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The Pattern Recognition Receptors and Lipopolysaccharides (LPS)-induced Systemic Inflammation

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ABSTRACT

The inflammatory response of innate immune system deals with infection of microorganism, tissue injury and malfunction. It is triggered by pattern recognition receptors (PRRs) which recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Among PRRs (toll-like receptors (TLRs), C-type lectin receptors (CLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) and receptor for advanced glycation end products (RAGE)), toll-like receptor 4 (TLR4) is a pivotal receptor to recognize lipopolysaccharides (LPS), and mediates several signaling to produce pro-inflammatory mediators and cytokines. The uncontrolled inflammation leads to overproduction of pro-inflammatory mediators and cytokines, and contributes to systemic inflammatory response syndrome (SIRS), multiple organ failure and sepsis. Thus, to regulate TLR4-mediated signaling plays an important role in therapeutic targets for LPS-induced systemic inflammation.

Keywords: *inflammation, pattern recognition receptors, toll-like receptor 4, lipopolysaccharides, and sepsis*

INTRODUCTION OF INFLAMMATION

The redness, swelling, fever, pain and dysfunction of tissue are the features of acute inflammation. From cellular and molecular aspects, the increasing recruitment of leukocytes and production of pro-inflammatory mediators and cytokines lead to such acute inflammation. It is initiated by harmful stimuli and conditions such as infection of microorganism, tissue injury and malfunction. Inflammation plays an important role in process of host defence and tissue repair [1]. The inflammatory response of innate immune system is the primary response to microbial infection and damaging cells. The phagocytic cell, macrophages and dendritic cells (DCs) not only produce pro-inflammatory mediators and cytokines against microorganism, but also have a role in antigen presentation to induce adaptive immune system [2]. Inflammatory response of immune cells is initiated by germline-encoded pattern recognition receptors (PRRs) which recognize compounds of microorganisms and the molecules of damaging cells. The pathogen-associated molecular patterns (PAMPs) are considered that microbe-specific molecular compounds include bacterial lipo-polysaccharides (LPS), flagellins, CpG-DNA, fungal glucans and viral DNA/RNA. The damage-associated molecular patterns (DAMPs) are regarded that molecules represent endogenous alarms. DAMPs are released forms of damaged cells such as mitochondrial and nuclear DNA and advanced glycation end products (AGEs). A part of DAMPs are considered that danger signals to induce inflammatory responses such as high mobility group box 1 (HMGB1), heat-shock proteins and S100 proteins [3, 4]. The PRRs include toll-like receptors (TLRs), C-type lectin receptors (CLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) and receptor for advanced glycation end products (RAGE) [5, 6].

The Pattern Recognition Receptors

The TLRs are important PRRs in host cell recognition and response to various microbial pathogens such as bacteria, mycobacteria, viruses, fungi and parasites. TLRs comprise extracellular domain leucine-rich repeat (LRR) motifs to recognize pathogens and cytosolic domain toll-interleukin-1 receptor (TIR) domains to transduce signaling pathways [7]. TLRs, including transmembrane receptor TLR1, TLR2, TLR4, TLR5, TLR6, cytoplasmic receptor TLR3, TLR7, TLR8, and TLR9, play critical roles in recognition of PAMPs and DAMPs. The ligands of transmembrane receptor TLR1 are lipopeptides, TLR2 (lipoprotein/ lipopeptides), TLR4 (LPS, HMGB1 and heat-shock proteins), TLR5 (flagellins), and TLR6 (lipopeptides), whereas cytoplasmic receptor TLR3 recognizes double-stranded RNA, TLR7 (single-stranded RNA), TLR8 (singe-stranded RNA), and TLR9 (CpG-DNA) [8, 9]. Until now, the ligand of TLR10 is unknown.

