1) [13], respectively. FXR is a member of the nuclear

Abbreviations: FXR, Farnesoid X receptor; TGR5, Takeda G-protein-coupled receptor; BMDM, bone marrow-derived macrophages.

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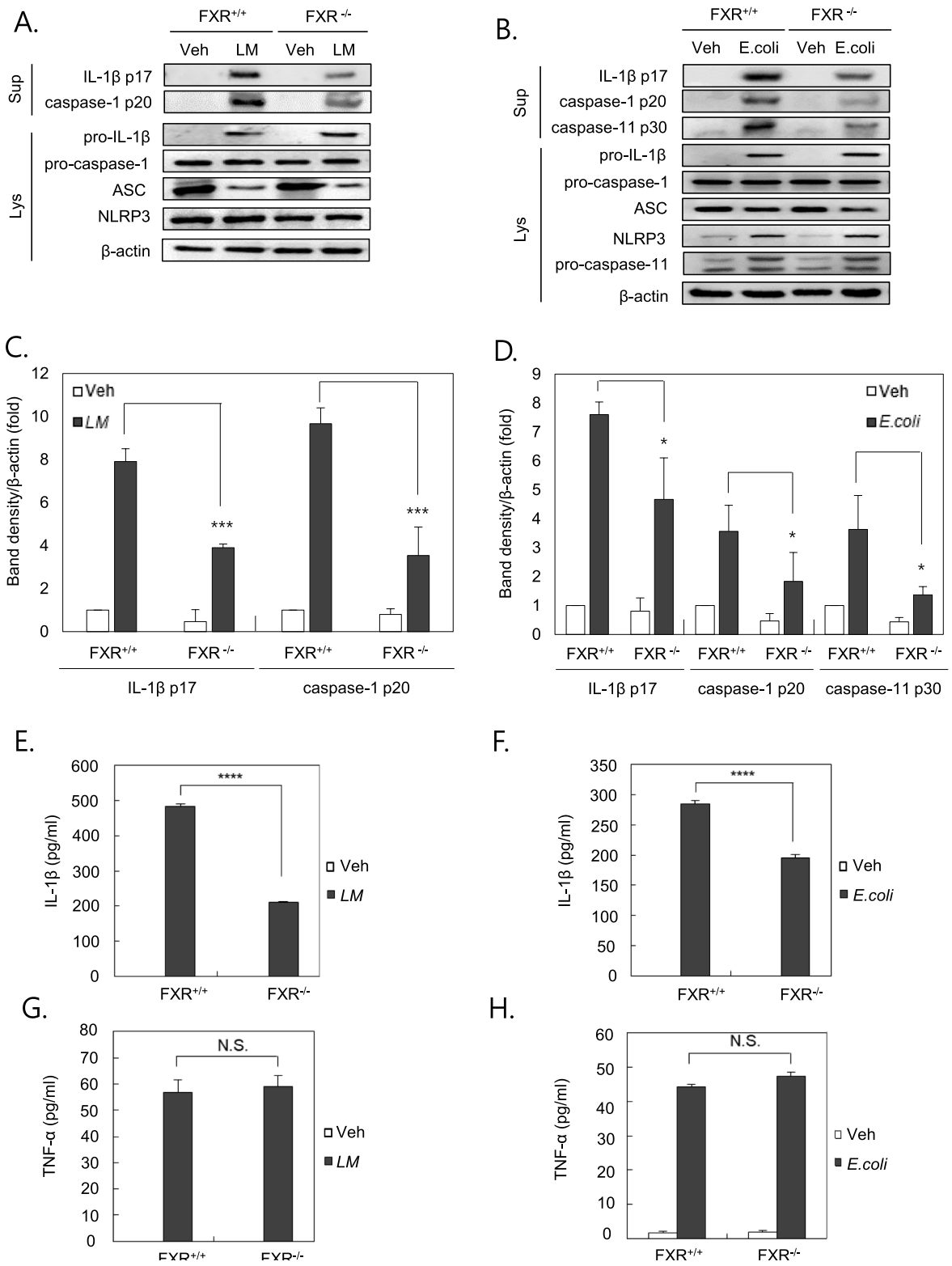

Fig. 1. Macrophages lacking FXR display decreased levels of inflammasomes and IL-1β. Primary BMDMs were derived from wild-type (WT) or FXR$^{-/-}$ mice and were infected with *L. monocytogenes* (A, C, E and G) for 5 h, or *E. coli* for 16 h (B, D, F and H) at MOI 50. (A, B) Immunoblotting of cell lysates (Lys) and supernatants (Sup). (C, D) Graphs of the densitometry for immunoblots. (E, F) IL-1β level in the supernatant of BMDMs. (G, H) TNF-α level in the supernatant of BMDMs. Data represent three independent experiments (n = 3). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ significantly different from WT.

receptor superfamily of transcription factors that regulate multiple biological processes [14]. Upon ligand-induced activation, FXR binds to FXR response elements [15] as a monomer or heterodimer with the retinoid X receptor (RXR) [16,17] and modulates BA, lipid, and glucose metabolism, energy metabolism, tumor formation, and immune homeostasis [11,18].

TGR5 (also known as GPAR1, M-BAR, or BG37) is a surface receptor in the G protein-coupled receptor family [19–22]. TGR5 is known to

activate cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) signaling to stimulate phosphorylation of cAMP response element-binding protein, resulting in the transcriptional activation of multiple pathways [23]. TGR5 is considered a metabolic regulator involved in BA synthesis, glucose metabolism, and energy homeostasis [24]. TGR5 reportedly participates in cancer, liver regeneration, and inflammatory responses [25].

FXR and TGR5 may contribute to immune functions [26–30]. However, the roles of FXR and TGR5 in controlling inflammasomes during bacterial infection are unknown. The present study addressed this issue using $FXR^{-/-}$ and $TGR5^{-/-}$ mice and analyzed their roles in antimicrobial responses.

