Chapter 5

Role of Soluble Fas Ligand in Severity of Dengue Disease

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.74617

Abstract

Dengue disease, which is caused by dengue virus infection, is a major public health in the tropical and subtropical countries in the world. It has a wide spectrum of clinical manifestations ranging from an undifferentiated fever in a mild clinical form (dengue fever [DF]) to the severe clinical and potentially fatal dengue hemorrhagic fever and shock syndrome (DHF/DSS). Recently, a study has suggested that excessive inflammation and apoptosis contribute to the pathogenesis of severe dengue disease. Soluble FasL is a type II membrane protein belonging to the tumor necrosis factor (TNF) family, which induces apoptosis in Fas-bearing cells and neutrophil chemotactic functions. The apoptosis of microvascular endothelial cells may explain the plasma leakage mechanism in DHF and there was a significant increase in soluble Fas-ligand level in DHF patients compared to DF patients. It can be concluded that the soluble Fas ligand is related to the pathogenesis of dengue infection.

Keywords: soluble Fas ligand, dengue fever, dengue hemorrhagic fever, apoptosis, immune response

1. Introduction

Dengue is a public health problem in much of the tropical and subtropical countries in the world. Two-thirds of the world's population is at risk of dengue infection; an estimated 50 million cases occur annually, and around 2.5% of those affected die [1]. Dengue has a wide spectrum of clinical presentations and often has unpredictable clinical outcomes, may be asymptomatic, or may cause undifferentiated febrile illness (viral syndrome), dengue fever (DF), or dengue hemorrhagic fever (DHF) including dengue shock syndrome (DSS), and this

can cause death [2]. Despite much research, pathogenesis which can explain the severity of dengue remains unclear [3, 4]. Severe dengue is characterized by plasma leakage and abnormal bleeding that can lead to shock and death [1, 2, 5]. Pathogenesis of severe dengue diseases (DHF/DSS) has been suggested to be caused by the amplified production of cytokines that ultimately targets the vascular endothelium and leads to an increase in vascular permeability [4, 6, 7]. There is currently no specific treatment for severe dengue due to gaps in understanding the underlying mechanisms.

Soluble FasL is a type II membrane protein belonging to the tumor necrosis factor (TNF) family, which induces apoptosis in Fas-bearing cells [8] and neutrophil chemotactic functions [9]. A recent study showed that in addition to the immune response, apoptosis also contributes to the pathogenesis of DHF. An autopsy examination showed that dengue cases show apoptosis in liver cells, brain, intestine, and lungs. The apoptosis of microvascular endothelial cells may explain the plasma leakage mechanism in DHF [10].

2. Role of soluble Fas ligand in the severity of dengue disease

2.1. Dengue infection

Dengue fever (DF) and its severe forms, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), have become a major international public health problem, especially in the tropical and subtropical regions around the world. An estimated 50 million infections per year occur across approximately 100 countries, with potential for further spread [1, 2]. The disease is caused by a virus belonging to the family Flaviviridae that is spread by Aedes mosquitoes. There are four distinct serotypes of dengue virus (DENV 1–4). All dengue serotypes are capable of causing diseases with a wide spectrum of clinical manifestations, ranging from an undifferentiated fever in a mild clinical form (DF) to the severe clinical and potentially fatal DHF/DSS. Infection with one serotype confers protective immunity against that serotype but not against other serotypes [11]. Dengue fever (DF) is an acute and self-limited illness manifested by fever, headache, myalgia, and arthralgia, and on physical examination there occurs rash. Laboratory tests reveal leukopenia and thrombocytopenia. The more severe dengue DHF is complicated by plasma leakage that occurs around 3–5 days after the disease. A sudden and extensive plasma leakage may result in shock or death, a phenomenon called DSS. Then, patients undergo a defervescence phase marked by an abrupt drop in body temperature, at which point the illness may either wane to recovery or proceed to serious complications [1, 5].

DENV infection in humans starts with a DENV-infected mosquito bite. DENV can replicate in a wide spectrum of cells, including liver, spleen, lymph node, kidney, and other organs, but monocytes, macrophages, and dendritic cells (DC) have been shown to be the major targets for DENV [12]. Monocytes and T lymphocytes, which are infected by DENV, produce several pro-inflammatory mediators which become sources of intense cytokine production [13].

