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Recent advances in dengue pathogenesis and clinical management

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ABSTRACT

This review describes and commentates on recent advances in the understanding of dengue pathogenesis and immunity, plus clinical research on vaccines and therapeutics. We expand specifically on the role of the dermis in dengue virus infection, the contribution of cellular and humoral immune responses to pathogenesis and immunity, NS1 and mechanisms of virus immune evasion. Additionally we review a series of therapeutic intervention trials for dengue, as well as recent clinical research aimed at improving clinical diagnosis, risk prediction and disease classification.

1. Introduction

The underlying mechanistic causes of the dominant clinical features of severe dengue, i.e. a transient increase in vascular permeability and a hemorrhagic diathesis, remain enigmatic. In principle, acquiring deeper insights into the mechanistic drivers of the clinically important features of dengue should enable improved treatment strategies and uncover novel drug targets. Yet neatly dissecting the pathogenesis of any infectious disease syndrome is never straightforward and dengue is no exception. Host and virus variables shape the clinical outcome of any given dengue virus (DENV) infection. For the host, there is undoubtedly a physiological and immunological component (humoral and cellular) that influences whether infection (or re-infection) has a benign outcome or results in disease that manifests across a gradient of severity. There must also be a virological aspect, such that some viruses are simply better equipped to replicate and reach high titers in a human (or mosquito) host. Neither of these processes work in isolation. Rather, the outcome of exposure to an infectious *Aedes* mosquito will always depend on a constellation of "positive" and "negative" host and viral factors that each influences the overall clinical evolution of the infection. Layered upon this are the benefits that careful clinical management can have in preventing or treating the life-threatening complications that may occur; in many endemic countries improvements in clinical management mean that case fatality rates amongst hospitalized cases have been reduced from 20% to less than 0.5%. Yet there is still room to do better. This might be via development of more effective, evidence-based fluid resuscitation strategies for cases with severe shock, or the arrival of specific anti-viral therapeutics or disease modifiers able to reduce the duration and/or severity of generalized symptoms in the tens of millions of uncomplicated dengue cases that occur globally. Central to all considerations of patient-centered research findings in dengue is an understanding of the temporal "windows" that exist in the evolution of disease. These "windows" are represented schematically in Fig. 1. Beyond all else, they underscore the dynamic nature of disease evolution and that clinical research studies must always consider timing of interventions, observations and sampling in their design and reporting.

Following the bite of an infected mosquito the virus disseminates and infects multiple lymphoid and non-lymphoid tissues. A viremia ensues that is presumed to be a proxy for the underlying severity of tissue infection. The viral burden accumulates to the point that generalized clinical symptoms (fever, headache, myalgia) develop, presumably secondary to a host antiviral state in which interferon expression is abundant. Viremia peaks shortly

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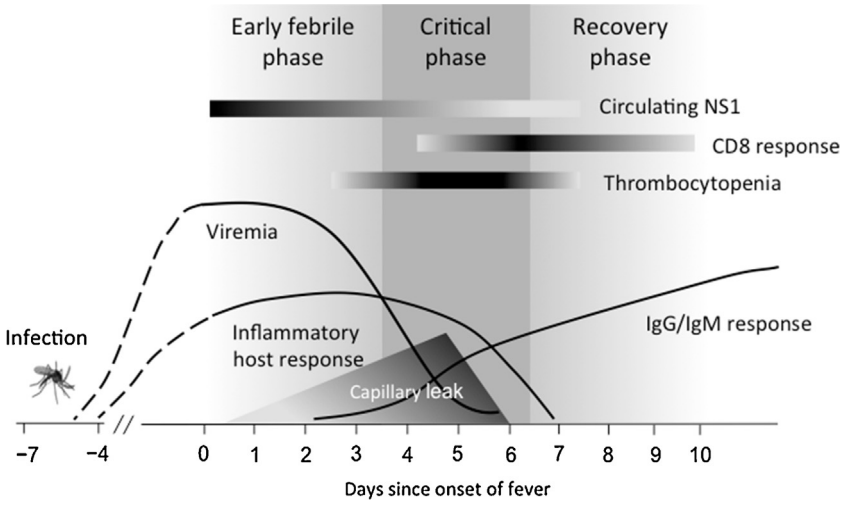