2. Materials and methods

2.1. Reagents

Antibody to caspase-1 was purchased from Cell Signaling Technology (Beverly, MA, USA). Antibody against apoptosis-associated speck-like protein (ASC) was purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Antibodies against IL-1β and NLR family pyrin domain containing 3 (NLRP3) were purchased from R&D Systems (Minneapolis, MN, USA). β-Actin antibody and all other chemicals including FXR agonists were purchased from Sigma-Aldrich (St. Louis, MO, USA).

2.2. Animals

$FXR^{-/-}$ mice with a C57BL/6 background were originally from Frank Gonzalez (National Cancer Institute, National Institutes of Health). $TGR5^{-/-}$ mice with a C57BL/6 background were originally from Merck Research Laboratories (Kenilworth, NJ). $NLRP3^{-/-}$ mice with a C57BL/6 background were purchased from The Jackson Laboratory (Bar Harbor, ME). All mice were maintained on a standard chow diet and water *ad libitum* and housed in a room with a 12 h light/dark cycle. All animal experiments were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals and the Association for Assessment and Accreditation of Laboratory Animal Care of Sookmyung Women's University.

2.3. Cells and culture systems

Mouse primary bone marrow cells were obtained from the femur of 12-week-old male mice. Cells were cultured in DMEM containing 10% fetal bovine serum and 1% antibiotics along with 10 ng/ml macrophage colony stimulating factor (M-CSF) in a humidified 5% CO_2 atmosphere at 37 °C overnight. Non-adherent cells were harvested and cultured for 6 d. Adherent bone marrow-derived macrophages (BMDMs) were used as required in various experiments.

2.4. In vivo infection

Eight to ten-week-old male mice were administered intravenously (i.v.) with 1×10^5 colony forming units (CFU) of *Listeria monocytogenes* or 2×10^9 CFU of *Escherichia coli*. After 2 d (for *L. monocytogenes*) or 6 h (for *E. coli*), blood was collected by retro-orbital venous plexus puncture. After sacrifice, liver and spleen were obtained and homogenized in sterile phosphate buffered saline (PBS). Serially diluted homogenates were plated in triplicate on brain heart infusion (BHI) broth (for *L. monocytogenes*) or Luria broth (*E. coli*). For hematoxylin and eosin (H&E) staining, mouse livers were fixed with 4% paraformaldehyde and analyzed by GENOSS Co., Ltd (Yeongtong-gu, Suwon). For the survival test, 8-10-week-old male mice were infected with either *L. monocytogenes* (5×10^5 CFU) or *E. coli* (5×10^9 CFU). Mice were observed for 6 d (for *L. monocytogenes*) or 48 h (*E. coli*) to ascertain survival. For FXR agonist treatment, mice were intraperitoneally (i.p.) treated with 5 mg/kg/day 6-ECDCA or vehicle daily from 1 day before infection.

2.5. In vitro infection

BMDMs were infected with *L. monocytogenes* or *E. coli* at a multiplicity of infection of 50. Cells were harvested and cultured using BHI or LB agar plates at 37 °C. Bacterial colonies were counted after 16 h.

2.6. Cytokine measurements

Cell culture supernatant or mouse serum was collected to determine the levels of IL-1β or tumor necrosis factor-alpha (TNF-α) using ELISA kits (Cusabio Technology LLC). The assay was performed in triplicate for each specimen, and the data were converted to ng/ml or pg/ml.

2.7. Western blot analysis

Whole cell lysates were separated using 8%–12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Resolved proteins were transferred onto Immobilon-P membranes (Millipore, Bedford, MA, USA). The membranes were blocked with 5% non-fat milk in PBS containing 0.1% Tween 20 (PBST) and incubated with antibody to anti-IL-1β, anti-NLRP3, anti-ASC, anti-caspase-1, or anti-β-actin (1:4000) followed by secondary horseradish peroxidase-conjugated antibody (1:5000). The membranes were detected using enhanced chemiluminescence reagent (Amersham Biosciences, Buckinghamshire, UK). The band intensity was quantified using the ImageJ program (NIH Image, Bethesda, MD, USA).

2.8. Statistical analyses

Survival data between wild-type (WT) and knockout (KO) mice were analyzed by Kaplan-Meier analysis with log-rank test using GraphPad Prism 7 software program. Data represent the mean±SD from three independent experiments. The Student's *t*-test was used to compare two means and ANOVA for multiple comparisons. $*p < 0.05$ was considered statistically significant.

3. Results

3.1. Lack of FXR impairs inflammasome activation

Macrophages are crucial in innate immune responses against bacteria [31]. Studies have demonstrated the role of the inflammasome and the pro-inflammatory cytokine IL-1β in the protection against bacterial pathogens [4–6]. Thus, we determined whether BA receptors are associated with inflammasome activation in mouse BMDMs upon infection with representative gram-negative (*E. coli*) and gram-positive (*L. monocytogenes*) bacteria. Bacterial infection induced robust pro-caspase-1, pro-caspase-11, and pro-IL-1β expression in both WT and FXR-deficient BMDMs (Fig. 1A and B). NLRP3 expression levels were also similar between WT and FXR-deficient BMDMs. However, FXR-deficient BMDMs showed reduced activation of pro-caspase-1 (p20) and pro-caspase-11 (p30) compared to WT cells. Bacterial infection-induced IL-1β secretion (IL-1β p17) was consistently decreased in $FXR^{-/-}$ BMDMs (Fig. 1A–D). IL-1β levels in BMDMs upon *L. monocytogenes* or *E. coli* infection assessed by ELISA revealed the significant decrease in IL-1β production in $FXR^{-/-}$ BMDMs compared to WT BMDMs (Fig. 1E and F). However, FXR-deficient BMDMs displayed similar TNF-α secretion, which was not dependent on the inflammasome (Fig. 1G and H). The findings suggested that impaired control of inflammasome activation in FXR-deficient BMDMs is associated with reduced IL-1β expression.

