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West Nile virus and its emergence in the United States of America

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Abstract – Zoonotic West Nile virus (WNV) circulates in natural transmission cycles involving certain mosquitoes and birds, horses, humans, and a range of other vertebrates are incidental hosts. Clinical infections in humans can range in severity from uncomplicated WNV fever to fatal meningoencephalitis. Since its introduction to the Western Hemisphere in 1999, WNV had spread across North America, Central and South America and the Caribbean, although the vast majority of severe human cases have occurred in the United States of America (USA) and Canada. By 2002–2003, the WNV outbreaks have involved thousands of patients causing severe neurologic disease (meningoencephalitis and poliomyelitis-like syndrome) and hundreds of associated fatalities in USA. The purpose of this review is to present recent information on the epidemiology and pathogenicity of WNV since its emergence in North America.

West Nile virus / zoonosis / arbovirus / epidemiology / pathogenicity

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1. INTRODUCTION

West Nile virus (WNV) is an emerging mosquito-borne RNA virus of global significance that can infect the central nervous system (CNS) of various host species and cause severe neurological disease [59]. Zoonotic transmis-

sion of WNV occurs between avian hosts and ornithophilic mosquito vectors [64, 141]. Horses and humans are regarded as dead-end hosts while sensitive to WNV-induced meningoencephalitis [59, 83]. For the first decades after its isolation in Uganda in 1937 [155], WNV was the frequent cause of epizootic in horses during which a high mortality was observed. It was mostly associated with

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asymptomatic, self-limiting childhood infections in humans [131]. The first introduction of WNV in the Western Hemisphere occurred in 1999 in New York City (NYC) of United States of America (USA) [4, 5], presumably by the transport of infected humans, birds or mosquitoes [85]. WNV amplified and extended its distribution across the USA where it has been declared endemic within the 10 years [57, 58]. The spread of WNV continues in the Western Hemisphere [54]. Neurological disease is a WNV complication that was increasingly observed in humans following to the introduction in USA [121, 123]. Up to now, WNV was responsible for over 12 000 cases of meningitis/encephalitis and over 1 100 human fatalities, survivors often suffering long-term neurological sequelae. Mass mortality of resident birds, especially crows, was also observed. The American WNV strains causing the outbreaks in USA might be derivative of a highly neuroinvasive Israeli strain introduced in the Western Hemisphere in 1999 [52]. WNV pathogenesis is complex and involves viral and host factors as well as antiviral immunity in the periphery and the CNS [44]. Control of WNV infection is orchestrated by host cell defenses that are partly mediated by Type-I interferon (IFN) [50]. However, WNV has evolved strategies able to counteract the IFN-mediated antiviral immunity in the infected host [55]. In the present review, we discuss on the emergence of zoonotic WNV in the USA since 1999 and the recent informations on the specific viral and host factors that may have an influence on virus virulence in host species.

2. WNV IS A NEUROTROPIC FLAVIVIRUS

WNV is a member of *Flavivirus* genus (*Flaviviridae* family) [26]. The flaviviruses are positive sense, single-stranded RNA viruses [94]. Classically, they are subdivided into 10 serological complexes. WNV belongs to the Japanese encephalitis virus (JEV) serogroup of flaviviruses. JEV serogroup also contains Murray Valley encephalitis virus (MVEV), St. Louis encephalitis group (SLEV), and Usutu virus

(USUV) [102, 138]. The WNV species also contains the Kunjin (KUNV) subtype that is endemic in Australia and Malaysia [56]. The flaviviruses of the JEV serocomplex are the leading cause of arboviral encephalitis in vertebrate hosts including humans.

After virus inoculation in the dermis by the bite of a chronically infected vector, most infections by members of the flavivirus JEV serogroup result in no symptoms or a mild febrile illness [57, 117]. It was shown that mosquito saliva modulates early infection steps and alters the host immune response against arboviruses including WNV [147, 148]. Less than 1% of flavivirus infections cause natural infection of the CNS [34, 57, 115]. Following CNS infection, disease syndromes range from mild meningitis to severe encephalitis with variable morbidity and mortality [34, 117] and possible sequelae [75, 122]. Once inside the CNS, encephalitic flaviviruses infect neurons [33, 78, 151, 164], cause severe immunopathology [2, 90] and apoptosis [43, 89, 129, 132, 169].