The CLRs such as Dectin-1, Dectin-2, mannose receptor (MR), Dendritic cell-specific intercellular adhesion molecule-3 grabbing non-integrin (DC-SIGN) and macrophage-inducible C-type lectin (Mincle) recognize bacterial, fungal and viral carbohydrates, and directly contribute to antifungal immune response [10]. Dectin-1 recognizes β-glucan which is the component of fungal cell wall and transduces the spleen tyrosine kinase (Syk) signaling. Dectin-2 and MR contribute to binding of high mannose-type carbohydrates. DC-SIGN binds high mannose and fucose to recognize fungi and virus. In particular, Mincle not only binds with α-mannose and glycolipids, but also recognizes spliceosome-associated protein 130 (SAP130) which is ribonucleoprotein of death cells [11].

The RLRs are cytoplasmic receptors that recognize RIG-I, melanoma differentiation-associated gene 5 (MDA5) and laboratory of genetics and physiology gene 2 (LGP2). The viral double-stranded RNA activates RIG-I and MDA5. Activated RIG-I and MDA5 bind with RLRs, and transduce the essential adaptor protein mitochondrial antiviral signaling (MAVS) to trigger antiviral immune response. By contrast, LGP2 is a negative regulator of RIG-I and MDA5 [12]. Thus, the RLRs are critical PRRs that recognize RNA virus and exert antiviral effects.

The NLRs are cytoplasmic receptors that recognize not only PAMPs such as microbial toxins, bacterial peptidoglycans and viral RNA, but also bind to DAMPs such as monosodium urate (MSU) crystals and adenosine triphosphate (ATP). NLRs include four subfamilies NLRA/Class II transactivator (CIITA), NLRB/neuronal apoptosis inhibitor proteins (NAIPs), NLRC, and NLRP [13]. Additionally, NLRs contain a C-terminal series of LRR and an N-terminal homotypic protein-protein interaction domain. The interaction domain of NLRAs is acid transactivation domain. NLRBs contain baculovirus inhibitor of apoptosis protein repeat (BIR). NLRCs comprise a caspase-recruitment domain (CARD), and pyrin domain (PYD) is in NLRPs [14]. Among NLRC, NOD 1 and NOD 2 initiate inflammatory response by recognition of peptidoglycan from Gram-negative and Gram-positive bacteria. NLRPs are key regulators of inflammasomes which are a group of protein complexes and produce pro-inflammatory cytokine interleukin-1β (IL-1β) and IL-18 [15].

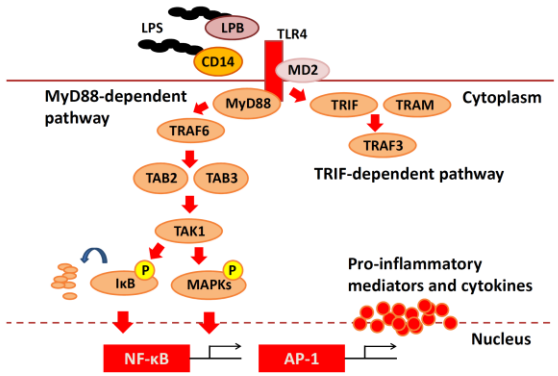
The RAGE is a transmembrane receptor of DAMPs such as AGEs, HMGB1, S100 proteins, phosphatidylserine and advanced oxidation protein products (AOPPs). However, RAGE also recognizes LPS and triggers inflammatory response [6]. RAGE is a crucial regulator for inflammation and cell migration by recognition of different ligands. The engagement of HMGB1 induces monocyte migration, and binding with S100 proteins initiates synthesis of pro-inflammatory cytokines [4].

Taken together, the different PRRs recognize different set of microbial pathogens such as RLRs for virus recognition, but TLRs wildly recognize a variety of microbe-specific molecules and endogenous alarms. TLRs play an important role in recognition of PAMPs and DAMPs. It is considered that TLRs initiate several signaling transduction pathways to induce inflammation [7].

TLR4 Signaling Transduction Pathways

Among several TLRs, TLR4 is a pivotal receptor to recognize bacterial LPS and initiates inflammatory response. TLR4 combines with myeloid differentiation 2 (MD2) to recognize LPS, and then LPS-binding protein (LBP) and CD14 enhance LPS binding to TLR4/MD2 receptor complex. Subsequently, TIR-like domains are recruited, and transduce signal to other adaptor proteins. The downstream adaptor proteins include myeloid differentiation primary response protein 88 (MyD88), MyD88 adaptor-like (Mal) as known as TIR domain containing adaptor protein (TIRAP), TIR domain-

containing adaptor inducing interferon-β (TRIF, also known as TIR-containing adapter molecule-1 (TICAM-1)), TRIF related adaptor molecule (TRAM, also called TICAM-2) and sterile-α and armadillo motif containing protein (SARM) [16].