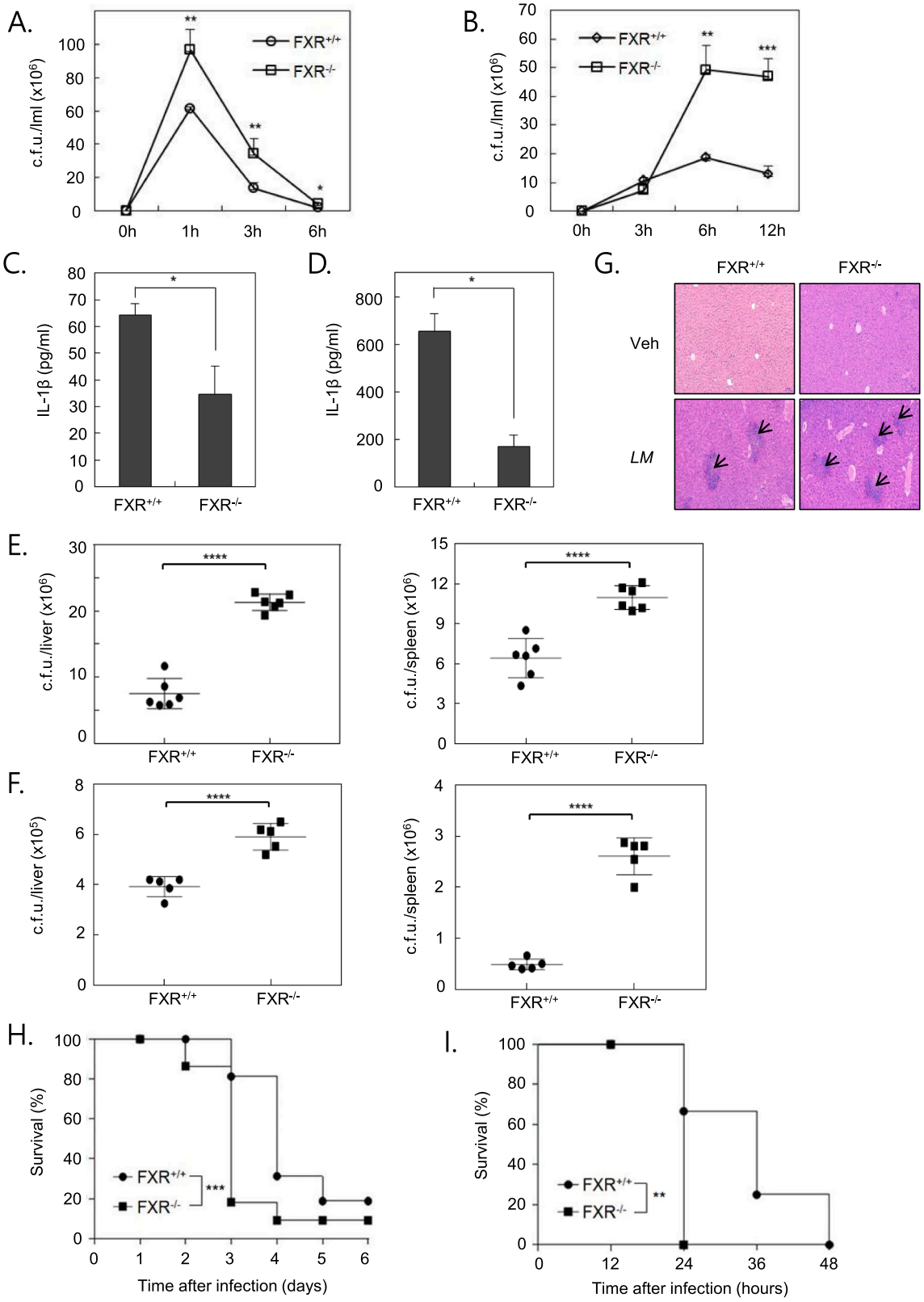

Fig. 2. FXR deficiency results in an enhanced bacterial burden associated with increased mortality. (A, B) BMDMs were derived from WT or FXR$^{-/-}$ mice and infected with *L. monocytogenes* (A) for 5 h or *E. coli* (B) for 16 h at MOI 50. Quantification of bacterial burdens in BMDMs at indicated times post-infection (n = 3). (C, D) IL-1β serum levels in WT and FXR$^{-/-}$ mice infected with 1×10^5 CFU *L. monocytogenes* (C) or 2×10^9 CFU *E. coli* (D) at day 2 (*L. monocytogenes*) or 24 h (*E. coli*) post-infection (n = 3) (E, F) Bacterial burden in the liver or spleen at day 2 (*L. monocytogenes*) or 6 h (*E. coli*) post-infection. (G) Stained WT and FXR$^{-/-}$ livers 2 days after *L. monocytogenes* infection. Infiltration of inflammatory cells are indicated by arrowheads. H&E stain; × 100. (H, I) Percentage survival of WT and FXR$^{-/-}$ mice infected with 5×10^5 CFU *L. monocytogenes* (n = 16–22, H) or 5×10^9 CFU *E. coli* (n = 10–12, I). $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$ significantly different from WT. Scale bar = 100 μm; veh: vehicle; *LM: L. monocytogenes*.

