Public Health Reviews

Understanding dengue pathogenesis: implications for vaccine design

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Abstract In the second half of the twentieth century dengue spread throughout the tropics, threatening the health of a third of the world's population. Dengue viruses cause 50–100 million cases of acute febrile disease every year, including more than 500 000 reported cases of the severe forms of the disease — dengue haemorrhagic fever and dengue shock syndrome. Attempts to create conventional vaccines have been hampered by the lack of suitable experimental models, the need to provide protection against all four serotypes simultaneously and the possible involvement of virus-specific immune responses in severe disease.

The current understanding of dengue pathogenesis is outlined in this review, with special emphasis on the role of the immune response. The suspected involvement of the immune system in increased disease severity and vascular damage has raised concerns about every vaccine design strategy proposed so far. Clearly more research is needed on understanding the correlates of protection and mechanisms of pathogenesis. There is, however, an urgent need to provide a solution to the escalating global public health problems caused by dengue infections. Better disease management, vector control and improved public health measures will help reduce the current disease burden, but a safe and effective vaccine is probably the only long-term solution. Although concerns have been raised about the possible safety and efficacy of both conventional and novel vaccine technologies, the situation is now so acute that it is not possible to wait for the perfect vaccine. Consequently the careful and thorough evaluation of several of the current candidate vaccines may be the best approach to halting the spread of disease.

Keywords Dengue virus/pathogenicity/immunology; Dengue hemorrhagic fever/immunology; Antibody-dependent enhancement/immunology; T-Lymphocytes/immunology; Cross reactions; Vaccines, Attenuated; Review literature (*source: MeSH, NLM*).

Mots clés Virus dengue/pathogénicité/immunologie; Fièvre hémorragique, Dengue/immunologie; Facilitation dépendante anticorps/immunologie; Lymphocyte T/immunologie; Réaction croisée; Vaccin atténué; Revue de la littérature (*source: MeSH, INSERM*).

Palabras clave Virus del dengue/patogenicidad/inmunología; Fiebre dengue hemorrágica/inmunología; Acrecentamiento dependiente de anticuerpo/inmunología; Linfocitos T/inmunología; Reacciones cruzadas; Vacunas atenuadas; Literatura de revisión (*fuente: DeCS, BIREME*).

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Voir page 312 le résumé en français. En la página 312 figura un resumen en español.

Introduction

Dengue is the most widespread vector-borne viral disease of humans. It is currently estimated that there are 50–100 million cases of dengue fever (DF) per annum worldwide, 500 000 of which result in the severe forms of the disease, dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) (*1*). The main mosquito vector, *Aedes aegypti*, is present in nearly every tropical country, and consequently a third of the world's human population is at risk of infection. Economic disruption and human population migration during and immediately after the Second World War spread the disease beyond its usual geographical locations and resulted in its reintroduction into some areas. During the second half of the twentieth century, a rapid increase in the numbers of air travellers, further population dislocations and poor public health measures worsened the situation. Media and epidemiological reports revealed that 2001 saw the highest level of dengue activity ever recorded, and that dengue has a global distribution similar to that of malaria (*2*). Epidemics occurred in Brazil, Cambodia, Colombia, Cuba, Ecuador, the Lao People's Democratic Republic, Malaysia, Myanmar, Peru, Thailand, Venezuela and Viet Nam. The outbreak in Cuba was the first for 4 years and that in Hawaii the first since the Second World War.

A licensed vaccine against dengue is not yet available, although vaccines against diseases caused by related viruses such

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as yellow fever, Japanese encephalitis and tick-borne encephalitis are available (*3*). Moreover, vaccine development has been complicated by the apparent involvement of the immune system in disease pathogenesis. This review summarizes the present knowledge of dengue pathogenesis, describes how this affects vaccine design, and outlines some approaches to overcoming the problems.