It has been defined MyD88-dependent pathway and TRIF-dependent pathway (MyD88-independent pathway) in TLR4 signaling transduction pathways. The MyD88-dependent pathway is early stage of acute inflammation, and the TRIF-dependent pathway is late stage of acute inflammation [17]. In the MyD88-dependent pathway, the recruitment of MyD88 activates IL-1R-associated kinases 1 (IRAK1), IRAK2, IRAK4 and TNF-receptor-associated factor 6 (TRAF6). Subsequently, transduce transforming growth factor β-activated kinase 1 (TAK1)-binding protein 2 (TAB2) and TAK1-binding protein 3 (TAB3) are activated, and then TAB2 and TAB3 induce activation of TAK1, which mitogen-activated protein kinase kinase kinase (MAPKKK) controls MAPKs activity. MAPKs including c-JUN N-terminal kinase (JNK), p38 MAPK and extracellular signal-regulated kinases (ERK) are crucial regulator of downstream transcription factors such as activator protein-1 (AP-1) and nuclear factor-κB (NF-κB) [8]. These transcription factors regulate production of pro-inflammatory mediators and cytokines. Moreover, the Mal (TRIF) regulates activation of NF-κB through the bridging of MyD88-dependent pathway.

On the other hand, the TRIF-dependent pathway is triggered by recruitment of TRIF and TRAM, and activates TRAF3, tank-binding kinase 1 (TBK1) and Inhibitor-κB kinase ε (IKKε). These signaling transduction factors induce nuclear translocation of interferon regulatory factor-3 (IRF-3) and IRF-7. Subsequently, type I interferon (IFN), interferon inducible protein-10 (IP-10) and regulated on activation, normal T cell expressed and secreted (RANTES) are produced [9]. TRIF and TRAM also regulate activation of NF-κB independent of MyD88 [18]. Furthermore, the SARM is a negative regulator of TRAM, and inhibits activation of IRF-3, IRF-7 and NF-κB by TRAM [17].

Taken together, the LPS-induced TLR4 signaling is regulated by these five adaptor proteins, and produces pro-inflammatory mediators and cytokines by activated transcription factor AP-1, NF-κB, IRF-3 and IRF-7. The MyD88-dependent pathway is a pivotal regulator of inflammatory host response to LPS. For this reason, the signaling transduction factors of MyD88-dependent pathway are critical contributors for acute inflammation such as MAPK and NF-κB.

LPS-induced Pro-inflammatory Mediators and Cytokines

The several pro-inflammatory mediators and cytokines are produced by LPS-activated macrophages. The LPS-induced TLR4 signaling transduction factors play a crucial role in inflammatory response of LPS stimulation. The major pro-inflammatory mediators including nitric oxide (NO) and prostaglandin E_2 (PGE_2) lead to redness, swelling, fever and pain. Inducible NO synthase (iNOS, also called NOS2) synthesizes NO by converting L-arginine to L-citrulline. The production of iNOS is regulated by NF-κB after immunological stimulation [19]. NO is converted to cytotoxic free radical peroxynitrite ($ONOO^-$) by superoxide (O_2^-), and exerts microbicidal effects by free radical reaction. The overproduction of NO contributes cell death (necrosis and apoptosis) and tissue destruction by cytotoxicity and oxidative stress [20]. Additionally, iNOS is a harmful enzyme involved in pathogenesis of inflammatory diseases [21].