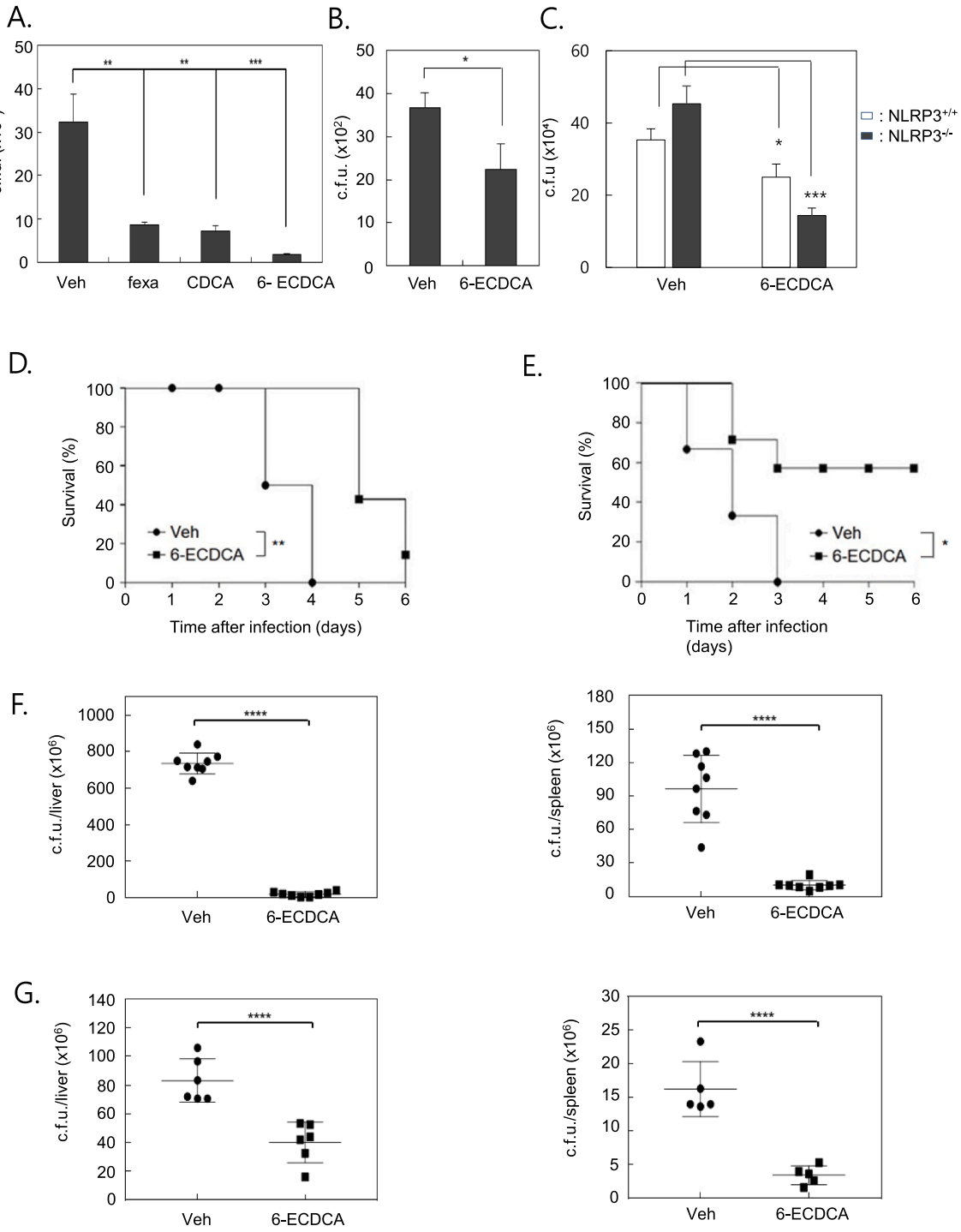

Fig. 3. FXR agonists enhance mouse survival by improving bacterial clearance (A–C) Quantification of bacterial burden in BMDMs 2-h post-infection. Primary BMDMs were pretreated with fexaramine (5 μM), CDCA (50 μM), or 6-ECDCA (50 μM) before *L. monocytogenes* (A) or *E. coli* (B) infection (n = 3). Primary BMDMs from WT or NLRP3$^{-/-}$ mice were pretreated with 6-ECDCA (50 μM) before *L. monocytogenes* infection (n = 3) (C). (D, E) Percentage survival of mice infected with 5 × 10^5 CFU *L. monocytogenes* (n = 7–8, D) or 5 × 10^9 CFU *E. coli* (n = 6, E) and treated with 6-ECDCA. Mice were injected i.p. with 5 mg/kg/day 6-ECDCA or with vehicle daily for 6 days starting from 1 day before bacterial infection. (F, G) Bacterial burden of the liver or spleen in response to 6-ECDCA treatment. Bacterial burden was enumerated on day 2 (*L. monocytogenes*, F) or 6 h (*E. coli*, G) post-infection. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ significantly different from Veh. *LM*: *L. monocytogenes,* fexa: fexaramine, *E: E. coli*.

3.2. FXR is a positive regulator of bactericidal activity

Since the absence of FXR significantly impaired inflammasome activation in BMDMs, we hypothesized that FXR may mediate the elimination of bacteria in macrophages. To assess this, we examined macrophage killing abilities *in vitro* using BMDMs of WT and FXR$^{-/-}$ mice. Cultured FXR-deficient BMDMs displayed reduced ability to kill *L. monocytogenes* and *E. coli* compared to WT cells (Fig. 2A and B).

We further investigated the role of FXR in the antimicrobial response *in vivo*. First, we confirmed that FXR deficiency resulted in a reduction in IL-1β serum levels in bacteria-infected WT and FXR KO mice, consistent with the *in vitro* data (Fig. 2C and D). Examination of the bacterial load