Highly neurovirulent flaviviruses exhibit an upregulation of genes involved in IFN signaling, T-cell recruitment, MHC class I and II antigen presentation, and apoptosis [162, 163]. The mechanism by which encephalitic flaviviruses cross the blood-brain barrier (BBB) and invade the CNS has still not been fully elucidated [34, 74, 107]. It was first assumed that neuroinvasiveness depends on initial virus spread before the establishment of an immune response [107]. Some studies suggest disruption of BBB as mode of entry [37, 81, 121]. Alternatively, endocytosis into the CNS across vascular endothelium was demonstrated [51, 95]. Another suggested mode of CNS entry was the infection of olfactory neurons that are unprotected by the BBB [63, 105, 113]. Cohort and case-control studies have shown that hypertension and vascular disease may predispose to neuroinvasive disease [103, 121, 124]. Although asymptomatic in a majority of cases, WNV infection has been associated with neurotropic human manifestations including meningo-encephalitis and acute flaccid paralysis [43, 59, 123].

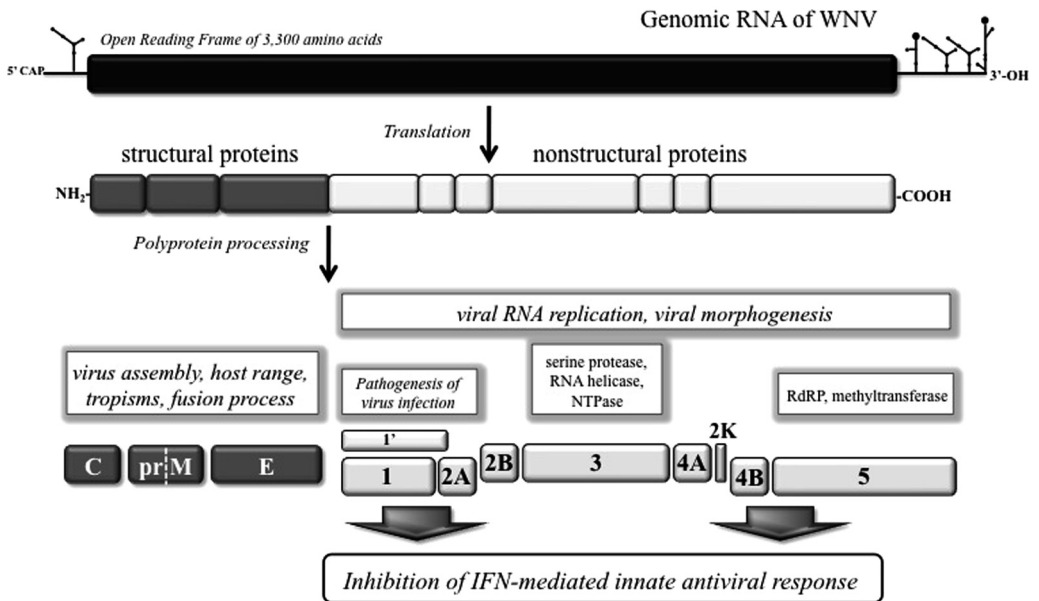


Figure 1. Schematic representation of WNV genomic RNA and the translation of the viral proteins. Functions of individual proteins are shown. See the text for details.

3. MOLECULAR BIOLOGY OF WNV

WNV replication and assembly occur in the reticulum endoplasmic (ER) of infected cells [25]. Genomic RNA encodes a large polyprotein precursor, which is processed by host and cellular proteins to yield individual structural (C, prM/M and E) and nonstructural (NS) proteins NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5 [25] (Fig. 1). The NS proteins are assumed to be involved primarily in the replication of viral RNA. Within infected mammalian cells, WNV NS1 is secreted to high levels [101]. Recent studies revealed an involvement of NS1 in modulation of signaling pathways of the innate immune response to WNV [166]. Interestingly, it has been observed that a larger NS1-related protein, designated NS1', might play a critical role in neurovasiveness of the members of JEV serogroup [109]. The NS3 protein is a viral enzyme which exhibits serine protease activity from its N-terminal domain and ATPase and helicase activity from its C-terminal domain. The viral RNA-dependent RNA polymerase, the product of NS5

gene, is responsible for replication of the viral genome within putative complexes comprising both viral and host proteins. NS3 and NS5 have been identified as the major components of the viral RNA replicase complexes (RC). Viral RC were shown to induce rearrangement of intracellular membranes. The functions of small membrane-associated NS2A, 2B, 4A and 4B proteins remain still largely unknown.