The publications reviewed for this article were obtained using the following search strategy. Two Boolean searches were carried out on the PubMed database, the first used the search terms "dengue" and "pathogenesis" and the second "dengue" and "enhancement". Publications were also selected from a monthly search of the MEDLINE database using the names of all the common flaviviruses and "flavivirus(s)" as search terms. This methodology identified all the major publications in this area, but as the search did not identify unpublished reports, there could be a bias towards reports of positive correlation with disease.

Background

All forms of dengue are associated with an infection by dengue virus, a member of the *Flavivirus* genus of the *Flaviviridae*. The virus particle has an icosohedral core, 40–50 nm in diameter, containing the C protein encapsulating the single-stranded, positive-sense RNA viral genome. Surrounding this core is a lipid envelope with two viral proteins, M and E, the latter being *N*-glycosylated. Infected cells contain seven additional non-structural proteins as well as the precursor to the M protein (*4*).

Most primary infections result in clinically silent infections, at least in young children. Clinical disease usually takes the form of an acute febrile illness, DF (historically known as "break-bone fever") from which nearly all patients recover. Occasionally the severe forms of the disease, DHF and DSS, occur; these forms may have case fatality rates of 1% or higher, especially in infants and young children (*5*). Although DF is a debilitating disease it is DHF and DSS which cause most concern. About 95% of cases occur in children under 15 years of age and at least 5% of these in infants, although higher adult morbidity has been reported in some recent outbreaks (*6*). In the case series studied by Halstead et al. they found that DHF and DSS were 15–80 times more likely in secondary infections than in primary infections and were positively associated with pre-existing dengue-virus-specific antibodies, thus implicating the immune response in the pathogenesis of severe forms of dengue (*7*).

Dengue virus exists as four serotypes, within which are several genotypes. Serotypes can be distinguished by virus-neutralizing antibodies, but non-neutralizing antibodies against the E protein and non-structural proteins such as NS1 and NS3 are cross-reactive. Halstead observed that the incidence of DHF and DSS peaked in two populations of young children (*7*). The first peak occurred from 6 to 9 months of age when levels of maternal antibody had declined, but not disappeared, and the infant was exposed to infection with a serotype different from that which had infected the mother. The second peak occurred in young children who had experienced an earlier, usually mild or subclinical, infection and were later infected with a different virus serotype. This observation indicated that the immune response to successive infections could exacerbate rather than mitigate disease, and suggested that vaccine design would be difficult. Thus successful vaccines would have to stimulate a protective immune response to all four serotypes and the timing of booster doses would have to be carefully calculated so that residual antibodies circulating in a vaccinee did not fall to levels where only cross-reacting enhancing antibodies remained, in the absence of protective levels of neutralizing antibodies. Consequently many research programmes have tried to identify viral targets that could circumvent these potential problems.

Despite the biological plausibility of the "antibody enhancement" hypothesis it does not adequately explain all the clinical and epidemiological observations. It is important therefore to understand the molecular basis of dengue pathogenesis to aid diagnosis and treatment, and facilitate the design of vaccines which will be protective, but not enhance disease.

The antibody enhancement hypothesis

The proposed role of antibody in DHF and DSS has stimulated much research into the mechanism of antibody enhancement of infection (ADE). Although ADE in vitro was first reported in the 1930s, the first definitive studies were performed by Hawkes several decades later. The many factors influencing ADE in vitro have been reviewed elsewhere (*8*). A critical component in this phenomenon is the presence of Fcγ receptors on the surface of a permissive cell, usually a member of the mononuclear phagocytic lineage. Enhancing immunoglobulin G (IgG) antibodies bound to virus attach to the cell surface, bringing the infectious virion into close proximity to the normal virus receptor (*9*). Although detailed studies have been performed on only a few viruses, the virus does not appear to enter cells through binding to Fcγ receptors alone, but requires the normal virus receptor. Thus virus-specific antibody and the Fc receptor together appear to act together as a co-receptor, enhancing the efficiency of virus binding and increasing the number of infected cells. Enhancement via IgM and complement C3 receptors has also been reported (*10*). ADE in vitro has been observed with many viruses, including both the mosquito-borne (*11*) and tick-borne flaviviruses (*12*). Thus in an infected patient, pre-existing antibody could result in increased viral load, shortened incubation times and increased disease severity. Moreover, as many components of the cell-mediated immune system (CMI) display Fcγ receptors on their cell surface, ADE could act by destroying these cells and further compromising recovery from disease.

