EDITORIAL VIEW

The role of cytokines in dengue fever and its pathogenesis mediated by antibody dependent enhancement

Muhammad Faisal Yaseen, MBBS*, Kashif Nisar, MBBS**, Sheikh Zeeshan Mohiuddin, BDS, C.Orth ***

*Senior lecturer
Biochemistry Department, Ziauddin University Karachi (Pakistan)

**Senior lecturer
Biochemistry Department, Jinnah Medical and Dental College Karachi (Pakistan)

***Consultant orthodondist
Dental Department, Usman Memorial Hospital Karachi (Pakistan)

Correspondence: Dr Muhammad Faisal Yaseen MBBS, Senior Lecturer, Department of Biochemistry, Ziauddin University, Clifton, Karachi (Pakistan); Email; drfais@hotmail.com Cell No. 0092-300-9279388

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Dengue fever, or just dengue in short, is an acute infectious disease of viral etiology, transmitted to humans by the mosquito Aedes aegypti, and less frequently by Aedes albopictus and Aedes scutellaris species of mosquitoes. The disease attained an epidemic dimension in Pakistan this year. The dengue virus is classified as a single stranded RNA-virus of the Flavivirus (Flaviviridae) genre. Presently, there are four known serotypes of this virus namely DEN 1, 2, 3 and 4, which are antigenically strongly related to each other[1].

Two-thirds of the population of the world is at the risk, and approximately 50 million infections occur worldwide each year with a mortality rate that can vary from <1% to 20% depending on the type and quality of treatment offered[2]. Dengue is an emerging disease in South East Asia with 5,00010,000 cases reported per year only in India[3].

The clinical presentation of dengue varies from the self-resolving dengue fever (DF) to the more severe form, dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). Immunity against one serotype does not provide protection against other serotypes. The more lethal form, DHF occurs mostly in those patients who acquire a heterotypic type of secondary infection. The severity of this dengue infection varies with age of the affected individual, the infecting DENV serotype/genotype, the immunity status, and the genetic makeup of the population. Humoral type of immunity which was considered as the major factor contributing to its pathogenesis was supported by demonstration of antibody dependent enhancement (ADE) in vitro, and sero-epidemiological studies. Later on, memory T cells and cytokines with T regulatory cells have also been seen taking part in the disease pathogenesis. Several groups have increased levels of inflammatory cytokines, i.e. gamma interferon (IFN-γ), tumour necrosis factor alpha (TNF- α) and interleukin-6 (IL-6) in DHF patients. Most of the reported levels are based on studies in infants and children from South-East Asia and Tahiti. In contrast, higher levels of IFN-γ, TNF-α and IL-6 have been reported in adult DF patients from Brazil and India. Moreover, increased IL-8 levels have been seen associated with DHF and DSS in both adults and children. The significance in circulating levels of above mentioned cytokines as mediators of inflammation in dengue patients is still controversial and difficult to interpret. This variation of cytokine levels is present probably due to variation in the time of sample collection, age of the patients, their clinical presentation and the genetic makeup of the population studied. Only few studies have correlated .levels of the cytokines with day of illness[4].

The immunopathogenesis of DHF and DSS is believed to be mediated by a number of host factors, out of which enhancing antibodies are one of the key regulating molecules. These antibodies, via ADE of infection, are able to facilitate dengue virus (DENV) growth in Fc-bearing host cells. The mechanism of antibody dependant enhanced DENV production is thought to be

mediated through increasing number of infected cell mass. In some studies, the effect of ADE infection was analyzed further, focusing on the post-entry sequel of ADE infection. It was hypothesized that the increased amount of virus production in ADE infection compared with DENV infection can be due to the ability of this pathway of infection which suppresses the key antiviral molecules. Therefore, the influence of ADE infection on pro- and anti-inflammatory cytokines, namely IL-12, IFN-γ, TNF-α, IL-6 and IL-10, was explored and it was found that DENV infection via the Fc receptor mediated pathway has the ability to suppress the transcription and translation of IL-12, IFN-γ and TNF-α. In contrast to the infection via this route facilitated expression and synthesis of the anti-inflammatory cytokines IL-6 and IL-10[5].

Three immune components interact with each other to produce a confluence of symptoms that defines DHF/DSS. Dengue virus initially infects immature dendritic cells (mammalian immune cells) through the mediation of DC-SIGN. Infected dendritic cells contribute to pathogenesis through production of metalloproteases and cytokines. Downstream of dendritic cells causes the T-cells to become activated and generates those cytokines implicated in vascular leak and shock in addition to activating effector cells. Antibody enhancement is mediated by Fc receptors which are predominantly present on mature dendritic cells. Viral replication which is mediated by antibodies is enhanced upto one hundred fold. In addition to their effects on dengue replication, antibodies to viral epitopes also cross react with a cell protein which has the effect of stimulating CD8 effector cells as well as production of cytokines and anaphylatoxins. Anaphylatoxins can be directly generated through viral proteins or by the formation of an antibody-complement complex. Anaphylatoxins in turn can alter the T cells reactivity[6].

It is also known that antibodies to dengue viruses at subneutralizing levels of concentrations are responsible for enhancing dengue virus infection of Fc gamma R+ cells. This phenomenon is known as ADE, and this occurs when virus-antibody complexes bind to the Fc gamma receptor via the Fc portion of the immunoglobulin. It has been hypothesized that ADE may be responsible for the pathogenesis of the severe manifestations of dengue virus infection including DHF/DSS[7]. ADE is implicated in severe, usually secondary, dengue virus infections. Preexisting heterotypic antibodies, via their Fc-gamma receptor (Fcγ R) interactions, may increase disease severity through enhanced target cell infection. A well known proven fact is that greater numbers of target cells that are infected may contribute to higher viremia and highly increased cytokine levels often observed in severe disease[8].

According to a fact sheet of WHO each year 50 million people will acquire dengue fever; 2.5 billion people are at risk. There are few components of the immune system that remain unaffected by the virus. Studies suggest that ADE effects are cell type specific, and influenced by host genetics also depending on relative infection rates, may further contribute to the complexity of dengue virus pathogenesis. There are still some questions unanswered and the virus continues to spread unabated. However, these immune components and several other key elements like cytokines as well as its pathogenesis in the DF via ADE are attractive targets for study which hopefully can advance the field of research and can answer many questions.

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