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A REVIEW ON IMPORTANCE OF NS1 OF DENGUE VIRUS

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ABSTRACT: The non-structural 1 (NS1) dengue virus (DENV) protein plays an important role in the replication of viral RNA and has a key location in the pathogenesis of DENV. DENV NS1 is a glycoprotein expressed as soluble monomers in compromised mammalian cells that dimerize in the lumen of the endoplasmic reticulum; NS1 is then transferred as a hexameric complex to the cell surface where it persists aligned with the membrane or is secreted into the extracellular environment. The DENV NS1 protein has also been intensively studied as a possible candidate for vaccines and antiviral drugs over the last three decades. Moreover, the main diagnostic marker for dengue infection is NS1. This analysis highlights several critical topics relating to the role of NS1 in the pathogenesis of DENV and its biotechnological applications, both as a target for the production of effective and safe vaccinations and antiviral medicines and as an instrument for the production of precise diagnostic methods.

KEYWORDS: DENV, NS1, Protein, Target, Vaccine.

INTRODUCTION

The impact of dengue virus (DENV) on public fitness Dengue virus (DENV) belongs to the Flavivirus genus of the Flaviviridae family and exists as 4 serotypes: DENV-1, DENV-2, DENV-three, and DENV-4. These serotypes are arboviruses (arthropod-borne viruses) transmitted by mosquitoes of the Aedes genus. In people, DENV may additionally reason an acute febrile illness that isn't life-threatening, that is called dengue fever (DF), or greater excessive forms of the disease, called dengue hemorrhagic fever(DHF) and dengue shock syndrome (DSS). This severe paperwork is lifestyles threatening, causing vascular leakage that can lead to dying. Dengue contamination represents a major global public fitness concern, affecting billions of humans living in tropical and subtropical areas: globally, billions of human beings are exposed to DENV contamination, and hundreds die each 12 months. A recent file estimates 390million dengue infections per 12 months, with ninety six million main to enough severity to modify the person's ordinary routine[1].

Previous research estimate that, among the mentioned obvious dengue infections, at least 500,000 cases bring about intense signs and symptoms, which includes DHF and DSS. The mortality quotes of these organizations could be about 10% for hospitalized patients and about 30% for non-hospitalized patients. Those information surely point to the pressing need for a extra complete knowledge of DENV pathogenesis, that can lead to the discovery of latest manage techniques for this pathogen[2]

Importance of the non-structural 1 (NS1) protein in the DENV life cycle

DENV is an enveloped virus, and its genome is composed ofa positive-sense, single-stranded RNA coding for three structural proteins (C, capsid; prM, pre-membrane; and E, envelope) present in the virion and infected cells and seven non-structural (NS) proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5) not present in the virion. Most of the DENV proteins contain signal peptides and/or hydrophobic anchors that direct the protein to a precise location in the host cell that is suitable for viral replication. DENV NS1, the focus of this review, is a 43–48-kDa glycoprotein that is expressed in infected mammalian cells as soluble monomers that dimerize in the lumen of the endoplasmic reticulum. The NS1 protein is sub-sequently transported to the cell surface where the protein remains membrane associated or is released into the extracellular milieu as a hexameric form. The proper processing of the NS1 protein requires a signal sequence in the C-terminus of the DENV envelope glycoprotein, and this processing was shown to be significantly disturbed following the alteration of N-linked glycosylation sites. Although the functions of DENV NS1have not yet been fully elucidated, experimental evidence indicates that the protein is involved in RNA replication. The functions of the extracellular forms of DENV NS1 are also not clear, though as pecific involvement in pathogenesis and immune evasion mechanisms has been proposed[3][4].

A recently published review comprehensively explores the physiological role of the DENV NS1 protein and also describes the attempts to utilize this protein as a target for preventive, therapeutic, and diagnostic approaches. We strongly recommend that review article to those interested in further details regarding the fascinating history of this protein and the efforts of those dedicated to unveil some of its intriguing features. Herein, we present a considerably shorter review on the DENV NS1protein in which we offer our own points of view concerning the relevant aspects that continue to raise doubts with regard to the risks and benefits of using this protein, particularly as a target for anti-dengue vaccines[5].