Although the phenomenon of ADE in vitro is well established, evidence that it results in increased disease severity in either animal models or human disease is less abundant. Halstead et al. studied ADE in a non-human primate model of dengue. In sequential infections with different serotypes, some animals infected with dengue virus 2 (DENV-2) showed physiological signs consistent with DHF and some animals had peak levels of viraemia 10-fold greater than those measured in response to primary infections (reviewed in *8*). However no similar findings have been reported in animals infected with other serotypes. Animals given dengue immune serum and then challenged with the homotypic virus had higher levels of viraemia than those that received non-immune human sera (*8*).

Despite several clinical studies, evidence for the role of ADE in human disease remains circumstantial. High levels of viraemia are correlated with the incidence of DHF and DSS, as are secondary infections with heterotypic virus (*13–16*). Low levels of viraemia and high levels of pre-existing homotypic neutralizing antibodies in secondary infections are associated with mild disease. A detailed analysis of the outbreaks in Cuba

in 1977–79 and in 1997 supported the role of ADE and indicated that it could affect disease severity as long as 20 years after the primary infection (*17*, *18*). The recent careful cohort studies by Endy et al. (*14*) support these general conclusions, but emphasize that dengue pathogenesis is a multifactorial process and exceptions frequently occur. In addition, children in the first year of life who have acquired maternal antibodies with ADE characteristics experience DHF with a primary immune response (*7*). This observation is consistent with the role of ADE in DHF, but it is difficult to assign a role for T cells in such young children. It has also been suggested that the fact that different dengue serotypes can coexist in the same human population is consistent with an enhancement phenomenon (*19*). However direct evidence for the role of virus-specific antibody in DHF or DSS is still lacking.

Do virulent virus genotypes play a role in dengue haemorrhagic fever or dengue shock syndrome?

The most logical explanation for the different forms of dengue infection is that they are correlated with virus virulence, and indeed extensive genetic variation can be detected (reviewed in *20*). The strongest evidence comes from observations of infections associated with "American" strains of DENV-2 which are only rarely associated with DHF or DSS, unlike Asian strains. However not all the data are consistent with the virus virulence hypothesis. American genotype DENV-2 viruses isolated in the Pacific islands and Venezuela are associated with DHF and DSS, and the absence of DHF and DSS in a Peruvian outbreak could be attributed to antibodies from a previous outbreak of dengue caused by dengue virus 1 (DENV-1). Furthermore, virulence is usually associated with high virus load and high transmission rates, but in the Peruvian outbreak, transmission rates of over 86% were observed with American-type virus. Also, analyses of individual genotypes within a single population have provided little evidence that isolates from patients with dengue fever are distinct from those isolated from patients with DHF or DSS, although exceptions have been reported. On balance, evidence for the association of clinical outcome with a distinct virus genotype is tenuous at present.

Host susceptibility

For many viral diseases, genetically determined host susceptibility can play a role in clinical outcome. Although predisposition to DHF or DSS, determined by human histocompatibility (HLA) haplotype, has been proposed by several authors (reviewed in *21*), no clear associations with these genetic loci, or other host genetic factors, have been unequivocally described for severe forms of dengue. However in vitro studies have shown that the viral non-structural protein NS4B interferes with the nuclear signal transducer and transcription activator STAT1, blocking both interferon β (IFNβ) and interferon γ (IFNγ) production (*22*). Models of West Nile fever in experimental animals have shown that disease susceptibility is associated with a major locus WNv on chromosome 5 encoding a cluster of IFN-inducible genes, including the 2′-5′-oligoadenylate synthetases (*23*). Nevertheless very few studies have been reported on host susceptibility, especially mechanisms of innate immunity, and clearly more research is needed in this area.