Another major pro-inflammatory mediator, PGE_2 is a lipid pro-inflammatory mediator. The cell membrane phospholipid and phospholipase A_2 (PLA_2) release arachidonic acid (AA), and cyclooxygenase-2 (COX-2) converts AA to PGH_2 by cyclooxygenase and peroxidase activity. Subsequently, PGH_2 is converted to PGE_2 by PGE synthase [22]. These are the process of prostanoid biosynthesis. The PGE_2 contributes to vascular hyper permeability, plasma leakage and immune cell infiltration in acute inflammation. Therefore, COX-2 inhibitors suppress prostanoid biosynthesis, and decrease vasodilatation, vascular permeability and recruitment of immune cells in inflammation [22]. On the other hand, NO leads

to vascular dysfunction characterized by vascular hyperpermeability due to endothelial cell death [20]. Interestingly, it has been reported that there is a cross-talk between iNOS and COX-2. NO elicits prostaglandin synthesis via upregulation of COX-2 activity. In contrast, COX-2 inhibitor does not affect iNOS expression [23].

TNF-α, IL-1β and IL-6 are central pro-inflammatory cytokines produced by LPS-activated macrophages and lymphocytes. TNF-α and IL-1β contribute to fever and coagulation in inflammation, and activation of immune cells. Particularly, TNF-α is a master regulator of inflammatory cytokine production. Both TNF-α and IL-1β augment inflammatory cascades by activated macrophages, and induce severe inflammatory reaction in an autocrine and paracrine manner. IL-6 is also a contributor of fever, and activate B and T lymphocytes [24]. Additionally, IL-6 and IL-12 are family cytokines that share subunit and receptor by structural relation. IL-12 is a critical contributor to connect innate immune system to adaptive immune system [25].

LPS-induced Systemic Inflammation

The high plasma level of LPS (known as endotoxin) causes systemic inflammation such as endotoxemia and sepsis. The endotoxemia presents overspilling of LPS in the bloodstream, which triggers production of lipid mediators and pro-inflammatory cytokines by activation and recruitment of leukocytes. Subsequently, these uncontrolled immune responses cause harmful systemic inflammation referred to systemic inflammatory response syndrome (SIRS). SIRS is defined by two or more clinical finding (1. body temperature <36°C or >38°C, 2. heart rate >90 beats/min, 3. respiratory rate >20 times/min or $PaCO_2$ <32 mmHg, 4. white blood cell (WBC) count >12000 cells/μl or <4000 cells/μl, or >10% immature (band) forms) [24].

The Pathogenesis of Sepsis

In the pathogenesis of sepsis, the infection of gram-negative bacteria and other pathogens lead to sepsis. The bacterial LPS and other microorganism components initiate harmful systemic host response by innate immune cells. The overproduction of pro-inflammatory mediators and cytokines by activated innate immune cells causes cell death (apoptosis and necrosis). The inflammatory cascades contribute to multiple organ failure, sepsis and septic shock [26]. TLR4/MD2 receptor complex plays a pivotal role in triggering systemic inflammation of endotoxemia, and transduces a series of signalings to produce pro-inflammatory mediators and cytokines. The hypercytokinemia (known as cytokine storm or cytokine cascade) is overwhelmingly elevated cytokines in blood. TNF-α, IL-1β, IL-6, IL-12 and IL-17 are main cytokines in pathogenesis of sepsis. It has been found these pro-inflammatory cytokines are elevated in sepsis [27]. On the other hand, it has been reported that HMGB1 is a late pro-inflammatory mediator in pathogenesis of sepsis [28]. HMGB1 is also a ligand of TLR4, and triggers TLR4-mediated response. The hypercytokinemia leads to endothelial cell necrosis and dysfunction, and then causes the vascular hyperpermeability and plasma leakage. Concurrently, pyrogenic cytokine TNF-α and IL-1β contribute fever and coagulation, and IL-6 also leads to fever. Additionally, these pro-inflammatory cytokines induce PGE_2 and NO synthesis. The hypercytokinemia contributes fever, coagulopathy, vasodilation and capillary leak. As such, the hypercytokinemia leads to multiple organ failure, sepsis, and septic shock [26].