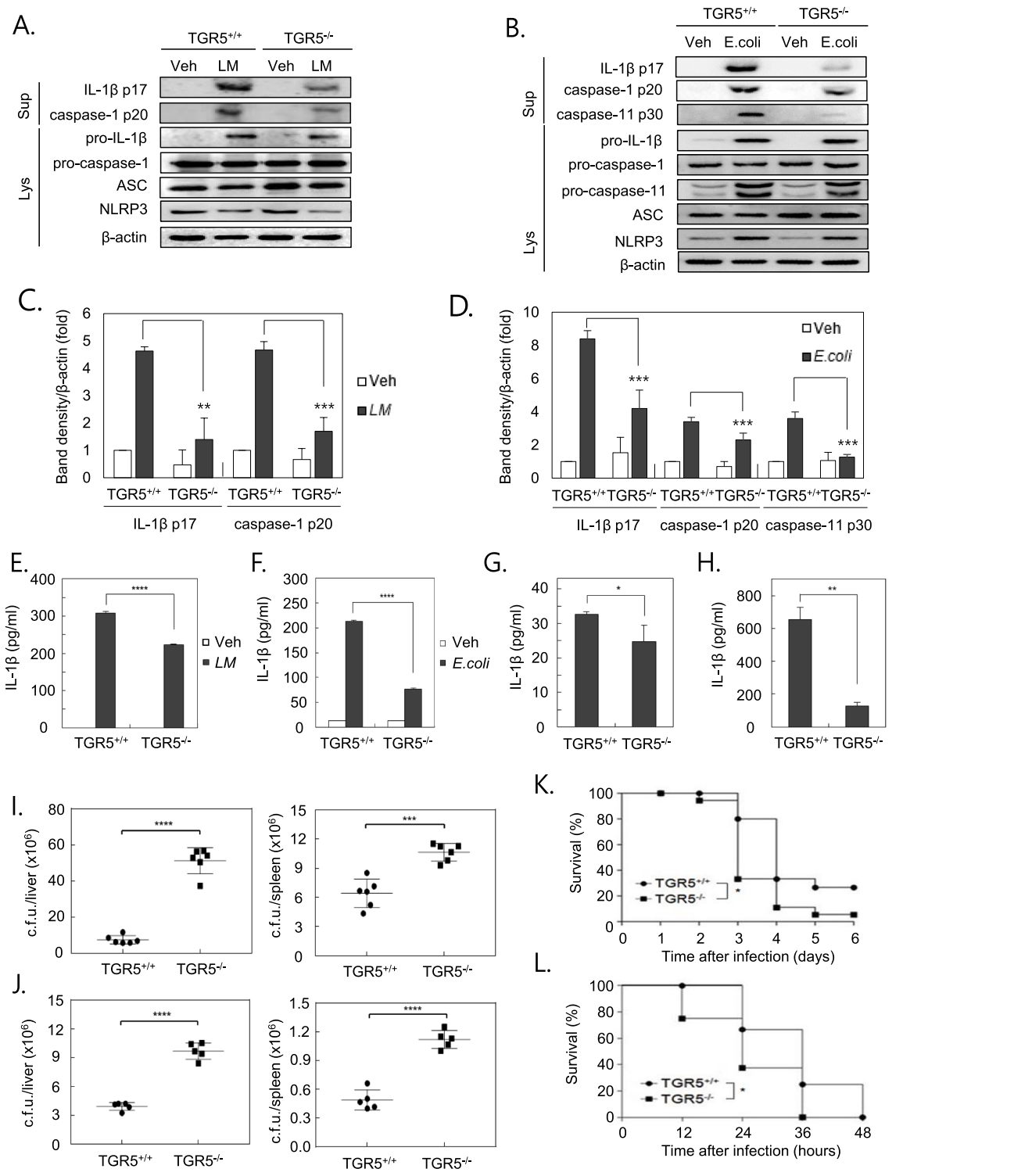

Fig. 4. TGR5 deficiency is associated with decreased levels of inflammasomes and enhanced bacterial burden. (A, B) BMDMs were derived from WT or TGR5$^{-/-}$ mice and infected with *L. monocytogenes* (A) for 5 h or *E. coli* (B) for 16 h at MOI 50. Immunoblotting of cell lysates (Lys) and supernatants (Sup). (C, D) Graphs of the densitometry for immunoblots (n = 3). (E, F) The level of IL-1β in the supernatant of BMDMs (n = 3). (G, H) Serum levels of IL-1β in WT and TGR5$^{-/-}$ mice infected with 1×10^5 CFU *L. monocytogenes* (G) or 2×10^9 CFU *E. coli* (H) infection at day 2 (*L. monocytogenes*) or 24 h (*E. coli*) (n = 3). (I, J) Quantification of bacterial burden. The bacterial burden of the liver or spleen was enumerated on day 2 (*L. monocytogenes*, I) or 6 h (*E. coli*, J) post-infection. (K, L) Percentage survival of WT and TGR5$^{-/-}$ mice infected with 5×10^5 CFU *L. monocytogenes* (n = 15–19, K) or 5×10^9 CFU *E. coli* (n = 12–16, L). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ significantly different from WT.

in the spleen and liver of WT and FXR KO mice infected with *L. monocytogenes* or *E. coli* revealed high titers in the liver and spleen in FXR KO mice, with significantly lower titers in WT mice (Fig. 2E and F). The increased tissue bacterial loads were accompanied by exacerbated tissue damage, as evidenced by the histopathological analysis of livers from WT and FXR KO mice with and without *L. monocytogenes* infection. Massive necrosis was evident in both WT and FXR-deficient mice, while FXR KO mice presented more pronounced and extensive hepatic lesions compared to WT mice (Fig. 2G). These results suggested that *L. monocytogenes* infection of FXR KO mice exacerbated tissue injury in the liver due to the higher number of bacteria in the tissue.

To verify whether higher titers of bacteria in FXR KO mice were associated with mortality, we infected WT and FXR KO mice with a lethal dose of either L. monocytogenes or *E. coli* (Fig. 2H and I). Survival of FXR KO mice was less at all time points compared to WT mice. The majority of FXR KO mice succumbed within 3 days (for *L. monocytogenes*) or 24 h (for *E. coli*), whereas the majority of the WT mice survived at these times.

3.3. FXR agonists enhance mouse survival by improving bacterial clearance

We further explored the functional relevance of FXR in bacterial infection. CDCA is a physiological ligand for FXR. Fexaramine and 6-ECDCA (INT-747, obeticholic acid) are synthetic FXR agonists. When we assessed the effect of FXR activation on bacterial infection, pretreatment with fexaramine, CDCA, or 6-ECDCA decreased bacterial burdens in *L. monocytogenes* or *E. coli* infected BMDMs (Fig. 3A and B). However, we found that the deficiency of NLRP3 did not abolish the bacterial clearance induced by 6-ECDCA (Fig. 3C). Increased survival was observed when mice were i.p. injected with 6-ECDCA (5 mg/kg body weight) before *L. monocytogenes* or *E. coli* infection (Fig. 3D and E). Consistent with this, the bacterial burden in the liver and spleen was significantly reduced in the 6-ECDCA group compared to the vehicle group (Fig. 3F and G). These results indicated that FXR agonist potentiated the bacterial clearance *in vivo* in mice.