The role of T cells

A role for T-cell activation in DHF and DSS has been proposed by several authors. Based on data from both in vitro and in vivo studies, Rothman & Ennis (*24*, *25*) proposed a mechanism whereby T-cell activation is involved in plasma leakage. Virus entry into monocytes and macrophages, whether through the putative virus receptor or enhanced by the binding of virus–antibody complexes to Fcγ receptors, results in the presentation of viral peptides on the cell surface, in association with HLA molecules. Interaction of these antigen-presenting cells with memory T cells induces proliferation and the production of proinflammatory cytokines such as IFNγ and tumour necrosis factor α (TNFα). These cytokines can directly affect vascular endothelial cells, resulting in plasma leakage. The rapid induction of cross-reactive memory T cells (mainly NS3-specific) during a secondary infection would be consistent with the increased incidence of DHF and DSS. This model predicts that DHF patients would have higher levels of serum cytokines and T-cell activation, and clones of cross-reactive T cells would be preferentially expanded. Several studies support this hypothesis (reviewed in *21*) and changes in levels of both pro-inflammatory serum cytokines, such as IFNγ, IL1-β, IL8 and TNFα, and anti-inflammatory cytokines, such as IL6 and IL10 have been reported (reviewed in *26*). On the basis of such observations these authors have hypothesized an alternative mechanism for dengue pathogenesis. When dengue virus replicates in macrophages they rapidly induce $CD4^+$ T cells to produce a unique (but as yet uncharacterized) cytokine (hCF). Subsequently hCF induces the macrophages to produce free radicals, reactive oxygen, nitrite and peroxynitrite which induces apoptosis in the target cells, shifting the balance of the cell-mediated immune (CMI) response from Th1 to Th2. Vascular permeability increases as a result of the combined effects of pro-inflammatory cytokines, histamine and free radicals, resulting in increased disease severity. However, levels of these cytokines are raised in several other infectious diseases without resulting in increased vascular permeability.

The magnitude of T-cell responses has also been correlated with disease severity (*27*, *28*). Studies in humans, both volunteers and patients, have indicated that the T-cell response to infection can include both serotype-specific and cross-reactive T cells, with the latter playing a role in severe disease arising from secondary infections. Moreover, some T-cell clones cross-react with other flaviviruses such as yellow fever and Japanese encephalitis (*29*). However, most of these studies were performed with volunteers from developed countries and not on people with the HLA haplotypes prevalent in south-east Asia where most cases of the severe forms of dengue occur. Recently Mongkolsapaya et al. (*30*) have carried out a detailed study of dengue-virus-specific T-cell responses in Thai children. In patients with DHF and DSS few virus-responsive $CD8^+$ T cells were recovered and most of these were highly activated cells undergoing apoptosis. These authors concluded that severe infection is associated with high levels of T-cell activation, balanced by massive apoptosis, which returns to normal levels on viral clearance. Tetramer analysis of these cells, directed against a peptide from the NS3 protein, showed a relatively low affinity for the infecting virus serotype and a higher affinity for another virus serotype, presumably from a previous infection. This observation mirrors the phenomenon of "original antigenic sin" described many years

ago (*31*) where an antibody response to a secondary virus challenge is dominated by the activation of cross-reacting memory B cells induced by the primary infection. These activated memory B cells produce antibodies with a low affinity for the virus causing the secondary infection. Thus high levels of T-cell activation, coupled with rapid cell death and the domination of the cellular immune response by cells with a low affinity for the infecting virus may suppress or delay virus clearance leading to high viral loads and increased immunopathology.