4. WNV STRATEGY FOR EVADING HOST INNATE IMMUNITY

WNV has developed strategies for enhancing viral replication in the host by blocking the action of type-I IFN and evading the antiviral activity of IFN-stimulated genes (ISG) [50, 55, 68, 92, 96, 97, 118, 146, 157]. Flaviviral IFN antagonists are involved in the inhibition of type-I IFN signaling. The nonstructural proteins NS1, NS2A, NS4B and NS5 may contribute to the control of IFN- α/β signaling by WNV [97, 118, 119] (Fig. 1). It has been observed that NS2A has the ability to inhibit the activation of

IFN- β transcription [96, 98]. The transcription factors involved in IFN- β mRNA expression whose activity is affected by NS2A are still unknown. A single amino acid substitution in WN NS2A (A30P) has been shown to enhance activation of IFN- α/β expression in vitro and in vivo [98]. Also, the A30P substitution in NS2A attenuates the neuroinvasiveness and neurovirulence of WNV in mouse model. Recent report showed that NS4B is able to block the IFN-signaling cascade at the level of nuclear STAT1 phosphorylation [118, 119]. The N-terminal region of NS4B determines its IFN antagonist activity whereas the central part of NS4B is believed to influence flavivirus virulence [165]. Expression of NS5 has been recently shown to block the IFN-stimulated JAK-STAT signaling [93].

The IFN-inducible 2', 5'-Oligoadenylate Synthetases (OAS) are part of a regulated RNA decay pathway known as the OAS/RNase L pathway, which has been shown to protect against flavivirus infection [71, 99, 104, 133, 145, 154]. Recently, a genetic case/control study on horses naturally infected with WNV showed a potential role for equine *OAS1* polymorphisms in the host innate resistance to WNV during the epidemics in USA [143]. Genetic variation in human *OAS1* is a host genetic risk factor for initial infection with WNV in North American populations [91]. Similar to human and horse *OAS1*, we and others provided evidence that the murine *Oas1b* plays a critical role in resistance to severe WNV infection in a mouse model of virally-induced encephalitis [71, 99, 104, 133]. Serial passage of WNV in mouse cells expressing *Oas1b* gave rise to a variant that displays resistance to the antiviral effect of *Oas1b* [110]. This is consistent with the assumption that WNV has the ability to counteract the antiviral activity of IFN-inducible OAS [71]. The resistance of WNV to *Oas1b* could be attributed to the S365G substitution in the viral NS3 NTPase/helicase domain and the V9M substitution in the hydrophobic 2K peptide that spans the ER membrane between NS4A and NS4B [110] (Fig. 1). The NS3 and 2K mutations promote WNV resistance to *Oas1b* through enhancement of viral RNA replication. It is of interest to note that a single amino-acid substitution in the NS3 heli-

case was sufficient to increase the virulence of WNV in American crow in North America [22]. Also, the 2K-V9M substitution has been detected in a WNV isolate collected from birds in North America [40]. So far, a single *OAS* gene has been identified in avian species [158].

These observations are consistent with a model in which the mutations in the nonstructural proteins could act as viral determinants to control IFN signaling or the antiviral effects of ISG such as *OAS* [23, 146]. This opens a new avenue for understanding how viral and host genetic diversity influences WNV pathogenicity in various hosts including humans, horses, and avian species. Whether viral factors that promote WNV subversion to antiviral innate immunity may have consequences for the amplification of WNV in the nature is a critical issue that remains to be investigated.

5. ENZOOTIC TRANSMISSION OF WNV

The principle mode of maintenance and amplification of WNV in nature occurs between avian hosts and ornithophilic mosquito vectors while human and horses are regarded as dead-end hosts unable to uphold transmission cycles (Fig. 2). *Culex* spp. is the key vector in this transmission cycle [66, 161], however, the virus has also been isolated from *Aedes* spp., *Anopheles* spp. and many other mosquito species in Europe and Africa [61, 62, 64, 168] as well as in North America [13, 14, 53, 83, 127]. Ticks and other blood-sucking arthropods were also found capable of WNV replication and transmission under experimental conditions [64, 65, 130], although the role of these potential vectors in a natural setting has not been determined. Avian hosts that maintain a sufficient viremia to subsequently infect mosquitoes are mostly passerine species, particularly corvids [1, 13, 14, 62, 70, 79, 83, 159, 168].