Dengue NS1 protein as a vaccine target

Within the context of the DENV lifestyles cycle, the NS1 protein represents a goal for vaccine development due to the fact infected cells gift both the total-period NS1 protein related to the plasma membrane and NS1 peptides presented by means of MHC elegance I molecules. The whole-duration protein represents a target for anti-bodies, which can also recruit complement proteins or effector cells to kill the inflamed mobile. Moreover, NS1 protein epitopes related to MHC I molecules are targets for T cells. Up to now, a full-size range of subunit vaccine procedures primarily based on the NS1 protein (both DNA, recombinant viruses, or purified proteins) were investigated under nonclinical conditions.

In 1987, it changed into reported for the primary time that immunization with purified NS1 protein recovered from inflamed Vero cells ought to confer protective immunity to mice. In the subsequent yr, Zhang and co-workers verified that the immunization of mice with dengue structural proteins and a recombinant NS1 protein expressed in eukaryotic cells induced resistance to the encephalitis caused by an intracranial task with DENV. Moreover, mice passively obtaining anti-NS1 antibodies have been additionally protected towards DENV challenge. The maximum shielding anti-NS1 antibodies were additionally proven to be capable of binding to complement components. Shielding immunity changed into again finished in 1993 with using a DENV NS1 protein produced in eukaryotic cells. Two years later, a fusion protein comprising NS1 and the envelope glycoprotein expressed in Escherichia coli become used in a vaccine system and triggered protective immunity in mice. Based totally on those

pioneering works, using recombinant sorts of the NS1 protein appears to be a promising target for vaccines against DENV contamination.

Dengue NS1 as a target for antiviral drugs

As mentioned above, NS1 is critical in DENV RNA replication and accordingly represents a putative target for chemotherapy. Present day stated examples of antiviral tablets targeting the NS1 protein are related to interference with the proper N-glycosylation of the protein, that's required for its biological pastime .for that reason, sulfoniumion glycosidase inhibitors have been studied with the purpose of lowering DENV replication. Lately, it was suggested that the compound 6-O-butanoyl castanospermine changed into able to inducing the buildup of misfolded proteins in the endoplasmic reticulum of inflamed cells, main to reduced viral replication. Further, this identical compound, the antiviral impact of that's attributed to inhibition of the NS1 protein N-glycosylation, become shown to be protective below in vivo situations in mice. Similarly, two mammalian certainly taking place intestinal-glucosidase inhibitors, kotalanol and its de-O-sulfated derivative, had been proven to decrease DENV replication beneath in vitro conditions. These reviews virtually display that naturalmolecules produced via mammalian metabolism might also target the DENV NS1 protein[1].

Roles of NS1 in dengue diagnosis

DF has a wide spectrum of scientific signs, some of which might be normally just like the signs prompted by different acute infections or illnesses; hence, an correct differential prognosis is difficult. The detection of DENV debris in mobile cultures has the very best specificity yet involves a quite volatile, hard, and time-eating technique. Further, the duration all through which DENV debris flow into in the blood is short. Despite the fact that the detection of the viral genome gives a fast, sensitive analysis, such an assay is labor intensive and luxurious, and the sensitivity of such genetic assays decreases after the onset of symptoms because of the low viremia at some stage in this era. Alternatively, serological assays based totally on the detection of IgM and/or IgG the use of enzyme-related immunosorbent assays(ELISAs) have been described and constitute recommended diagnostic options for DENV infections. But, pass-reactivity with different flaviviruses because of prior contamination or immunization with flavivirus based totally live vaccines has been demonstrated to intervene with the consequences[6].

The NS1 protein is secreted by using DENV-infected cells, and the soluble kinds of the protein may be detected within the bloodstream from the first day after the onset of signs and symptoms until day nine, a time while the scientific segment of the ailment is complete, with NS1 being detected in levels up to fifteen µg/ml. This protein can also be detected at some point of periods in which the viral RNA isn't always detectable by way of RT-PCR and IgM antibodies particular for structural proteins aren't yet circulating. However, in a secondary DENV infection, the immune complexes formed by way of NS1 and anti-our bodies growth hastily via an anamnestic immune reaction; as a consequence, the antigen is hardly ever observed at five-7 days after the onset of symptoms in secondary DENV-inflamed patients.