If cross-reactive T-cell responses play a role in dengue pathogenesis then it would be expected that natural selection conferring amino acid changes in cytotoxic T-lymphocyte (CTL) epitopes on one virus could affect CTL agonism and enhanced disease severity caused by other strains. Hughes (*32*) hypothesized that DENV-1 and dengue virus 3 (DENV-3) could be particularly subject to selection pressure on CTL epitopes. Therefore, if DHF or DSS is associated with CTL agonism, patients with severe forms of dengue are more likely to have experienced a primary infection with either of these serotypes and a secondary infection with another serotype. Just such a situation was reported by Burke et al. (*33*) where severe disease was associated with primary infection with DENV-1 or DENV-3 or a mixture of both.

Induction of cellular molecules and cross-reactive antibodies

The induction of a number of cellular proteins during dengue virus infection has been reported by several authors (reviewed in *34*), but possibly the most important is the induction of tissue plasminogen activator (tPA) in endothelial cells (*35*). These cells play a pivotal role in the regulation of haemostasis, and dengue virus infection has been shown to increase tPA production, but not that of plasminogen activator inhibitor-1. Furthermore, stimulation of tPA production in primary epithelial cell cultures treated with IL6 has been demonstrated. Severe forms of dengue are associated with raised levels of serum IL6 and thus infection of epithelial cells could result in raised local levels of tPA, stimulating the production of plasmin and the consequent degradation of fibrin.

Vascular damage could also be induced by cross-reactive antibodies. Lin et al. reported that antibody to the dengue virus NS1 protein can cross-react with antigens on the surface of endothelial cells and induce them to undergo nitric-oxide-mediated apoptosis (reviewed in *36*). Cross-reactions between NS1-specific monoclonal antibodies and cellular antigens have also been reported by Falconar (*37*) and thus vascular damage induced by anti-NS1 antibodies could play a role in dengue pathogenesis. Most antibodies however have lives of several months, i.e. they last much longer than most clinical symptoms.

Upregulation of several other cellular molecules, including intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and members of the major histocompatibility complex (MHC), MHC I and MHC II, has been reported for several flaviviruses. This activation appears to occur by the induction the nuclear transcription factor NF-κB (reviewed in *38*). The induction of some of these cellular molecules (e.g. MHC I and MHC II) is clearly part of the defensive response by the host, but other molecules could have a role in disease pathogenesis.

Implications for vaccine design

Conventional vaccines have played a major role in combating flavivirus diseases such as yellow fever, Japanese encephalitis and tick-borne encephalitis (reviewed in *3*), but dengue remains a significant challenge. Following the successful use of classical virological techniques to develop a live attenuated vaccine against yellow fever, similar methods have been used to produce a tetravalent dengue vaccine (reviewed in *39*). Two vaccines using viruses attenuated by serial passage in non-human cells have been developed and are in the advanced stages of evaluation. The first, developed at Mahidol University in Bangkok, Thailand, and licensed by Aventis Pasteur, produced 80–90% seroconversion rates to all four serotypes after the administration of two doses in young children. The second, produced by the Walter Reed Army Institute of Research in the USA and licensed by GlaxoSmithKline, produced similar seroconversion rates in adult volunteers. Although these results are encouraging, the molecular basis of attenuation is not understood and therefore concerns have been raised that interference in replication between the serotypes and/or interference in immune stimulation may lead to imbalanced immune responses resulting in incomplete protection and enhanced disease severity. In addition, reversion to virulence through mutation, or recombination between the vaccine components or with wild virus are causes for concern.

Several attempts have been made to overcome these potential difficulties, including the development of genetically modified infectious virus clones (reviewed in *40*). The most advanced of these is ChimeriVax-Dengue, licensed to Aventis-Pasteur, which uses the 17D yellow fever vaccine virus as its genetic backbone and replaces the yellow fever virion envelope protein genes with those from dengue viruses. Other groups have used cell-adapted DENV-2 viruses or dengue viruses with engineered attenuated mutations as genetic backbones. Proof-of-principle has been demonstrated with all these preparations and further clinical trials are in progress, although some concerns have been raised about the possibility of genetic recombination with virulent viruses (*41*).