3.4. Lack of TGR5 impairs inflammasome activation and bactericidal activity

The role of BA receptors in bacterial infection was further examined using TGR5$^{-/-}$ mice. We first evaluated whether TGR5 is involved in bacteria-induced inflammasome activation (Fig. 4A–F). Upon L. *monocytogenes* or *E. coli* infection, BMDMs derived from TGR5$^{-/-}$ mice displayed significantly reduced caspase-1 and/or caspase-11 activation and IL-1β secretion compared to BMDMs derived from WT mice. However, both WT and TGR5$^{-/-}$ BMDMs contained comparable protein levels of NLRP3, ASC, pro-caspase-1, pro-caspase-11, and pro-IL-1β. The effect of TGR5 deficiency on IL-1β secretion was examined *in vivo* (Fig. 4G and H). TGR5 deficiency decreased the level of IL-1β in serum in response to *L. monocytogenes* or *E. coli* infection, consistent with the *in vitro* data. Greater bacterial burden in the liver and spleen, and increased mortality related to *L. monocytogenes* or *E. coli* infection was observed in TGR5$^{-/-}$ mice than in WT mice, similar to FXR$^{-/-}$ mice (Fig. 4I-L). These results indicated that both FXR and TGR5 are essential for caspase-1 activation and IL-1β secretion in macrophages, with a critical role in immunity to bacterial infection.

4. Discussion

The inability to effectively kill invading bacteria or other pathogens due to immune dysregulation is a major cause of multiple organ dysfunction syndrome and death from bacterial infections [32–35]. Despite the current therapeutic options for bacterial infection, postmortem studies have revealed infectious foci in the majority of patients [36], indicating a deficit in bacterial clearance.

The inflammasome is an evolutionarily conserved cytosolic sensor that is crucial in host defense against bacteria [4–6]. Both gram-positive and gram-negative bacteria can activate inflammasomes. The activation is a response to PAMPs and induces immune responses that restrict pathogen replication [4,7,37,38]. Microbes or their subcellular components negatively regulate the inflammasome to evade host defenses [4,38–40]. Thus, impaired inflammasome activation is associated with increased susceptibility to bacterial infection [41,42].

Presently, the FXR and TGR5 BA receptors had an important protective role during *L. monocytogenes* or *E. coli* infection, with an increased bacterial burden in the absence of FXR or TGR5 *in vitro* and *in vivo*, and a reduced burden when FXR was stimulated by its ligand. BMDMs derived from FXR$^{-/-}$ or TGR5$^{-/-}$ mice displayed reduced inflammasome activation despite the unchanged expression of inflammasome-related molecules. Thus we speculate that FXR or TGR5 may regulate the activation signals, not the priming signals, in bacteria-activated inflammasomes. Since we could not exclude the possibility that FXR may regulate bacterial clearance independent of NLRP3 inflammasome, it needs further study to verify the exact mechanism. Our findings suggest an important role for FXR and TGR5 in controlling bacterial pathogens, at least by macrophages.

Clinical studies have demonstrated the biological safety of FXR agonists [43,44], implicating FXR as an ideal drug target. Presently, 6-ECDCA, a potent FXR agonist, decreased bacterial burdens and increased survival upon *L. monocytogenes* or *E. coli* infection. However, several studies reported cross-talk, synergistic alterations, and compensatory alterations between FXR and TGR5 signaling [45,46]. Thus, dual targeting of FXR and TGR5 may be more beneficial to treat bacterial infections. This needs further verification.

BMDMs derived from FXR$^{-/-}$ or TGR5$^{-/-}$ mice were used to show a positive regulation of bacteria-activated inflammasomes by BA receptors. The functional influence of BAs on the inflammasome may vary depending on different immune cell types and conditions [47]. It has also been reported that BAs are DAMPs that can activate both priming and activation of the NLRP3 inflammasome in inflammatory macrophages. FXR may physically interact with NLRP3 and caspase-1, preventing their assembly [47]. Some BA analogues were shown to activate pyrin inflammasome [48]. In contrast, BAs and their analogues inhibit NLRP3 inflammasome activation via the TGR5-cAMP-protein kinase A (PKA) axis or in a FXR-independent way. [49,50]. Thus, BAs and their receptors may have different influences on the inflammasome in different immunological cells and in different states of inflammation. Further studies are needed to verify the exact causal link and to reveal how FXR/TGR5 could be targeted to control inflammasomes in bacterial infection. Understanding the precise mechanism behind the role of BAs and their receptors would be helpful to use them as a therapeutic candidates in infectious diseases such as sepsis.

In conclusion, we demonstrated that FXR/TGR5 mediates inflammasome activation and host resistance to bacterial infection *in vitro* and *in vivo*. We expect that further investigations of FXR or TGR5 will facilitate the development of novel anti-infective agents.

CRediT authorship contribution statement

Ju-Hee Kang: Investigation, Methodology, Writing – original draft. **Minji Kim:** Methodology, Writing – original draft. **Mijung Yim:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrep.2021.101051.