Abnormal hemostasis and plasma leakage are the main pathophysiological hallmarks in DHF. There is no vasculitis and hence no injury to the vessel walls, and plasma leakage results from the cytokine-mediated increase in vascular permeability [14]. During inflammation, increased vascular permeability occurs primarily via changes in the integrity of inter-endothelial cell junctions. The increase vascular permeability is affected by a number of soluble factors on the endothelium and among them are thrombin, bradykinin, histamine, oxygen free radicals, vascular endothelial growth factor (VEGF), and tumor necrosis factor-α (TNFα) [15]. Some neutrophil products like arachidonic acid (AA) or leukotriene (LT) A4 are further processed by endothelial enzymes through transcellular metabolism before the resulting products thromboxane A2, LTB4, or LTC4 can activate their cognate receptors. Neutrophils also generate reactive oxygen species that induce vascular leakage [16].

2.2. Fas ligand

Fas ligand is a 40-kDa type II membrane protein belonging to the tumor necrosis factor (TNF) family of proteins which induce defined cellular responses upon binding to their respective receptors (Fas receptors). The interaction of Fas ligand with its receptor induced programmed cell death (apoptosis) [8].

FasL is expressed by many cell types; it is primarily recognized as associated with activated T lymphocytes and natural killer (NK) cells [17]. Fas ligand is expressed in three distinct forms:

1. a membranous form on the cell surface;
2. a membranous form stored in intracellular microvesicles which are excreted into the intercellular milieu in response to various physiologic stimuli; and
3. the soluble form generated from the cleavage of the membranous molecule by matrix metalloproteinases within minutes of cell surface expression [9].

   Membrane Fas ligand can be cleaved by metalloproteinases to release soluble protein segments. The soluble and membranous forms of the Fas ligand have different functions in apoptosis. Membranous Fas ligand is the primary mediator of apoptosis through formation of trimers and higher-order structures on the cell surface, while soluble Fas ligand can have proapoptotic, antiapoptotic, and neutrophil chemotactic functions, depending on the nature of other contextual mediators in the microenvironment. Soluble Fas ligand exists as a homotrimer, which is ineffective in co-aggregating Fas receptors. Soluble Fas ligand can induce apoptosis following aggregation with fibronectin of extracellular matrix proteins to form tetramers and higher-order structures. Besides its role in apoptosis, the soluble Fas ligand is a potent inflammatory agent; it induces B cell proliferation and IgE synthesis in conjunction with IL-4, and soluble B cell activating factor (BAFF) co-stimulates B cells.

   Expression of soluble Fas ligand in several cell types has been shown to induce an effusive neutrophil-mediated inflammatory response, as documented in vivo by either tissue transplant infiltration or neutrophil extravasation to the peritoneal cavity [18].

Soluble Fas ligand-binding cells express Fas receptors and lead to apoptosis whereas there are some cells that have a default death pathway that can be blocked by a survival factor such as a hormone or growth factor [19].

The binding of the Fas ligand to the Fas receptor results in the binding of the adapter protein Fas-associated death domain (FADD). FADD then associates with procaspase-8 via dimerization of the death effector domain forming a death-inducing signaling complex (DISC). Once caspase-8 is activated, the execution phase of apoptosis is triggered. Caspases are widely expressed in an inactive proenzyme form in most cells and once activated can often activate other procaspases, allowing initiation of a protease cascade. One caspase activates other caspases and causes the apoptotic signaling pathway to be activated. Caspases have proteolytic activity and are able to cleave proteins at aspartic acid residues. Once caspases are initially activated, it leads an irreversible commitment towards cell death. There are 10 major caspases that have been identified and categorized into initiators (caspase-2,-8,-9,-10), effectors or executioners (caspase-3,-6,-7), and inflammatory caspases (caspase-1,-4,-5) [20].