Genetic vaccination and the use of recombinant virus vectors, such as attenuated adenoviruses (reviewed in *42*, *43*) have also been investigated by several groups and the production of protective immune responses demonstrated in experimental animal models in most cases. Attempts to overcome ADE by using non-structural proteins such as NS1 and NS3 inserted into recombinant virus vectors have demonstrated protective immunity for both mosquito-borne and tick-borne flaviviruses (*44–47*), but concerns over the safety of these vectors and lack of knowledge about the mode of protection by these proteins remain. More worrying is the recent demonstration that both NS1 itself (*48*) and antibodies to it are associated with severity of disease.

Thus the development of successful vaccines against dengue continues to present significant challenges. As with all RNA viruses, vaccines based on live attenuated agents are subject to rapid genetic mutation and recombination, giving rise to concerns about reversion to a virulent phenotype. These concerns can only be allayed by extensive human trials which employ modern molecular techniques to assess the frequency of these events. Because dengue virus occurs as four distinct serotypes, all of which occur in most endemic areas, any vaccine must protect against them all. For any live vaccine, whether

made by traditional or molecular technologies, the replication of each of these four components and the immune response to it must not suppress that of any other component. As significant cross-reaction between serotyopes can be demonstrated for both B-cell and T-cell epitopes, this could be difficult to achieve. For any vaccine dependent on stimulating responses to the major virion envelope protein, the possibility of generating enhancing antibodies will always be a potential threat unless a complete and balanced immune response to all serotypes can be guaranteed. Even then the kinetics of antibody decline must also be matched to prevent the occurrence of an excess of enhancing antibodies over neutralizing antibodies. These concerns have led several groups to explore the possibility of developing vaccines based on non-structural proteins such as NS1 and NS3. Indeed such vaccines have shown good protection in many experimental systems, but recent observations that antibodies against NS1 could induce vascular damage and that high levels of circulating NS1 protein are associated with disease severity, have raised doubts about the suitability of this vaccine candidate. This leaves just one potential new vaccine candidate, the non-structural protein NS3, and both patients and volunteers have been shown to elicit good CMI responses to this protein. Disappointingly, the elegant studies by Screaton et al. which demonstrated the phenomenon of "original antigen sin" in T-cell populations and the consequent domination of the immune response by cells with a low affinity for the infecting virus, were based on studies of a NS3 epitope.

Conclusions

Infections with dengue viruses continue to present a major and escalating global public health problem. Vector control programmes have been largely unsuccessful or of only short-term local benefit and thus vaccine development continues to be potentially the most effective control strategy. The pathogenesis of dengue infections and the apparent involvement of the immune response in both protection and disease has proved complex and difficult to understand and therefore more research on these topics is required. Many of the studies carried out so far have raised questions about the possible safety and efficacy of every vaccine design strategy developed to date. In this rather gloomy environment there has been one recent ray of hope. At a meeting in Viet Nam in 2001 (*49*) it was recognized that a key step towards accelerating the introduction of a dengue vaccine would be the establishment of an international network of phase III clinical trial centres. This meeting has led to the establishment of the Paediatric Dengue Vaccine Initiative and it is important that this key international resource is provided with several vaccines as rapidly as possible. Thorough evaluation of experimental vaccines is time consuming and therefore this process should not be halted by theoretical concerns, but the issues fully investigated by rigorous pre-clinical and clinical evaluation. Only then will the Paediatric Dengue Vaccine Initiative be able to assess the efficacy of a variety of weapons for use in the global battle against dengue. ■

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Résumé

Compréhension de la pathogénie de la dengue : conséquences pour la conception du vaccin

