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REVIEW

Cell and Molecular Pathology of Dengue Viral Infection

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ABSTRACT

Dengue viral infection has been threatened to almost all Pakistanis and its re-emergence in last few years has posed a major health challenge to the health policy makers of Pakistan. Peoples are well aware now on how to control dengue viral infection. Its first epidemic attack claims the lives of more than 300 peoples and more than 15000 persons were infected with viral infection in one year. In spite of taking national and international control measures, the threat of this breakout still exists. Since 2011, its molecular and cellular pathology was ignored in academic levels and it can be considered that by understanding the exact cellular and molecular pathology of dengue viral infection, this threat can be reduced to the lowest level.

Keywords: Dengue viral infection, Human endothelial cells, dengue outbreak in Pakistan, Viral borne diseases in Pakistan

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Dengue viral (DENV) infection is a well-known and threatening viral borne diseases in Pakistan. The one of the Pakistani metropolitan, Lahore was severely infected with this epidemics in 2011 causing mortality of nearly 300 patients and prevalence of upto 20,000. A lot of efforts were done to control this epidemics but threat is still remained and government is trying to take control in future eruption (1, 2). Dengue viral infections is a viral borne diseases affecting more than 100 million individuals every year around the world (3). The infection arises from mild to severe due to the loss of intravascular fluid, termed as dengue haemorrhagic fever (DHF). A number of efforts have been done in characterizing its pathological mechanism which is still unknown but it has been defined that virological and immunopathological factors are important in its pathology (4). It remains a major global health concern for decades as its still very rare information is available about the pathogenesis of DENV infection which is classified into four categories, i) sub-clinical infection, ii) dengue fever, iii) dengue hemorrhagic fever (DHF) and eventually iv) dengue shock syndrome (DSS) (3, 5). Cell based studies describing cellular modulation has could be a major determinant severity of dengue viral pathogenesis and the molecular factors involved in it to design a precise treatment strategy (6). In this

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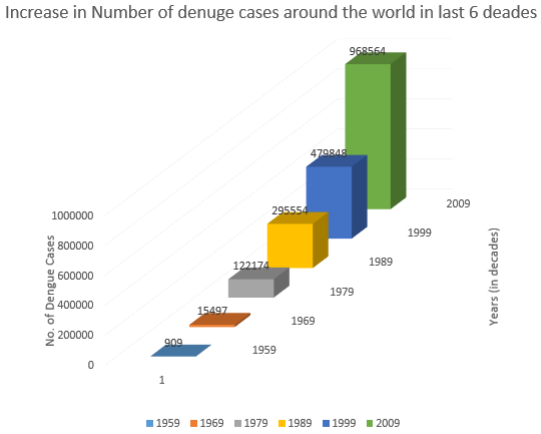

A: No. of Dengue Registered Cases/10 years

B: Tropical and sub-tropical regions infected with dengue virus

Figure 1: Increase in Dengue viral infections and infected regions in last 5 decades (Data and picture source, WHO).

review, we have reviewed and described what happens at cellular level when a dengue viral invade the human body, what its molecular mechanisms are and how it can be treated as a precision medicinal approach.

Molecular Basis of Viral Infection

Dengue disease is an infectious viral diseases caused by the dengue virus introduced in host by the bite of mosquitoes carrying these viruses. When the mosquitos bite the human skin, the outer highly keratinized epidermis containing several layers of keratinocytes act as a physical barrier as a part of innate immunity which is highly interspread with a dense network of capillaries. In addition to keratinocytes, langerhans cells and dendritic cells are also found in thin and thick part of epidermis, respectively. These cells are the first encounters of viral deposition and start activation of defensive mechanisms via increasing interactions among them (7). Morphological studies of these skin cells in dengue infected area could be a valuable tool of very early detection of viral infection.

Deposited dengue viruses inside the skin epidermis, start binding and entering to the Langerhans cells. The exact mechanism of viral binding and entrance is unknown but it has been explained that DC-SIGN (c-type lectins), CLEC5A and mannose receptor are the main surface proteins of Langerhans cells which interact with the viral proteins and DC-SIGN act as the main entrance point for viruses to enter in the Langerhans cells (8, 9). When these dendritic cells reach to the lymph nodes, the endoplasmic reticulum of these cells translate the viral genome into membrane-bounded vesicles and cellular translational machinery start translating these genomic components into proteins and new immature viral particles start synthesising there which get matured when reaches to the Golgi's bodies where they get final modifications and mature virus particles released from the cells via exocytosis following lysis of cell. These released cells now are ready to attack other white blood cells such as monocytes/macrophages and start causing host infections (8). The infection is directly related to the severity of disease. It has been hypothesized that of antibody-dependent enhancement (ADE) could be a mechanism of infection that places people at risk of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). How this enhancement happens is not clear now but it is suggested that poor ingestion of viruses by WBC for destruction is the reason that ADE happens and cells start replicating viral particles and increasing the severity of diseases leading to the dengue hemorrhagic fever and eventually death (10, 11).

