Microbes and Infectious Diseases 2022; 3(2): 241-245

Microbes and Infectious Diseases

Journal homepage: https://mid.journals.ekb.eg/

Mini-review article

Japanese encephalitis virus infection in South-East Asia: An immuno-epidemiological twist

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ARTICLE INFO

Article history:
Received 9 August 2021
Received in revised form 14 September 2021
Accepted 21 September 2021

Keywords:
Japanese encephalitis virus
Immunogenicity
Molecular epidemiology
Southeast Asia

ABSTRACT

Background: Japanese encephalitis (JE) is one of the most important zoonotic diseases in a cosmopolitan manner. Japanese encephalitis virus (JEV) infection represents at least 70 % of emerging diseases caused by the mosquito-borne JEV. Nearly 20-30% of case fatality corroborated in JEV infections with 30-50% neurologic and psychiatric disorders. A strong epidemic distribution is observed mainly in South-East Asia, demonstrating typical seasonal characteristics and occasional outbreaks. Depending on the genetic diversity, geographical distribution, and emerging natures of JEV, the disease surveillance, and immunization strategies are also varied. Uncontrolled population growth, haphazard agro-animal farming, and ecological imbalance steer the emergence and reemergence of JEV occurrences. Some murine models elucidate the immunological phenomena of JEV infections, the more detailed pathogenesis depending on the genetic variation is yet to be well defined. And the immune-epidemiological traits also address significant concerns regarding the effective vaccines and immunotherapeutics against JEV infections. Therefore, we summarized some critical notions on molecular epidemiology, immunogenicity, and genetic variance of JEV in South-East Asia.

Introduction

The Japanese encephalitis virus (JEV) infection is an arthropod-borne neglected disease in the temperate and sub-tropical countries, ensuing either epidemic or sporadic patterns, respectively [1]. The emerging and re-emerging patterns of JEV are predominantly related to multifaceted risk factors, including ecological, environmental, and immunological aspects related to amplifying hosts and vector vessels [2]. Most recently, upon Immunoglobulin M (IgM) seroconversion, JEV is known to be transferred from a blood transfusion from infected to immune-compromised humans [3]. Japanese encephalitis virus incidence and distributions vary with host-vector lineages, topography, and primary distribution of genotypes [4]. Genotypes I, II, and III are distributed throughout Asia; genotype IV to Eastern Indonesia, and genotype V is scattered in Malaysia, China, and South Korea [5]. Japanese encephalitis virus

DOI: 10.21608/MID.2021.93295.1188
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genotype shifting is a proven phenomenon in spatial epidemiological patterns, like genotype II shifting to genotype I in Vietnam and Thailand [6]. Moreover, genotype I emerge as the more lethal after substituting genotype III in Asia's southeast temperate regions [7]. And these are positively related with global and landscape scales, with deep interactions between vectors and final hosts to predict initiations, emergence, or re-emergence [8].

Nearly 4 billion people are at risk of JE. And the occurrence severity is resulting almost 25% fatality, neuropsychiatric sequelae in 30% of cases [9], as well as permanent neurological disability in Southeast Asian infant survivors [10]. Significant outbreaks of JE transmission intensify during the rainy season due to the rapid breeding of vector populations. The spread of JEV in new areas has been reported to be interlinked with rice cultivation, and agricultural development works. Safe and effective JE vaccines are proposed to prevent disease in endemic areas. The JE prevention and control activities strengthened surveillance and immunization in all regions where the condition is a recognized public health hazard. In JEV infection preventive purposes, the human vaccination program is vital other than immunizing pigs' population or mosquito control measures [11]. But due to genetic and antigenic heterogeneity, precise prevention, and control measures of JEV are drawing essential concerns for South-East Asia [4]. However, different animal disease models and molecular epidemiological studies are applying to define immunomodulatory signatures of JEV infection [1].

So, JEV invasion in South-East-Asia is infrequent and depends on the genetic variations. Precise epidemiological data on immunization and surveillance could assist in public health decision-making regarding vaccine formulation and campaign strategies. Therefore, in this review, we aim to identify the vaccines or other immunotherapeutics available against JEV in this region.