The Exercise-induced Endotoxemia and Systemic Inflammation

The endotoxemia is not only initiated by the infection of pathogenic bacteria, but also triggered by translocation of intestinal gram-negative bacteria. The prolonged and strenuous exercise-induced redistribution of blood flow increases the blood supply of muscle and cardiopulmonary system, but decreases the blood supply of gastrointestinal (GI) system. The exercise-induced redistribution of blood flow causes gastrointestinal ischemia, and perfusion of gastrointestinal evolves formation of reactive oxygen species (ROS) and inflammation after exercise [29]. The exercise-induced redistribution of blood flow contributes to hyperpermeability of intestinal epithelium via gastrointestinal ischemia and intestinal barrier dysfunction [29]. Concurrently, the prolonged and strenuous exercise increases core body temperature that causes hyperthermia. It has been demonstrated that exercise-induced hyperthermia augments intestinal hyperpermeability [30].

The translocation of intestinal gram-negative bacteria increases circulatory bacterial LPS by the intestinal hyperpermeability, and it leads to endotoxemia during prolonged and strenuous exercise. Increasing circulatory bacterial LPS

triggers production of pro-inflammatory mediator PGE_2, pro-inflammatory cytokine TNF-α, IL-1β and IL-6 by activated macrophages. The PGE_2, TNF-α, IL-1β and IL-6 are contributor of fever. It also augments exercise-induced hyperthermia by pyrogenic response, and even result in exertional heat stroke. The heat stroke is initiated by not only hyperthermia but also endotoxemia-induced inflammatory response [31]. Lim and Suzuki suggested that the pathogenesis of heat stroke is explained by dual-pathway model (DPM) of hyperthermia and endotoxemia [32].

Although non-steroidal anti-inflammatory drugs (NSAIDs) decreases core body temperature by inhibition of COX-2, it has been found that NSAID aspirin and ibuprofen increase permeability of intestine [33]. The probiotic supplementation improves exercise-induced intestinal barrier dysfunction, but the result of pro-inflammatory cytokine production after exercise showed no significant difference between probiotic supplementation and placebo [34, 35]. On the other hand, the ascorbic acid supplementation suppresses the increase of plasma LPS and nitrite levels after exercise [36], and reduces sepsis-induced organ damage [37]. Many natural products from herbs and functional foods exhibit anti-oxidant and anti-inflammatory effects and these natural products might attenuate LPS-induced inflammation and sepsis [38-40].

CONCLUSION

The uncontrolled LPS-triggered inflammatory response causes systemic inflammation, multiple organ failure, sepsis, and septic shock. TLR4-mediated signaling cascades are crucial regulators of LPS-induced inflammation. Hence, TLR4-mediated signaling factors are therapeutic targets for LPS-induced systemic inflammation. Many natural products have some potentiality to suppress TLR4-mediated signaling.

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REFERENCES

[1] R. Medzhitov, Origin and physiological roles of inflammation, Nature 454(7203) (2008) 428-35.

[2] A. Iwasaki, R. Medzhitov, Regulation of adaptive immunity by the innate immune system, Science 327(5963) (2010) 291-5.

[3] S. Akira, S. Uematsu, O. Takeuchi, Pathogen recognition and innate immunity, Cell 124(4) (2006) 783-801.

[4] S.L. Raymond, D.C. Holden, J.C. Mira, J.A. Stortz, T.J. Loftus, A.M. Mohr, L.L. Moldawer, F.A. Moore, S.D. Larson, P.A. Efron, Microbial recognition and danger signals in sepsis and trauma, Biochim Biophys Acta (2017) (In press).

[5] O. Takeuchi, S. Akira, Pattern recognition receptors and inflammation, Cell 140(6) (2010) 805-20.

[6] Z.A. Ibrahim, C.L. Armour, S. Phipps, M.B. Sukkar, RAGE and TLRs: relatives, friends or neighbours?, Mol Immunol 56(4) (2013) 739-44.

[7] T. Kawai, S. Akira, Toll-like receptors and their crosstalk with other innate receptors in infection and immunity, Immunity 34(5) (2011) 637-50.

[8] S. Akira, K. Takeda, Toll-like receptor signalling, Nat Rev Immunol 4(7) (2004) 499-511.