There are morphological changes that occur during apoptosis. At the early process of apoptosis, cell shrinkage and pyknosis occur. At the cell shrinkage stage, the cells are smaller in size, the cytoplasm is dense, and the organelles are more tightly packed. Pyknosis is the result of chromatin condensation. Furthermore, plasma membrane blebbing occurs followed by karyorrhexis and separation of cell fragments into apoptotic bodies. The organelle integrity is still maintained and all of this is enclosed within an intact plasma membrane. Then, apoptotic bodies are subsequently phagocytosed by macrophages degraded within phagolysosomes. There is essentially no inflammatory reaction associated with the process of apoptosis [21].

The recent studies show that soluble Fas ligand also induces cellular activation signals. Soluble Fas ligand induced monocyte responses to secrete pro-inflammatory cytokines and chemotactic factors [22, 23]. Soluble Fas ligand-induced monocyte cytokine responses were associated with rapid expression of pro-inflammatory cytokine genes, suggesting at least partial regulation at the transcriptional level and involving nuclear factor-kappa beta (NF-kB) activation. There are important maturation-dependent differences in the soluble Fas ligand that depend on the signaling pathway whether inducing apoptosis or the silent disappearance of inflammatory cells. Soluble Fas ligand may serve to activate circulating monocytes and recruited macrophages to produce pro-inflammatory mediators that can initiate acute inflammation. This is may play an important role in the regulation of innate immune responses and may contribute to the pathogenesis of a variety of clinically important inflammatory diseases [24].

2.3. Role of soluble Fas ligand in pathogenesis in dengue

Soluble Fas ligand can induce apoptosis and inflammatory responses. Recently the study has suggested that excessive inflammation and apoptosis contribute to the pathogenesis of severe dengue disease. Although elevated-level cytokines occur in DF patients, the higher level was found in severe dengue disease (DHF/DSS) [25]. The evidence has suggested that there is

significantly an increase in the number of human tissues that undergo apoptosis in dengue disease [26]. Apoptosis in white blood cells, brain cells, intestine, and pulmonary endothelial cells form microvasculature in DENV cases. The apoptosis of microvascular endothelial cells may be associated with plasma leakage and hemorrhage during DHF/DSS [27].

The interaction between DENV and humans leads to the activation of transcription factors, cytokines, and enzymatic factors. These interactions may induce not only inflammatory responses but also apoptotic responses that influence the severity and progression of the disease. The human monocytes infected in vitro by DENV have upregulated Fas expression concomitant with the viral peak, indicating that DENV apoptosis is induced by extrinsic apoptotic pathway [13].

The dengue patients during acute infection found that TNF-α is the first cytokine detected in patients in the peripheral blood mononuclear cell (PBMC) cultures [28]. These findings showed that TNF-α and its family members are important apoptosis mediators during DENV infection. Among the TNF-α family, the Fas ligand is related to the pathogenesis of dengue infection [29–31]. The apoptotic event is an important event in life and is involved in pathogenesis of dengue infection, and these events occur in response to the variety of signals and stimuli, both internal and external. Mitochondria play a central role in mediating intrinsic apoptotic signals. Changes in the external membrane mitochondria lead to the production of reactive oxygen species related to initial apoptotic events. The extrinsic signal that usually induced apoptosis is by a death receptor such as Fas receptor binding to Fas ligand. After signaling, an enzymatic cascade leads to the activation of a series of cysteinyl aspartate proteases known as caspases and then to cell degradation [29]. DENV can induce apoptosis in DENV-infected cells and disseminate its viral progenies to the neighbor cells. The induction of apoptosis may be an attempt by the host immune system to limit the extent of the infection [13].

Apoptotic signaling may first be triggered by the interaction of the DENV envelope protein with the endosomal membrane during the fusion process while newly synthesized viral proteins may enhance apoptosis. There was indicate the involvement of NF-kB in mediating apoptosis. DENV triggers an apoptotic pathway through phospholipase A2 (PLA2) activation to superoxide anion generation and subsequently to NF-kB activation.

This apoptotic effect can be either directly derived from the action of arachidonic acid (AA) and superoxide anion on the mitochondria or indirectly derived from the products of apoptosis-related genes activated by NF-kB [32].

The recent study showed that soluble Fas ligand can be used as a potential marker of severity of dengue infection because the study showed that there was a significant increase in the soluble Fas ligand level in DHF patients compared to DF patients [33].