6. EPIDEMIOLOGY OF ZOONOTIC WNV

WNV was first isolated from a febrile woman in the West Nile district of Uganda in 1937 [155]. WNV infection was mostly associated with

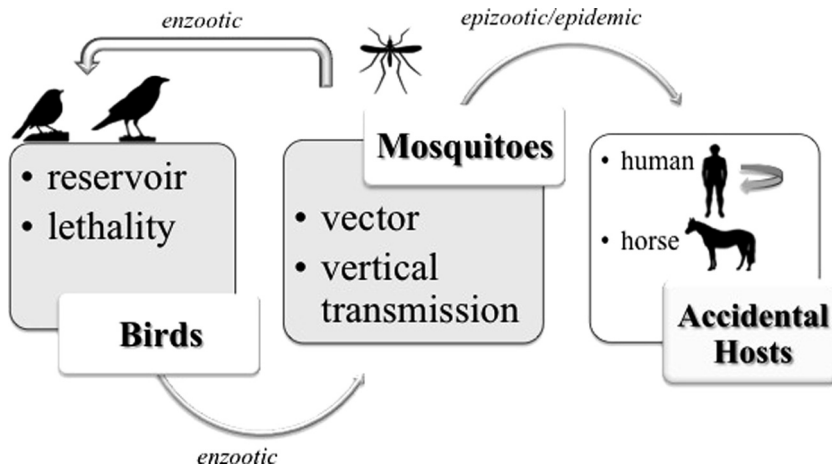


Figure 2. WNV transmission cycle.

asymptomatic, self-limiting childhood infection, with adults showing a high percentage of immunity [159]. The earliest epidemics were associated with low mortality, however severe neurological disease was reported in Israel [15], France [131], and South Africa [70, 106]. Historically, WNV was the frequent cause of epizootics in horses, during which a high mortality was observed [69, 120].

At present, WNV is endemic to Europe [61, 82], the Middle East, Africa [49, 113], Asia [74], Australia [74], and now North America. The first introduction of WNV into the Western Hemisphere occurred in 1999 in NYC [5, 24, 28, 128], probably by transport of infected humans, birds or mosquitoes [54, 140, 141].

Two predominant genetic lineages of WNV have been identified by phylogenetic analysis [16]. Lineage 1 contains an antigenically diverse group of isolates from Europe, the Middle East, India, Africa, Australia and the Western Hemisphere [19]. Lineage 2 contains isolates from Southern Africa and Madagascar. Lineage 2 strains were considered less virulent than lineage 1 strains [9] but recently also southern African strains have been associated with cases of severe encephalitis. WNV lineage 1 strains were mostly associated with severe and neuroinvasive disease, but recent studies show that viruses with high and low neuroinvasive phenotype exist in each of the lineages [9,

10, 21, 164]. Evidence for further genetic lineages was recently reported. It was reported that a single amino-acid substitution in the WNV NS3 helicase was sufficient to increase virulence in avian hosts [22, 44]. Change in pathology and neuroinvasiveness observed in some WNV strains was suggested to have originated from a change in the N-glycosylation pattern of the envelope protein resulting in altered virion stability [10, 12, 32, 108, 150].

Since the mid-1990s, three epidemiologic trends have emerged regarding WNV: (1) increased frequency of outbreaks in humans and horses, (2) increase in reported cases of neuroinvasive disease in humans, and (3) high case fatality rates in birds coinciding with human outbreaks, mainly in the USA and Israel [134]. Beginning in 1996, the Eastern Hemisphere has experienced several WNV-encephalitis outbreaks with human fatalities in Algeria [86], Romania [27, 86, 160], Tunisia [120], Israel [17, 38, 153] and Russia [100, 136]. These more recent outbreaks have been attributed to evolution of a new, more pathogenic WNV variant belonging to lineage 1.

7. EMERGENCE OF WNV IN THE USA

In late August of 1999, an unusual cluster of encephalitis cases was reported to NYC's

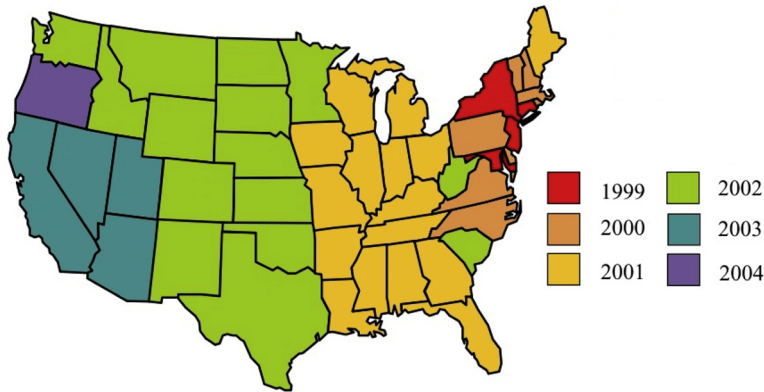


Figure 3. The enzootic spread of WNV across the lower continental USA since its first introduction in Western Hemisphere in 1999. (A color version of this figure is available at www.vetres.org.)