Discussions

Animal models to study the immune responses

Diverse animal models (murine, porcine, monkey, etc.) are used to determine the exact mechanisms and immune cells, signaling pathways, immunomodulation patterns involving innate and adaptive immunity of JEV infections. As the first line of defense against JEV infection, the natural immune system restricts virus-mediated pathology and communicates for programming humoral and cell-mediated protective immune responses [12]. As JEV is an RNA virus and due to variations in genome, having risks of integration of viral genes into the host genome. Thus, JEV enhances the viral infectivity inside the host, and can invalidate the effect of both innate and humoral immune responses. Both innate and adaptive immunity are addressing important signatures for effective preventive measures in JEV infection. The innate immune response is characterized by a level of IFN-α detection in the plasma and CSF of JEV infected patients [13]. Upon infection, JEV can bypass the innate response of type I, II, or III via interfering with the host-cell gene expression, inhibiting the IFN mechanism, and limiting the viral PAMPs. JEV infection activates IRF3, NF-κB, and AP-1 signaling through the secretion of type I (α/β) IFNs, thus evading the host immune response [14,15]. Moreover, JEV NS5 is shown to block the JAK/STAT signaling pathway, hindering IFNs induced the antiviral response of host cells and exacerbates the JEV pathogenesis. JE severity reveals a high level of type I IFNs in plasma and CSF, and virus burden significantly increased in those model animals lacking IFN-α-receptor [16].

It is found that JEV altered the splenic dendritic cell (DC) subpopulation and infected DCs release antiinflammatory cytokine IL-10, which led to a reduction in the priming of CD8(+) T cells, but not CD4(+) T cells. Recently, employing IFN-α-receptor knock-out mice, we also found that type I IFN signaling is crucial in regulating JE progression and severity [13,14]. The humoral immune response in either the final hosts or vectors is well defined with JEV specific IgG and IgM to protect JEV dissemination to CNS [17]. Moreover, we have reported that blood-brain-barrier (BBB), adhesion molecules, and tight junctions play critical roles in CNS attack [18]. And conversely, immediate failure to generate JEV specific neutralizing Abs may exacerbate case fatalities [19]. The cell-mediated immunity in JE infection is yet to draw definite mechanisms. However, like others [11], we have also applied in-vivo murine models addressing the roles of CD4+ and CD8+ T cells in the protective streams of JEV with a convincing window [13, 14, 20] Some murine models reported influential immunomodulatory roles of CTLs in JE infection. Furthermore, solenocytes reported being protective against lethal challenges [14, 21].

In one of our mice models for JEV infection, we corroborated that 4-1BB triggering is an effective way to make the positive cellular changes, resulted in increased CD8(+) T and decreased CD4(+) T cells. The triggering of 4-1BB also suppresses autoimmunity by accumulating indoleamine 2,3-dioxygenase (IDO) in dendritic cells (DCs) in an interferon (IFN)-γ-dependent manner of JEV infected mice [13,14]. In the absence of IDO activity the JEV induced pathogenesis become reduced through reducing the JEV burden in lymphoid and CNS tissues and resulted in early and increased CNS infiltration by Ly-6C(hi) monocytes, NK, CD4(+), and CD8(+) T-cells [18]. More interestingly, IDO ablation induced rapid enhancement of type I IFN (IFN-I) innate responses in CD11c(+) dendritic cells (DCs), including conventional and plasmacytoid DCs, following JEV infection [14, 18].

Vaccines and immunotherapeutics against JEV

Many certified vaccines are currently administering against JEV, though the specificity and safety index goes through coherent screening in model animals [22,23]. Three JEV vaccines are widely used in Asia-pacific to prevent JE infection in children. And a meta-analysis study was reported earlier regarding their efficacy and safety [24]. A reported meta-analysis earlier regarding the efficacy and safety of 3 JEV vaccines widely used in Asia-Pacific to protect infants and children against JE [25]. Immunologists raised some logical questions about using JEV-I(PHK), and JEV-L (PHK) as those vaccines produced by PHK cells contain heterogeneous cellular matrix proteins. This cellular matrix protein has the potential sensitizing capabilities to hosts against the vaccines. However, the vaccine JEV (Vero) represented good safety, but the immunogenicity is very low [24]. Several murine models also described the beneficial therapeutic roles of IgM, TLR7, type I IFNs in JE pathogenesis. Similarly, chemicals like rivabarin, arctigenin, curcumin, minocycline and glucosidase inhibitors help in regulating the cellular apoptosis, activation and differentiation of microglia, caspase-3 activation, and the induction of pro-inflammatory mediators in JEV infection [10, 17, 25].