[9] S.K. Drexler, B.M. Foxwell, The role of toll-like receptors in chronic inflammation, Int J Biochem Cell Biol 42(4) (2010) 506-18.

[10] S.E. Hardison, G.D. Brown, C-type lectin receptors orchestrate antifungal immunity, Nat Immunol 13(9) (2012) 817-22.

[11] F. Osorio, C. Reis e Sousa, Myeloid C-type lectin receptors in pathogen recognition and host defense, Immunity 34(5) (2011) 651-64.

[12] K.M. Quicke, M.S. Diamond, M.S. Suthar, Negative regulators of the RIG-I-like receptor signaling pathway, Eur J Immunol 47(4) (2017) 615-28.

[13] Y. Zhong, A. Kinio, M. Saleh, Functions of NOD-Like Receptors in Human Diseases, Front Immunol 4 (2013) 333.

[14] Y.K. Kim, J.S. Shin, M.H. Nahm, NOD-Like Receptors in Infection, Immunity, and Diseases, Yonsei Med J 57(1) (2016) 5-14.

[15] T. Strowig, J. Henao-Mejia, E. Elinav, R. Flavell, Inflammasomes in health and disease, Nature 481(7381) (2012) 278-86.

[16] L.A. O'Neill, A.G. Bowie, The family of five: TIR-domain-containing adaptors in Toll-like receptor signalling, Nat Rev Immunol 7(5) (2007) 353-64.

[17] E.F. Kenny, L.A. O'Neill, Signalling adaptors used by Toll-like receptors: an update, Cytokine 43(3) (2008) 342-9.

[18] K.A. Fitzgerald, D.C. Rowe, B.J. Barnes, D.R. Caffrey, A. Visintin, E. Latz, B. Monks, P.M. Pitha, D.T. Golenbock, LPS-TLR4 signaling to IRF-3/7 and NF-kappaB involves the toll adapters TRAM and TRIF, J Exp Med 198(7) (2003) 1043-55.

[19] C. Bogdan, Nitric oxide synthase in innate and adaptive immunity: an update, Trends Immunol 36(3) (2015) 161-78.

[20] C. Szabo, K. Modis, Pathophysiological roles of peroxynitrite in circulatory shock, Shock 34 Suppl 1 (2010) 4-14.

[21] M. Lind, A. Hayes, M. Caprnda, D. Petrovic, L. Rodrigo, P. Kruzliak, A. Zulli, Inducible nitric oxide synthase: Good or bad?, Biomed Pharmacother 93 (2017) 370-75.

[22] K. Kawahara, H. Hohjoh, T. Inazumi, S. Tsuchiya, Y. Sugimoto, Prostaglandin E2-induced inflammation: Relevance of prostaglandin E receptors, Biochim Biophys Acta 1851(4) (2015) 414-21.

[23] R. Zamora, Y. Vodovotz, T.R. Billiar, Inducible nitric oxide synthase and inflammatory diseases, Mol Med 6(5) (2000) 347-73.

[24] W. Schulte, J. Bernhagen, R. Bucala, Cytokines in sepsis: potent immunoregulators and potential therapeutic targets--an updated view, Mediators Inflamm 2013 (2013) 165974.

[25] H. Hasegawa, I. Mizoguchi, Y. Chiba, M. Ohashi, M. Xu, T. Yoshimoto, Expanding Diversity in Molecular Structures and Functions of the IL-6/IL-12 Heterodimeric Cytokine Family, Front Immunol 7 (2016) 479.

[26] J. Cohen, The immunopathogenesis of sepsis, Nature 420(6917) (2002) 885-91.

[27] B.G. Chousterman, F.K. Swirski, G.F. Weber, Cytokine storm and sepsis disease pathogenesis, Semin Immunopathol 39(5) (2017) 517-28.

[28] H. Wang, O. Bloom, M. Zhang, J.M. Vishnubhakat, M. Ombrellino, J. Che, A. Frazier, H. Yang, S. Ivanova, L. Borovikova, K.R. Manogue, E. Faist, E. Abraham, J. Andersson, U. Andersson, P.E. Molina, N.N. Abumrad, A. Sama, K.J. Tracey, HMG-1 as a late mediator of endotoxin lethality in mice, Science 285(5425) (1999) 248-51.