Au cours de la seconde moitié du vingtième siècle, la dengue s'est propagée à travers les régions tropicales, menaçant la santé d'un tiers de la population mondiale. Les virus de la dengue provoquent chaque année entre 50 et 100 millions de cas de maladie fébrile aiguë, et notamment plus de 500 000 cas signalés de formes graves de la maladie, c'est-à-dire de fièvre dengue hémorragique et de dengue avec syndrome de choc. Les tentatives pour élaborer des vaccins classiques se sont heurtées au manque de modèles expérimentaux appropriés, à la nécessité de fournir une protection contre les quatre sérotypes à la fois et à l'intervention éventuelle de réponses immunitaires spécifiques au virus dans les formes graves.

La présente étude expose la compréhension actuelle de la pathogénie de la dengue, en soulignant en particulier le rôle de la réponse immunitaire. L'implication présumée du système immunitaire dans l'accroissement du degré de gravité de la maladie et dans les dommages vasculaires a soulevé des inquiétudes à propos de toutes les stratégies de conception vaccinale proposées jusqu'à présent. Il est clair que la compréhension des corrélats entre la protection et les mécanismes de pathogénie nécessite des travaux de recherche supplémentaires. Il est cependant urgent d'apporter une solution aux problèmes grandissants de santé publique mondiale, posés par les infections de type dengue. Des progrès dans la prise en charge de la maladie et dans la lutte antivectorielle, ainsi qu'une amélioration des mesures de santé publique, contribueront à réduire la charge morbide actuelle, mais la seule solution à long terme réside probablement dans la mise au point d'un vaccin sûr et efficace. Bien que des inquiétudes aient été exprimées à propos de l'innocuité et de l'efficacité potentielles des technologies de vaccination classiques et novatrices, la situation est maintenant si grave qu'il est impossible d'attendre le vaccin parfait. En conséquence, l'évaluation méthodique et approfondie de plusieurs des vaccins candidats actuels semble la meilleure approche pour stopper la propagation de la maladie.

Resumen

Comprender la patogenia del dengue: implicaciones para el diseño de vacunas

Durante la segunda mitad del siglo XX el dengue se propagó a través de las regiones tropicales, amenazando a la salud de una tercera parte de la población mundial. Los virus del dengue causan entre 50 y 100 millones de casos de enfermedad febril aguda cada año, incluidos más de 500 000 casos notificados de las formas graves de la enfermedad, esto es, el dengue hemorrágico y el síndrome de choque por dengue. Los intentos de desarrollar vacunas convencionales se han visto dificultados por la falta de modelos experimentales idóneos, por la necesidad de ofrecer protección frente a los cuatro serotipos simultáneamente y por la posible implicación de una respuesta inmunitaria específica para el virus en los casos graves de la enfermedad.

En la presente revisión se describen a grandes rasgos los conocimientos actuales sobre la patogenia del dengue, haciendo

especial hincapié en el papel de la respuesta inmunitaria. La sospecha de que el sistema inmunitario contribuye a agravar la enfermedad y las lesiones vasculares asociadas ha sido motivo de preocupación ante cada una de las estrategias de diseño de vacunas propuestas hasta ahora. No cabe duda de que se precisan más investigaciones para comprender los factores de protección y los mecanismos patogenéticos, pero es necesario hallar urgentemente una solución ante la creciente repercusión del dengue en la salud pública mundial. Los avances en el tratamiento de la enfermedad, la lucha antivectorial y las mejoras de las medidas de salud pública ayudarán a reducir la actual carga de morbilidad, pero la única solución a largo plazo es probablemente una vacuna segura y eficaz. Aunque se ha expresado cierta inquietud en torno a la seguridad y eficacia de las tecnologías, nuevas o convencionales, de producción de vacunas, la situación es ya tan desesperada que no es posible esperar a disponer de la vacuna perfecta. En consecuencia, una evaluación minuciosa de varias de las vacunas experimentales actuales podría ser la mejor alternativa para detener la propagación de la enfermedad.

Arabic

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