References

[1] A. Rivera, M.C. Siracusa, G.S. Yap, W.C. Gause, Innate cell communication kick starts pathogen specific immunity, Nat. Immunol. 17 (2016) 356–363, https://doi.org/10.1038/ni.3375.
[2] X. Cao, Self-regulation and cross-regulation of pattern-recognition receptor signalling in health and disease, Nat. Rev. Immunol. 16 (2016) 35–50, https://doi.org/10.1038/nri.2015.8.
[3] D. Sharma, T.-D. Kanneganti, The cell biology of inflammasomes: mechanisms of inflammasome activation and regulation, J. Cell Biol. 213 (6) (2016) 617–629, https://doi.org/10.1083/jcb.201602089.
[4] S. Shin, I.E. Brodsky, The inflammasome: learning from bacterial evasion strategies, Semin. Immunol. 27 (2015) 102–110, https://doi.org/10.1016/j.smim.2015.03.006.
[5] K. Shimada, T.R. Crother, J. Karlin, et al., Caspase-1 dependent IL-1beta secretion is critical for host defense in a mouse model of Chlamydia pneumoniae lung infection, PloS One 6 (2011), e21477, https://doi.org/10.1371/journal.pone.0021477.
[6] S.M. Brewer, S.W. Brubaker, D.M. Monack, Host inflammasome defense mechanisms and bacterial pathogen evasion strategies, Curr. Opin. Immunol. 60 (2019) 63–70, https://doi.org/10.1016/j.coi.2019.05.001.
[7] E. Latz, T.S. Xiao, A. Stutz, Activation and regulation of the inflammasomes, Nat. Rev. Immunol. 13 (2013) 397–411, https://doi.org/10.1038/nri3452.
[8] M. Lamkanfi, V.M. Dixit, Mechanisms and functions of inflammasomes, Cell 157 (5) (2014) 1013–1022, https://doi.org/10.1016/j.cell.2014.04.007.
[9] S.M. Crowley, B.A. Vallance, L.A. Knodler, Noncanonical inflammasomes: antimicrobial defense that does not play by the rules, Cell Microbiol. 19 (4) (2017), https://doi.org/10.1111/cmi.12730. Epub 2017.
[10] A.F. Hofmann, The function of bile salts in fat absorption. The solvent properties of dilute micellar solutions of conjugated bile salts, Biochem. J. 89 (1) (1963) 57–68, https://doi.org/10.1042/bj0890057.
[11] A. Molinaro, A. Wahlström, H.U. Marschall, Role of bile acids in metabolic control, Trends Endocrinol. Metabol. 29 (1) (2018) 31–41, https://doi.org/10.1016/j.tem.2017.11.002.
[12] B.M. Forman, E. Goode, J. Chen, et al., Identification of a nuclear receptor that is activated by farnesol metabolites, Cell 81 (1995) 687–693, https://doi.org/10.1016/0092-8674(95)90530-8.
[13] Y. Kawamata, R. Fujii, M. Hosoya, et al., A G protein-coupled receptor responsive to bile acids, J. Biol. Chem. 278 (2003) 9435–9440, https://doi.org/10.1074/jbc.M209706200.
[14] F.Y. Lee, H. Lee, M.L. Hubbert, et al., FXR, a multipurpose nuclear receptor, Trends Biochem. Sci. 31 (2006) 572–580, https://doi.org/10.1016/j.tibs.2006.08.002.
[15] B.A. Laffitte, H.R. Kast, C.M. Nguyen, et al., Identification of the DNA binding specificity and potential target genes for the farnesoid X-activated receptor, J. Biol. Chem. 275 (2000) 10638–10647, https://doi.org/10.1074/jbc.275.14.10638.
[16] W. Seol, H.S. Choi, D.D. Moore, Isolation of proteins that interact specifically with the retinoid X receptor: two novel orphan receptors, Mol. Endocrinol. 9 (1995) 972–985, https://doi.org/10.1210/mend.9.1.7760852.
[17] S. Modica, R.M. Gadaleta, A. Moschetta, Deciphering the nuclear bile acid receptor FXR paradigm, Nucl. Recept. Signal. 8 (2010) 1–28, https://doi.org/10.1621/nrs.08005.
[18] Y.D. Wang, W.D. Chen, M. Wang, et al., Farnesoid X receptor antagonizes nuclear factor kappaB in hepatic inflammatory response, Hepatology 48 (5) (2008) 1632–1643, https://doi.org/10.1002/hep.22519.
[19] T. Maruyama, Y. Miyamoto, T. Nakamura, et al., Identification membrane-type receptor for bile acids (m-bar), Biochem. Biophys. Res. Commun. 298 (2002) 714–719, https://doi.org/10.1016/s0006-291x(02)02550-0.
[20] T. Maruyama, K. Tanaka, J. Suzuki, et al., Targeted disruption of g protein-coupled bile acid receptor 1 (gpbar1/m-bar) in mice, J. Endocrinol. 191 (2006) 197–205, https://doi.org/10.1677/joe.1.06546.
[21] V. Keitel, M. Donner, S. Winandy, et al., Expression and function of the bile acid receptor tgr5 in Kupffer cells, Biochem. Biophys. Res. Commun. 372 (2008) 78–84, https://doi.org/10.1016/j.bbrc.2008.04.171.
[22] V. Keitel, R. Reinehr, P. Gatsios, et al., The G-protein coupled bile salt receptor tgr5 is expressed in liver sinusoidal endothelial cells, Hepatology 45 (2007) 695–704, https://doi.org/10.1002/hep.21458.
[23] C. Thomas, A. Gioiello, L. Noriega, et al., TGR5-mediated bile acid sensing controls glucose homeostasis, Cell Metabol. 10 (2009) 167–177, https://doi.org/10.1016/j.cmet.2009.08.001.
[24] T.W. Pols, L.G. Noriega, M. Nomura, et al., The bile acid membrane receptor TGR5 as an emerging target in metabolism and inflammation, J. Hepatol. 54 (2011) 1263–1272, https://doi.org/10.1016/j.jhep.2010.12.004.
[25] C. Guo, W.D. Chen, Y.D. Wang, TGR5 not only a metabolic regulator, Front. Physiol. 7 (2016) 646, https://doi.org/10.3389/fphys.2016.00646.
[26] S. Cipriani, A. Mencarelli, M.G. Chini, et al., The bile acid receptor GPBAR-1 (TGR5) modulates integrity of intestinal barrier and immune response to experimental colitis, PloS One 6 (2011), e25637, https://doi.org/10.1371/journal.pone.0025637.