Conclusions

Japanese encephalitis virus utilizes series of molecules to make repressive responses for determining infection inside the host. However, in response to a virus invasion, the cells of innate immune mechanisms become activated to eliminate the viral proteins. But the repeated exposures and influx of virus population may escalate the neurodegenerative disorders. Considering in-vivo or ex-vivo JEV infectious models, findings should be re-authenticated through coherent studies on molecular and spatial-temporal epidemiological signatures. Due to the shifting of genotype virulence, JEV shows unpredictable traits depending on ecological evolutions. So, we need to reconsider the genetic and environmental change during any meta-analysis on JEV epidemiology and immunogenicity in the preferred study areas. Due to the reemerging nature of JEV infections, it is crucial to implement strategies in strengthening JE surveillance systems to understand the disease burdens and subsequent immunization programs.

Conflict of interest: None.

Financial disclosure: None.

References

1-**van den Hurk AF, Ritchie SA, Mackenzie JS.** Ecology and geographical expansion of Japanese encephalitis virus. Annual Review of Entomology 2009; 54:17-35.

2-**Oliveira ARS, Cohnstaedt LW, Strathe E, Hernández LE, McVey DS, Piaggio J, et al.** Meta-analyses of the proportion of Japanese encephalitis virus infection in vectors and vertebrate hosts. Parasites & Vectors 2017; 10(1):418.

3-**Cheng V, Sridhar S, Wong S, Wong SCY, Chan JFV, Yip C, et al.** Japanese encephalitis virus transmitted via blood transfusion, Hong Kong, China. Emerging Infectious Diseases 2018; 24(1): 49-57.

4-**Le Flohic G, Gonzalez J**. When Japanese encephalitis virus invaded eastern hemisphere – the history of the spread of virus genotypes. In: Ru ˚zˇek D, editor. Flavivirus encephalitis. Volume I. InTech. 2011. pp. 405-26.

5-**Li YX, Li MH, Fu SH, Chen WX, Liu QY, Zhang HL, et al.** Japanese encephalitis, Tibet, China. Emerging Infectious Diseases 2011; 17: 934-36.

6-**Pan XL, Liu H, Wang HY, Fu SH, Liu HZ, Zhang HL, et al.** Emergence of genotype I of Japanese encephalitis virus as the dominant genotype in Asian Journal of Virology 2011; 85(19) :9847-53.

7-**Schuh AJ, Tesh RB, Barrett ADT.** Genetic characterization of Japanese encephalitis virus genotype II strains isolated from 1951 to 1978. Journal of General Virology 2011; 92: 516-27.

8-**Fang Y, Zhang Y, Zhou ZB, Xia S, Shi WQ, Xue JB, et al.** New strains of Japanese encephalitis virus circulating in Shanghai, China after a ten-year hiatus in local mosquito surveillance. Parasites & Vectors 2019; 12: 22.

9-**Connor B, Bunn WB.** The changing epidemiology of Japanese encephalitis and New data: the implications for New recommendations for Japanese encephalitis vaccine. Tropical Diseases, Travel Medicines and Vaccines 2017; 3:14.

10-**Kumar R.** Prevention, diagnosis, and management of Japanese encephalitis in children. Pediatric Health Medicine and Therapeutics 2014; 5: 99-110.

11-**Biswas SM, Ayachit VM, Sapkal GN, Mahamuni SA, Gore MM.** Japanese encephalitis virus produces a CD4+ Th2 response and associated immunoprotection in an adoptive-transfer murine model. Journal of General Virology 2009; 90:818-26.