Monocytes and macrophages are the second infected cells after the keratinocytes and Langerhans cells

which are easily detectable from the peripheral blood of dengue patients. To understand the molecular basis of pathogenesis of DHF/DSS, huge work has been done to identify dengue viral antigens in the infected monocytes or macrophages of infected patients (). Studies showed that dengue virus NS3 antigen was present in almost all types of cells of infected patients (12, 13) explaining the viral expansion from WBC to almost all organs of the body increasing severity of disease. However, clarifications on how these cells contribute to *in vivo* dengue viral infections are urgently needed as these cells were found positive for dengue viral antigens or RNA, Pre-membrane protein (prM) and NS3 (7, 13, 14).

Complications of Dengue Fever

WBCs produce a number of signalling proteins such as cytokines and interferons when dengue viral genome enters into the WBCs and replicate there while cells moving throughout the body. This is known as the pre-infection which arises many symptoms, such as the fever, flu and severe pains. While increasing the severity of diseases, viral particles destroy the WBCs and enter into associated organs such as liver and bone marrow etc. This damaging continues breaking the capillary permeability and bloodstream fluid leaks from the blood vessels into body cavities causing the reduction in blood pressure and blood is losing from. In the last form of severity of diseases, bone marrow become dysfunctional and platelets production declined resulting in the increased risks of bleeding (11, 15, 16).

Molecular Diagnosis and Management

Dengue viral infection happens in many steps as it has been mentioned earlier from infecting epidermal cells to the damages of vital organs like liver, bone marrow. It can be managed well if its viral presence can be detected at very early stage. A number of molecular techniques are available to detect viral RNA, antibodies and antigens. The most common type of approach is RT-PCR using consensus primers based on the conserved non-structural-3 gene. This approach along with amplifying all four dengue virus types, can also help to detect certain types of flaviviruses. Molecular analysis at early stage can also explain the molecular epidemiology and evolution of geographicaly and temporally separated viral particles using the RT-PCR (17). The genome of dengue virus is composed of about 11,000 nucleotide bases encoding for three proteins i.e. C, prM and E, which are responsible to form viral particle and sever other associated proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) required for the replication of virus inside the host cell. Five strains of dengue viruses have been characterized yet, known as serotypes and named as DENV-1, DENV-2, DENV-3, DENV-4 and DENV-5 (18, 19). These serotypes are classified based on their antigenicity (3, 20).

Cure to dengue viral infection is an ongoing debate which has been attracted by the attention of global policy makers as it has been known as the most deadliest animals of the world killing more than 700,000 peoples around the world every year (https://www.megacatch.com/). The emergency way to manage the dengue fever is the maintenance of proper body fluid balance taking anti fever medicine such as Paracetamol etc. Intensive care is provided to the patients until full recovery. Infection at primary and secondary level is easy to manage whereas at tertiary and quaternary level, an urgent demand of approved vaccine is required. CYD-TDV, which is currently known as the most advanced form of vaccine to treat dengue fever patient is very near to be approved from WHO. CYD-TDV is formed from four chimeric yellow fever 17D vaccine viruses, which are responsible to generate surface envelope and prM (membrane) proteins for all of the dengue serotypes (21).

Conclusion

Dengue, a viral vector borne disease is a continuous emerging health threat to the global community and efforts at WHO level are in practice to develop a vaccine against dengue viruses. It has been

announced recently in 2015 that first global dengue vaccine has been approved under the trade mark of DENGVAXIA® but its efficiency needs to be clarify in an epidemic infected area (http://www.dengue.info). Proper care management of dengue patients and its diagnosis at very early stage is the current gold standard to reduce the risks of dengue infections. Using molecular based available diagnostic approaches should be performed regularly for being updated with the disease status for proper care management. Techniques are growing and scientists are working on the determination of virus quantity in an infected person as the number of virus is directly related to the severity of disease (). Cellular morphology could also be an important factor in future in the determination of diseases status (7).

Conflict of Interest

Author declares no conflict of interest with any person and organization.