[27] B. Renga, A. Mencarelli, S. Cipriani, et al., The bile acid sensor fxr is required for immune-regulatory activities of tlr-9 in intestinal inflammation, PloS One 8 (2013), e54472, https://doi.org/10.1371/journal.pone.0054472.
[28] P. Vavassori, A. Mencarelli, B. Renga, et al., The bile acid receptor fxr is a modulator of intestinal innate immunity, J. Immunol. 183 (2009) 6251–6261. https://10.4049/jimmunol.0803978.
[29] A. Mencarelli, B. Renga, M. Migliorati, et al., The bile acid sensor farnesoid x receptor is a modulator of liver immunity in a rodent model of acute hepatitis, J. Immunol. 183 (2009) 6657–6666, https://doi.org/10.4049/jimmunol.0901347.
[30] T. Inagaki, A. Moschetta, Y.K. Lee, et al., Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor, Proc. Natl. Acad. Sci. U.S.A. 103 (2006) 3920–3925, https://doi.org/10.1073/pnas.0509592103.
[31] D.G. Russell, B.C. Vanderven, S. Glennie, et al., The macrophage marches on its phagosome: dynamic assays of phagosome function, Nat. Rev. Immunol. 9 (8) (2009) 594–600, https://doi.org/10.1038/nri2591.
[32] C.F. Benjamim, C.M. Hogaboam, S.L. Kunkel, The chronic consequences of severe sepsis, J. Leukoc. Biol. 75 (3) (2004) 408–412, https://doi.org/10.1189/jlb.0503214.
[33] D.J. Stearns-Kurosawa, M.F. Osuchowski, C. Valentine, et al., The pathogenesis of sepsis, Annu. Rev. Pathol. 6 (2011) 19–48, https://doi.org/10.1146/annurev-pathol-011110-130327.
[34] R.S. Hotchkiss, I.E. Karl, The pathophysiology and treatment of sepsis, N. Engl. J. Med. 348 (2) (2003) 138–150, https://doi.org/10.1056/NEJMra021333.
[35] T.J. Tracey, Understanding immunity requires more than immunology, Nat. Immunol. 11 (7) (2010), https://doi.org/10.1038/ni0710-561, 561–556.
[36] C. Torgersen, P. Moser, G. Luckner, et al., Macroscopic postmortem findings in 235 surgical intensive care patients with sepsis, Anesth. Analg. 108 (6) (2009) 1841–1847, https://doi.org/10.1213/ane.0b013e318195e11d.
[37] V.I. Maltez, E.A. Miao, Reassessing the evolutionary importance of inflammasomes, J. Immunol. 196 (2016) 956–962, https://doi.org/10.4049/jimmunol.1502060.
[38] A. Sokolovska, C.E. Becker, W.K. Ip, et al., Activation of caspase-1 by the NLRP3 inflammasome regulates the NADPH oxidase NOX2 to control phagosome function, Nat. Immunol. 14 (2013) 543–553, https://doi.org/10.1038/ni.2595.
[39] M. Fraunholz, B. Sinha, Intracellular Staphylococcus aureus: live-in and let die, Front. Cell. Infect. Microbiol. 2 (2012) 43, https://doi.org/10.3389/fcimb.2012.00043.
[40] L. Munzenmayer, T. Geiger, E. Daiber, et al., Influence of Sae-regulated and Agr-regulated factors on the escape of Staphylococcus aureus from human macrophages, Cell Microbiol. 18 (2016), https://doi.org/10.1111/cmi.12577, 1172–1118.
[41] I. Ceballos-Olvera, M. Sahoo, M.A. Miller, et al., Inflammasome-dependent pyroptosis and IL-18 protect against Burkholderia pseudomallei lung infection while IL-1beta is deleterious, PLoS Pathog. 7 (2011), e1002452, https://doi.org/10.1111/cmi.12577, 10.1371/journal.ppat.1002452.
[42] J. von Moltke, J.S. Ayres, E.M. Kofoed, et al., Recognition of bacteria byinflammasomes, Annu. Rev. Immunol. 31 (2012) 73–106, https://doi.org/10.1128/microbiolspec.BAI-0003-2019.
[43] B. Angelin, K.S. Hershon, J.D. Brunzell, Bile acid metabolism in hereditary forms of hypertriglyceridemia: evidence for an increased synthesis rate in monogenic familial hypertriglyceridemia, Proc. Natl. Acad. Sci. U.S.A. 84 (1987) 5434–5438, https://doi.org/10.1073/pnas.84.15.5434.
[44] R.R. Mudaliar, A.J. Henry, L. Sanyal, et al., Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease, Gastroenterology 145 (2013) 574–582, https://doi.org/10.1053/j.gastro.2013.05.042.
[45] P. Pathak, H. Liu, S. Boehme, et al., Farnesoid X receptor induces Takeda G-protein receptor 5 cross-talk to regulate bile acid synthesis and hepatic metabolism, J. Biol. Chem. 292 (2017) 11055–11069, https://doi.org/10.1074/jbc.M117.784322.
[46] S. Miyazaki-Anzai, M. Masuda, S. Kohno, et al., Simultaneous inhibition of FXR and TGR5 exacerbates atherosclerotic formation, J. Lipid Res. 59 (9) (2018) 1709–1713, https://doi.org/10.1194/jlr.M087239.
[47] H. Hao, L. Cao, C. Jiang, et al., Farnesoid X receptor regulation of the NLRP3 inflammasome underlies cholestasis-associated sepsis, Cell Metabol. 25 (4) (2017) 856–867, https://doi.org/10.1016/j.cmet.2017.03.007.
[48] I. Alimov, S. Menon, N. Cochran, et al., Bile acid analogues are activators of pyrin inflammasome, J. Biol. Chem. 294 (2019) 3359–3366, https://doi.org/10.1074/jbc.ra118.005103.
[49] C. Guo, S. Xie, Z. Chi, et al., Bile acids control inflammation and metabolic disorder through inhibition of NLRP3 inflammasome, Immunity 45 (4) (2016) 802–816, https://doi.org/10.1016/j.immuni.2016.09.008.
[50] S. Xie, C. Guo, Z. Chi, et al., A rapid administration of GW4064 inhibits the NLRP3 inflammasome activation independent of farnesoid X receptor agonism, FEBS Lett. 591 (2017) 2836–2847, https://doi.org/10.1002/1873-3468.12782.