Department of Health [4, 128]. Initially, laboratory findings suggested infection with SLEV which is serologically related to other flaviviruses in the JEV serogroup [28]. Laboratory sequencing of virus isolated from brain tissue of birds identified WNV lineage 1 [67]. Retesting of clinically ill human cases and testing of horses presenting with CNS disease in Long Island, NY revealed WNV as the cause of disease. A total of 62 human cases of WNV were identified during this outbreak, including seven deaths. By extrapolation from a household-based study it was estimated that the NYC WNV outbreak in 1999 caused around 8 200 asymptomatic infections, causing disease in approximately 1 700 individuals [115]. This was the first evidence of WNV activity in the Western Hemisphere.

Phylogenetic analysis suggests that American strains might be derivatives of an Israeli strain introduced into the Western Hemisphere [6, 36, 52, 67, 85]. Again, it is unknown as to how this virus was introduced into the USA. *Culex pipiens* mosquitoes collected during the NYC outbreak were susceptible and able to transmit WNV [161]. Overwintering mosquitoes showed low levels of WNV RNA by real-time PCR [29]. WNV spread into several Canadian states that border to the USA, causing infections in both humans and birds [46, 167]. Surveillance of WNV-infected horses and birds detected spread of WNV through Mexico [18],

the Caribbean [8, 39, 47, 80, 87, 139] into South America [20, 45, 80, 114].

During the first years of circulation in North America, WNV persistence over the winter months was attributed to continued transmission during winter [142], overwintering of the virus in mosquitoes [29, 126, 140], and vertical WNV transmission from infected females to their offspring [7, 111, 142]. WNV infection of migratory birds was suggested to contribute to the fast dissemination of WNV in North and South America [16, 54, 170]. WNV is also rarely isolated from mammals [1, 62, 137] and reptiles [77, 112] but, like humans, these species are regarded as dead-end hosts unable to uphold transmission cycles (Fig. 2). Contrasting to this, non-viremic transmission during co-feeding between mosquitoes on dead-end hosts was described [60]. Non-vector routes of WNV transmission include oral infection [79, 84, 112], intrauterine infection [31, 59], breast-feeding [30, 59], blood transfusion [35, 59].

In the following years monitoring of bird die-offs and intense mosquito control measures were established to minimize human infections [140]. Nevertheless, WNV amplified and extended its distribution across the lower 48 continental states and has been declared endemic within 10 years of its introduction (see Fig. 3) [3, 13, 59, 135]. For two years, a homogenous viral population (genotype NY99) prevailed in New York State before

Table I. Summary of WNV human cases reported annually to CDC, 2002–2009.

	1999	2000	2001	2002	2003*	2004	2005	2006	2007	2008	2009
Human cases	62	21	66	4 156	9 862	2 539	3 000	4 269	3 630	1 338	720
Deaths	7	2	10	284	264	100	119	177	124	44	32

* National surveillance practices changed to include reporting of West Nile fever cases.

introduction of a new genotype (WN02) in 2002 containing two non-coding changes in the E (C2466U) and NS5 (C9352U) gene and one coding change in the E gene (U1441C, V159A) [11, 41]. WN02 soon became the dominant genotype in the USA, displacing its predecessor by 2004 [156]. This displacement was a result of both earlier and more efficient transmission in *Culex* ssp. mosquitoes [48, 116] and increased adaptation to replication at higher temperatures by WN02 [73].

Human and equine clinical cases, avian mortality cases, positive sentinel chicken flocks, and positive mosquito pools are reported to CDC by each individual state through the ArboNet surveillance system. Initially, only WNV encephalitis and meningitis (also referred to as neuroinvasive disease) cases were reportable. Starting with the 2003 transmission season, CDC requested that uncomplicated fever cases also be reported, resulting in a dramatic increase the reported numbers. Since 1999, our knowledge of WNV infection has evolved and changed. Likewise, CDC definitions of the various clinical entities associated with infection have changed, as have the laboratory criteria for diagnosing infection.