3. Conclusions

Soluble Fas ligand contributes to the pathogenesis of the severe dengue disease. The interactions between DENV and humans induce not only inflammatory responses but also apoptotic

responses that influence the severity and progression of the disease. Soluble Fas ligand can induce apoptosis and is a potent inflammatory agent.

Acknowledgements

I greatly appreciate Professor Suhartono Taat Putra (University of Airlangga) for stimulating discussions which contributed to this chapter. This work was supported by University of Muhammadiyah Sumatera Utara, Indonesia.

Conflict of interest

The authors declare that they have no conflicts of interests with commercial or other affiliations.

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References

[1] World Health Organization. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva, Switzerland: World Health Organization; 2009

[2] World Health Organization. Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever. Regional offoce for South-East Asia; 2011

[3] Martina BE, Koraka P, Osterhaus AD. Dengue virus pathogenesis: An integrated view. Clinical Microbiology Reviews. 2011;**22**(4):564-581

[4] Chaturvedi UC, Agarwal R, Elbishbishi EA, Mustafa AS. Cytokine cascade in dengue hemorrhagic fever: Implications for pathogenesis. FEMS Immunology and Medical Microbiology. 2000;**28**:183-188

[5] World Health Organization. Handbook for Clinical Management of Dengue. Geneva, Switzerland: World Health Organization; 2011

[6] Costa VV, Fagundes CT, Sauza DG, Teixeira MM. Inflammatory and innate immune responses in dengue infection. The American Journal of Pathology. 2013;**186**(2): 1950-1960. DOI: 10.1016/j.ajpath.2013.02.027

[7] Mangione J, Huy NT, Lan NTP, Mbanefo EC, Ngoc Ha TT, Bao LQ, Phi Nga CT, et al. The association of cytokines with severe dengue in children. Tropical Medicine and Health. 2013;**42**(4):137-144. DOI: 10.2149/tmh.2014-09

[8] Nagata S. Cell. 1997;**88**:355-365

[9] Tanaka M, Itai T, Adachi M, Nagata S. Downregulation of Fas ligand by shedding. Nature Medicine. 1998;**4**:31-36

[10] Limonta D, Capó V, Torres G, Guzmán MG, López LX, Pérez AB, González D, et al. New evidence of the contribution of apoptosis to dengue hemorrhagic fever pathophysiology. Biotecnologia Aplicada. 2010;**27**(1)

[11] Azeredo EL, Monteiro RQ, Pinto LO. Thrombocytopenia in dengue: Interrelationship between virus and the imbalance between coagulation and fibrinolysis and inflammatory. Mediators of Inflammation. 2015. DOI : 10.1155/2015/313842

[12] Neves-Souza PC, Azeredo EL, Zagne SM, Valls-de-Souza R, Reis SR, Cerqueira DI, Nogueira RM, Kubelka CF. Inducible nitric oxide synthase (iNOS) expression in monocytes during acute dengue fever in patients and during in vitro infection. BMC Infectious Diseases. 2005;**5**:64

[13] Carvalho AT, Azeredo EL, Reis SRI, Miranda AS, Gandini M, Barbosa LS, Kubelka CF. Dengue-2 infection and the induction of apoptosis in human primary monocytes. Memórias do Instituto Oswaldo Cruz, Rio de Janeiro. 2009;**104**(8):1091-1099

[14] Sellahewa KH. Pathogenesis of dengue haemorrhagic fever and its impact on case management. ISRN Infectious Diseases. 2013. DOI: 10.5402/2013/571646

[15] Mehta D, Malik AB. Signaling mechanisms regulating endothelial permeability. Physiological Reviews. 2006;**86**(1):279-367

[16] DiStasi MR, Ley K. Opening the flood-gates: How neutrophil-endothelial interactions regulate permeability. Trends in Immunology. 2009;**30**(11):547-556. DOI: 10.1016/j.it.2009.07.012

[17] Brunner T, Wasem C, Torgler R, Cima I, Jakob S, Corazza N. Fas (CD95/Apo-1) ligand regulation in T cell homeostasis, cell-mediated cytotoxicity and immune pathology. Seminars in Immunology. 2003;**15**:167-176. DOI: 10.1016/ S1044-5323(03)00035-6