12-**Kim JH, Patil AM, Choi JY, Kim SB, Uyangaa E, Hossain FMA, et al.** CCR5 ameliorates Japanese encephalitis via dictating the equilibrium of regulatory $CD4^{(+)}$ $Foxp3^{(+)}$ T and IL-$17^{(+)}CD4^{(+)}$ Th17 cells. Journal of Neuroinflammation 2016; 13(1):223.

13-**Choi JY, Kim JH, Patil AM, Kim SB, Uyangaa E, Hossain FMA, et al.** Exacerbation of Japanese Encephalitis by $CD11c_{hi}$ Dendritic Cell Ablation Is Associated with an Imbalance in Regulatory $Foxp3_{+}$ and IL-$17_{+}CD4_{+}$ Th17 Cells and in Ly-$6C_{hi}$ and Ly-$6C_{low}$ Monocytes. Immune Network 2017; 17(3):192-200.

14-**Kim SB, Choi JY, Uyangaa E, Patil AM, Hossain FMA, Hur J, et al.** Blockage of indoleamine 2,3-dioxygenase regulates Japanese encephalitis via enhancement of type I/II IFN innate and adaptive T-cell responses. Journal of Neuroinflammation 2016; 13(1):79.

15-**Fagerlund R, Kinnunen L, Kohler M, Julkunen I, Melen K.** NF-{kappa}B is transported into the nucleus by importin {alpha}3 and importin {alpha}4. Journal of Biological Chemistry 2005; 280:15942-51.

16-**Lin RJ, Chang BL, Yu HP, Liao CL, Lin YL.** Blocking of interferon-induced Jak-Stat signaling by Japanese encephalitis virus NS5 through a protein tyrosine phosphatase-mediated mechanism. Journal of Virology 2006, 80:5908-18.

17-**Dutta K, Kumawat KL, Nazmi A, Mishra MK, Basu A.** Minocycline differentially modulates viral infection and persistence in an experimental model of Japanese encephalitis. Journal of Neuroimmune Pharmacology 2010; 5:553-65.

18-**Kim JH, Hossain FMA, Patil AM, Choi JY, Kim SB, Uyangaa E, et al.** Ablation of $CD11c^{(hi)}$ dendritic cells exacerbates Japanese encephalitis by regulating blood-brain barrier permeability and altering tight junction/adhesion molecules. Comperative Immunology, Microbiology and Infectious Diseases 2016; 48:22-32.

19-**Gupta AK, Lad VJ, Koshy AA.** Protection of mice against experimental Japanese encephalitis virus infections by neutralizing anti-glycoprotein E monoclonal antibodies. Acta Virology 2003; 47:141-5.

20-**Kim JH, Patil AM, Choi JY, Kim SB, Uyangaa E, Hossain FMA, et al.** CCL2, but not its receptor, is essential to restrict immune privileged central nervous system-invasion of Japanese encephalitis virus via regulating accumulation of $CD11b^{(+)}$ $Ly\text{-}6C^{(hi)}$ monocytes. Immunology 2016;149(2):186-203.

21-**Ye J, Zhu B, Fu ZF, Chen H, Cao S.** Immune evasion strategies of flaviviruses. Vaccine 2013; 31:461-71.

22-**Solomon T.** New vaccines for JEV. Lancet Neurology 2008; 7:116-18.

23-**Halstead SB, Thomas SJ.** New vaccines for Japanese encephalitis. Current Infectious Diseases Report 2010; 12:174-80.

24-**Wang SY, Cheng XH, Li JX, Li XY, Zhu FC, Liu P.** Comparing the immunogenicity and safety of 3 Japanese encephalitis vaccines in Asia-Pacific area: A systematic review and meta-analysis. Hum Vaccines and Immunotherapeutics 2015;11(6):1418-1425.

25-**Nga PT, Parquet MDC, Cuong VD, Ma SP, Hasebe F, Inoue S, et al.** Shift in Japanese encephalitis virus (JEV) genotype circulating in northern Vietnam: implications for frequent introductions of JEV from Southeast Asia to East Asia. Journal of General Virology 2004; 85:1625-31.

Hossain FMA, Sumaiya FI, ATM B, Rahman MM. Japanese encephalitis virus infection in South-East Asia: An immuno-epidemiological twist. Microbes Infect Dis 2022; 3(2): 241-245.