[29] K. van Wijck, K. Lenaerts, J. Grootjans, K.A. Wijnands, M. Poeze, L.J. van Loon, C.H. Dejong, W.A. Buurman, Physiology and pathophysiology of splanchnic hypoperfusion and intestinal injury during exercise: strategies for evaluation and prevention, Am J Physiol Gastrointest Liver Physiol 303(2) (2012) G155-68.

[30] W. Pires, C.E. Veneroso, S.P. Wanner, D.A.S. Pacheco, G.C. Vaz, F.T. Amorim, C. Tonoli, D.D. Soares, C.C. Coimbra, Association Between Exercise-Induced Hyperthermia and Intestinal Permeability: A Systematic Review, Sports Med 47(7) (2017) 1389-403.

[31] C.L. Lim, G. Wilson, L. Brown, J.S. Coombes, L.T. Mackinnon, Pre-existing inflammatory state compromises heat tolerance in rats exposed to heat stress, Am J Physiol Regul Integr Comp Physiol 292(1) (2007) R186-94.

[32] C.L. Lim and K. Suzuki, Systemic inflammation mediates the effects of endotoxemia in the mechanisms of heat stroke, Biol Med (Aligarh) 9(1) (2016) 1000376.

[33] G.P. Lambert, Intestinal barrier dysfunction, endotoxemia, and gastrointestinal symptoms: the 'canary in the coal mine' during exercise-heat stress?, Med Sport Sci 53 (2008) 61-73.

[34] M. Lamprecht, S. Bogner, G. Schippinger, K. Steinbauer, F. Fankhauser, S. Hallstroem, B. Schuetz, J.F. Greilberger, Probiotic supplementation affects markers of intestinal barrier, oxidation, and inflammation in trained men; a randomized, double-blinded, placebo-controlled trial, J Int Soc Sports Nutr 9(1) (2012) 45.

[35] C.M. Shing, J.M. Peake, C.L. Lim, D. Briskey, N.P. Walsh, M.B. Fortes, K.D. Ahuja, L. Vitetta, Effects of probiotics supplementation on gastrointestinal permeability, inflammation and exercise performance in the heat, Eur J Appl Physiol 114(1) (2014) 93-103.

[36] T. Ashton, I.S. Young, G.W. Davison, C.C. Rowlands, J. McEneny, C. Van Blerk, E. Jones, J.R. Peters, S.K. Jackson, Exercise-induced endotoxemia: the effect of ascorbic acid supplementation, Free Radic Biol Med 35(3) (2003) 284-91.

[37] B.J. Fisher, D. Kraskauskas, E.J. Martin, D. Farkas, P. Puri, H.D. Massey, M.O. Idowu, D.F. Brophy, N.F. Voelkel, A.A. Fowler, 3rd, R. Natarajan, Attenuation of sepsis-induced organ injury in mice by vitamin C, JPEN J Parenter Enteral Nutr 38(7) (2014) 825-39.

[38] X. Qin, X. Jiang, X. Jiang, Y. Wang, Z. Miao, W. He, G. Yang, Z. Lv, Y. Yu, Y. Zheng, Micheliolide inhibits LPS-induced inflammatory response and protects mice from LPS challenge, Sci Rep 6 (2016) 23240.

[39] H.H. Lee, J.S. Shin, W.S. Lee, B. Ryu, D.S. Jang, K.T. Lee, Biflorin, Isolated from the Flower Buds of Syzygium aromaticum L., Suppresses LPS-Induced Inflammatory Mediators via STAT1 Inactivation in Macrophages and Protects Mice from Endotoxin Shock, J Nat Prod 79(4) (2016) 711-20.

[40] C.M. Shing, J.M. Peake, K. Suzuki, D.G. Jenkins, J.S. Coombes, Bovine colostrum modulates cytokine production in human peripheral blood mononuclear cells stimulated with lipopolysaccharide and phytohemagglutinin. J. Interferon Cytokine Res. (2009), 29, 37–44.

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