Fig. 1. Schematic showing the clinical phases in the evolution of dengue.

after fever onset (day 0) and then plateaus for 1–2 days before gradually declining, driven by the host adaptive immune response. By the 4–6th day of illness the fever breaks in most patients and symptoms recede. Increased capillary permeability, often subclinical, is measurable in many patients during the critical phase, with likely onset during the febrile phase. The increased permeability, coagulopathy, thrombocytopenia and other laboratory derangements are most pronounced around the time of defervescence, and this is the timepoint where most of the severe complications manifest. During the recovery phase there is gradual normalization of clinical and laboratory features. Activated T cells and increasing concentrations of DENV reactive IgM and IgG are detected toward the end of the febrile phase and during the recovery phase.

2. Pathogenesis

2.1. Initiation of DENV infection: is the dermis an important site of virus infection?

Since the first description of DENV infection of dendritic cells (DCs) in cadaveric human skin explants [1], there has been growing interest in this aspect of the DENV-host interaction. Recent research interest has focused on DENV infection of dendritic cell populations (DCs) that are resident in the skin, plausibly the first anatomic location where DENV interacts with key actors in the human immune system when the virus is delivered via the probing of an infected mosquito. *In vitro*, Cerny et al. [2] challenged single cell suspensions derived from human skin with cultured DENV and detected productive infection of CD14(+) and CD1c(+) DCs, Langerhan cells and dermal macrophages. Of these, Langerhan cells supported the highest virus growth titers. Parallel findings were made in intra-dermally infected mice, where DENV-infected dermis DCs migrated to the skin-draining lymph nodes. In contrast, infection of lymph-node-resident DCs was negligible. These data indicate variability in the range of human skin antigen presenting cells that can be infected with DENV and highlight the potential double-edged sword of infected cells trafficking to the draining lymph nodes; this process enables an adaptive anti-viral immune response but plausibly helps facilitate systemic spread of DENV. Consistent with these previous data, Schmid et al. [3] used a murine model to identify that DENV infection occurs in resident dermis DCs and macrophages, followed by infection of monocytes and moDCs that are recruited from the bloodstream to the dermis, probably via chemoattractant molecules released at the site of infection. Collectively these data help to define the permissiveness of dermis-resident antigen presenting cells to DENV infection, but its uncertain if these artificial experimental systems reflect the natural history of DENV infection of humans. Thus, whilst some level of dermis infection may indeed be a common outcome after successful (or unsuccessful) probing by a female *Aedes* mosquito, there is no evidence that it is a *pre-requisite* for the systemic infection that characterizes dengue. Instead, direct introduction of infectious virions into the lumen of capillaries that are expertly breached by the mosquito proboscis, followed by almost immediate systemic spread of virus and infection of permissive cells in the largest vascularized lymphoid tissue, the spleen, seems a more parsimonious explanation for how successful, systemic DENV infection is initiated in most cases.

3. Recent advances in understanding cellular immune responses to dengue virus infection

3.1. The role of T cells

T cells, and in particular cross-reactive memory T cells recalled during secondary heterotypic infections, have been nominated as contributing to the clinical pathogenesis of dengue. This hypothesis is based on the observation that T cells having surface and functional phenotypes indicative of antigen-driven activation are more abundant in early convalescence in children/adults with severe dengue versus those with milder disease [4–6]. T cell responses cannot however explain the pathogenesis of severe dengue in infants with primary infection and thus there is particular context to the "T cell hypothesis". Stronger evidence, for or against, a mechanistic role for DENV-reactive memory T cells in the severe clinical complications of dengue is needed to help guide therapeutic intervention strategies. Similarly, a better understanding of how T cells might contribute to protection from re-infection is needed for the advancement of vaccine development and identification of immune correlates. Recent advances in understanding the targets of DENV-specific T cell responses, their functional phenotypes and their tissue tropisms goes some way to providing the tools to acquire stronger mechanistic insights into their role in pathogenesis and immunity.

3.2. CD8+ T cell responses: their targets and phenotypes

Substantial new data has been acquired on the targets of T cell responses after natural infection. Rivino et al. [7] confirmed and expanded upon previous work in determining that CD8(+) T cell

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