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References

1. Fatima Z, Afzal S, Idrees M, Rafique S, Akram M, Khubaib B, Saleem S, Amin I, Shahid M. Change in demographic pattern of dengue virus infection: evidence from 2011 dengue outbreak in Punjab, Pakistan. Public health. 2013 Sep;127(9):875-7. PMID: 23973044. DOI: 10.1016/j.puhe.2013.03.003.
2. Jahan F. Dengue Fever (DF) in Pakistan. Asia Pac Fam Med. 2011;10(1):1. PMID: 21349169. DOI: 10.1186/1447-056X-10-1.
3. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ, Hunsperger E, Kroeger A, Margolis HS, Martinez E, Nathan MB, Pelegrino JL, Simmons C, Yoksan S, Peeling RW. Dengue: a continuing global threat. Nature reviews Microbiology. 2010 Dec;8(12 Suppl):S7-16. PMID: 21079655. DOI: 10.1038/nrmicro2460.
4. McBride WJ, Bielefeldt-Ohmann H. Dengue viral infections; pathogenesis and epidemiology. Microbes and infection / Institut Pasteur. 2000 Jul;2(9):1041-50. PMID: 10967284.
5. Murray NE, Quam MB, Wilder-Smith A. Epidemiology of dengue: past, present and future prospects. Clinical epidemiology. 2013;5:299-309. PMID: 23990732. DOI: 10.2147/CLEP.S34440.
6. Martina BE, Koraka P, Osterhaus AD. Dengue virus pathogenesis: an integrated view. Clinical microbiology reviews. 2009 Oct;22(4):564-81. PMID: 19822889. DOI: 10.1128/CMR.00035-09.
7. Noisakran S, Onlamoon N, Songprakhon P, Hsiao HM, Chokephaibulkit K, Perng GC. Cells in dengue virus infection in vivo. Advances in virology. 2010;2010:164878. PMID: 22331984. DOI: 10.1155/2010/164878.
8. Kurane I, Kontny U, Janus J, Ennis FA. Dengue-2 virus infection of human mononuclear cell lines and establishment of persistent infections. Archives of Virology. 1990;110(1-2):91-101. DOI: 10.1007/bf01310705.
9. Theofilopoulos AN, Brandt WE, Russell PK, Dixon FT. Replication of dengue-2 virus in cultured human lymphoblastoid cells and subpopulations of human peripheral leukocytes. Journal of immunology. 1976 Sep;117(3):953-61. PMID: 1085314.
10. Halstead SB, O'Rourke EJ, Allison AC. Dengue viruses and mononuclear phagocytes. II. Identity of blood and tissue leukocytes supporting in vitro infection. The Journal of experimental medicine. 1977 Jul 1;146(1):218-29. PMID: 195000.
11. Sriurairatna S, Bhamarapravati N, Diwan AR, Halstead SB. Ultrastructural studies on dengue virus infection of human lymphoblasts. Infection and immunity. 1978 Apr;20(1):173-9. PMID: 669791.
12. Balsitis SJ, Coloma J, Castro G, Alava A, Flores D, McKerrow JH, Beatty PR, Harris E. Tropism of dengue virus in mice and humans defined by viral nonstructural protein 3-specific immunostaining. The American journal of tropical medicine and hygiene. 2009 Mar;80(3):416-24. PMID: 19270292.
13. Zellweger RM, Prestwood TR, Shresta S. Enhanced infection of liver sinusoidal endothelial cells in a mouse model of antibody-induced severe dengue disease. Cell host & microbe. 2010 Feb 18;7(2):128-39. PMID: 20153282. DOI: 10.1016/j.chom.2010.01.004.
14. Durbin AP, Vargas MJ, Wanionek K, Hammond SN, Gordon A, Rocha C, Balmaseda A, Harris E. Phenotyping of peripheral blood mononuclear cells during acute dengue illness demonstrates infection and increased activation of monocytes in severe cases compared to classic dengue fever. Virology. 2008 Jul 5;376(2):429-35. PMID: 18452966. DOI: 10.1016/j.virol.2008.03.028.
15. Miller JL, de Wet BJ, Martinez-Pomares L, Radcliffe CM, Dwek RA, Rudd PM, Gordon S. The mannose receptor mediates dengue virus infection of macrophages. PLoS pathogens. 2008 Feb 8;4(2):e17. PMID: 18266465. DOI: 10.1371/journal.ppat.0040017.

16. Yacoub S, Wertheim H, Simmons CP, Screaton G, Wills B. Cardiovascular manifestations of the emerging dengue pandemic. Nature reviews Cardiology. 2014 Jun;11(6):335-45. PMID: 24710495. DOI: 10.1038/nrcardio.2014.40.
17. Chow VT. Molecular diagnosis and epidemiology of dengue virus infection. Annals of the Academy of Medicine, Singapore. 1997 Nov;26(6):820-6. PMID: 9522986.
18. Rodenhuis-Zybert IA, Wilschut J, Smit JM. Dengue virus life cycle: viral and host factors modulating infectivity. Cellular and molecular life sciences : CMLS. 2010 Aug;67(16):2773-86. PMID: 20372965. DOI: 10.1007/s00018-010-0357-z.
19. Normile D. Tropical medicine. Surprising new dengue virus throws a spanner in disease control efforts. Science. 2013 Oct 25;342(6157):415. PMID: 24159024. DOI: 10.1126/science.342.6157.415.
20. Anoop M, Mathew AJ, Jayakumar B, Issac A, Nair S, Abraham R, Anupriya MG, Sreekumar E. Complete genome sequencing and evolutionary analysis of dengue virus serotype 1 isolates from an outbreak in Kerala, South India. Virus genes. 2012 Aug;45(1):1-13. PMID: 22729802. DOI: 10.1007/s11262-012-0756-3.
21. Simmons CP. A Candidate Dengue Vaccine Walks a Tightrope. The New England journal of medicine. 2015 Sep 24;373(13):1263-4. PMID: 26214040. DOI: 10.1056/NEJMe1509442.