The evaluation of NS1 as a diagnostic marker in early studies brought about the improvement of a massive range of dengue diagnostic kits and strategies using this protein because the analyte. Circulating NS1 is also a beneficial goal for the fast and early diagnosis of DENV infection; hence, NS1 capture ELISA can also be an amazing confirmatory check for the early detection of DENV. Although the diagnosis of DENV acute infection using NS1 strips has

been proven to be an excellent first-line test for DF, a few reviews have shown that sensitivity can be distinct for DENV serotype-2 infections. To enhance the sensitivity of dengue diagnostic kits, some authors have hypothesized that a mixture of procedures to come across the circulating antigen and anti-NS1 antibodies will boom the sensitivity and reliability of DENV contamination prognosis. In addition, it changed into proven that the combination of dengue NS1 antigen detection with anti-glycoprotein E IgM and IgG serology can notably boom the sensitivity of acute dengue prognosis, thereby allowing the prognosis of early acute positive samples and making this take a look at more useful for the clinical screening of DENV infection instances[7].

CONCLUSION

The dichotomy of thinking about the DENV NS1 protein a chief player in pathogenesis and a promising vaccine antigen nevertheless persists after almost 3 a long time of debate. Moreover, it remains unclear why anti-NS1 antibody ranges are commonly detectable at excessive degrees for plenty months after DENV infection, though there may be no evidence of scientific abnormalities associated with these antibodies in people who've recovered from the infection. Maximum of the above-noted research reporting proof of deleterious autoimmunity mechanisms with anti-NS1 antibodies were conducted in vitro, without a correlations with the observations in DENV-inflamed patients. Further, the reviews displaying that anti-NS1 antibodies pass-react with platelets and intervene with the coagulation pathway have been normally under pretty inflammatory situations, both in humans and mice. It is critical to be aware that surprisingly inflammatory conditions, which include those generated in mice after the management of several doses of the protein in the presence of Freund’s adjuvant or in human DHF cases, may result in the induction of antibodies with altered residences that might be deleterious to the host metabolism. Moreover, expanded anti-NS1antibody stages in patients with DHF seem to mirror better viremia, that's drastically higher inside the excessive forms of the ailment. An elevated viremia will glaringly bring about the extended expression of NS1 and for this reason in elevatedanti-NS1 antibody degrees. Regardless, this condition isn't located in patients with DF, which can also provide an explanation for why anti-NS1 antibodies capable of pass-reacting with platelets and proteins of the coagulation cascade are observed most effective in sufferers with severe dengue infections. Despite the fact that go-reactivity has been located in vitro, it is not clear how anti-NS1 antibodies make a contribution to DHF in humans, as full-size levels of these antibodies are discovered many months after excessive dengue contamination in patients who've recovered, without a proof of hemorrhagic occasions. Similarly, we discovered that high levels ofanti-NS1 antibodies in mice immunized with the NS1 protein do no longer induce any haematological disturbance.

The NS1 protein is one of the most conserved proteins the various 4 DENV serotypes. In this assessment, we speak several research which have validated that DENV replication might be disrupted by using concentrated on NS1. Despite conflicting proof concerning the technology of autoimmune responses, there's developing interest inside the use of the NS1 protein as a target for anti-DENV vaccines. Indeed, recent proof at the technology of NS1-established protecting immunity based on recombinant proteins or DNA vaccines, without the concomitant triggering of autoimmune responses, has inspired renewed interest within the improvement of secure and powerful anti-DENV vaccines. Extra advances in the manufacturing of recombinant

NS1 protein, with structural and immunological features much like the capabilities of the protein produced with the aid of the virus, will help inside the improvement of drugs and vaccines that can interfere with viral replication. Alongside these strains, the conserved nature of NS1 many of the four DENV kinds and the design of a consensus model of the protein may want to in addition enhance vaccine research centered on the right manipulate of the ailment caused by the 4 DENV serotypes.

In conclusion, we trust that, in a duration wherein new preventive approaches in opposition to dengue fever are urgently needed and investigated through corporations and research institutes, the NS1 protein must to be considered an vital player. Inside this context, as formerly cited, the DENV NS1 may play an critical role in the discovery of modern, secure, and effective approaches for the manipulate of this disease and can help us to higher understand DENV biology.

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