[18] Hohlbaum AM, Moe S, Marshak-Rothstein A. Opposing effects of transmembrane and soluble Fas ligand expression on inflammation and tumor cell survival. The Journal of Experimental Medicine. 2000;**191**:1209-1220

[19] Zeiss CJ. The apoptosis-necrosis continuum: Insights from genetically altered mice. Veterinary Pathology. 2003;**40**:481-495

[20] Elmore S. Apoptosis: A review of programmed cell death. Toxicologic Pathology. 2007;**35**(4):495-516

[21] Savill J, Fadok V. Corpse clearance defines the meaning of cell death. Nature. 2000;**407**:784-788

[22] Ahn J-H, Park S-M, Cho H-S, Lee M-S, Yoon J-B, Vilcek J, Lee TH. Non-apoptotic signaling pathways activated by soluble Fas ligand in serum-starved human fibroblasts: Mitogen- activated protein kinases and NF B-dependent gene expression. The Journal of Biological Chemistry. 2001;**276** 47100

[23] Daigle I, Ruckert B, Schnetzler G, Simon HU. Induction of the IL-10 gene via the fas receptor in monocytes—An anti-inflammatory mechanism in the absence of apoptosis. European Journal of Immunology. 2000;**30**:2991

[24] Park DR, Thomsen AR, Frevert CW, Pham U, Skerrett SJ, Kiener PA, Conrad Liles W. Fas (CD95) induces proinflammatory cytokine responses by human monocytes and monocyte-derived macrophages.. Journal of Immunology 2013; 170:6209-6216. DOI: 10.4049/jimmunol.170.12.6209

[25] Srikiatkhachorn A. Plasma leakage in dengue haemorrhagic fever. Thrombosis and Haemostasis. 2009;**102**:1042-1049

[26] Huerre MR, Lan NT, Marianneau P, Hue NB, Khun H, Hung NT, et al. Liver histopathology and biological correlates in five cases of fatal dengue fever in Vietnamese children. Virchows Archiv. 2001;**438**:107-115

[27] Limonta D, Capó V, Torres G, Guzmán MG, López LX, Pérez AB, González D, Álvarez M, Rosario D, Rodríguez R, Díaz J Pelegrino JL. New evidence of the contribution ofapoptosis to dengue hemorrhagic fever pathophysiology. Biotecnología Aplicada. 2010; 271

[28] Reis SR, Sampaio AL, Henriques MG, Gandini M, Azeredo EL, Kubelka CF. An in vitro model for dengue virus infection that exhibits human monocyte infection, multiple cytokine production and dexamethasone immunomodulation. Memórias do Instituto Oswaldo Cruz. 2007;**102**:983-990

[29] Limjindaporn T, Netsawang J, Noisakran S, Thiemmeca S, Wongwiwat W, Sudsaward S, Avirutnan P, et al. Sensitization to Fas-mediated apoptosis by dengue virus capsid protein. Biochemical and Biophysical Research Communications. 2007;**362**:334-339

[30] Cardier JE, Marino E, Romano E, Taylor P, Liprandi F, Bosch N, Rothman AL. Proinflammatory factors present in sera from patients with acute dengue infection induce activation and apoptosis of human microvascular endothelial cells: Possible role of TNF-alpha in endothelial cell damage in dengue. Cytokine. 2005;**30**:359-365

[31] Lemasters JJ. Dying a thousand deaths: Redundant pathways from different organelles to apoptosis and necrosis. Gastroenterology. 2005;**129**:351-360

[32] Jan JT, Chen BH, Ma SH, Liu C, Tsai HP, Wu HC, Jiang SY, et al. Potential dengue virus-triggered apoptotic pathway in human neuroblastoma cells: Arachidonic acid, superoxide anion, and NF-kB are sequentially involved. Journal of Virology. 2000:8680-8691

[33] Zain N, Putra ST, Zein U, Hariman H. Soluble Fas ligand as potential marker of severity of dengue infection. Malaysian Journal of Medical Science. 2017i;**24**(2):28-32. DOI: 10.21315/mjms2017.24.1.4