8. WNV INFECTION IN HUMANS

Since its introduction into the USA in 1999, WNV has been responsible for over 12 000 cases of meningitis/encephalitis and over 1 100 fatalities¹. Survivors often suffer long-term neurological disorders. Neurological disease is a WNV complication that is increasingly observed following to the introduction of WNV

into North America [128, 144]. Infection of spinal anterior horn motor neurons can cause acute flaccid paralysis during WNV infection [88, 149]. Upon WNV infection, neurons were observed to exhibit a direct antiviral response by secretion of the proinflammatory cytokine CXCL10 [76]. TNF- α was associated with accumulation of CD8⁺ T cells and activated macrophages in the CNS that contribute to increased clearance of WNV infection [152].

Very recently, WN viral RNA was identified in the urine of 20% of convalescing WNV patients up to seven years post-infection, leading to the discovery of persistent infection of the kidneys with associated renal pathology [124]. The authors speculate that persistent infection of the CNS is also possible and warrants investigation. Considering the vast number of human cases across the USA and in other parts of the world, further research is needed to understand the pathologic lesions and outcomes underlying persistent infection.

9. CONCLUDING REMARKS

Complex ecological factors determine the geographic spread of WNV. Since 1999, a dramatic westward and southward spread of WNV activity has occurred in the USA, likely due its emergence into areas with immunologically naïve reservoir populations, leading to vast numbers of viremic birds, as well as adaptation to New World *Culex* species mosquitoes, including *Cx. quinquefasciatus* and *Cx. tarsalis*. The number of USA counties reporting WNV activity increased dramatically (Fig. 3). Ten years after it was discovered in NYC, more than 25 000 cases of WNV had been reported in humans, including over 1 000 deaths (Tab. I). This virus is likely to establish an endemic cycle

¹ See the web site <http://www.cdc.gov/ncidod/dvbid/westnile/>

of transmission across the USA, Canada, and Central and South America, leading to a continued rise in cost associated with acute and long-term treatment of human cases and vaccination of horses, as well as the cost of continued surveillance, prevention and control measures.

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REFERENCES

- [1] Anderson J., Vossbrinck C., Andreadis T., Iton A., Beckwith W., Mayo D., Characterization of West Nile virus from five species of mosquitoes, nine species of birds, and one mammal, *Ann. NY Acad. Sci.* (2001) 951:328–331.
- [2] Andrews D.M., Matthews V.B., Sammels L.M., Carrello A.C., McMinn P.C., The severity of Murray Valley encephalitis in mice is linked to neutrophil infiltration and inducible nitric oxide synthase activity in the central nervous system, *J. Virol.* (1999) 73:8781–8790.
- [3] Artsob H., Gubler D.J., Enria D.A., Morales M.A., Pupo M., Bunning M.L., Dudley J.P., West Nile virus in the New World: trends in the spread and proliferation of West Nile virus in the Western Hemisphere, *Zoonoses Public Health* (2009) 56:357–369.
- [4] Asnis D.S., Conetta R., Teixeira A.A., Waldman G., Sampson B.A., The West Nile virus outbreak of 1999 in New York: the Flushing hospital experience, *Clin. Infect. Dis.* (2000) 30:413–418.
- [5] Asnis D.S., Conetta R., Waldman G., Teixeira A.A., The West Nile virus encephalitis outbreak in the United States (1999–2000): from Flushing, New York, to beyond its borders, *Ann. NY Acad. Sci.* (2001) 951:161–171.
- [6] Banet-Noach C., Malkinson M., Brill A., Samina I., Yadin H., Weisman Y., et al., Phylogenetic relationships of West Nile virus isolated from birds and horses in Israel from 1997–2001, *Virus Genes* (2003) 26:135–141.
- [7] Baqar S., Hayes C.G., Murphy J.R., Watts D.M., Vertical transmission of West Nile virus by *Culex* and *Aedes* species mosquitoes, *Am. J. Trop. Med. Hyg.* (1993) 48:757–762.
- [8] Barrera R., Hunsperger E., Muñoz-Jordán J.L., Amador M., Diaz A., Smith J., et al., First isolation of West Nile virus in the Caribbean, *Am. J. Trop. Med. Hyg.* (2008) 78:666–668.
- [9] Beasley D.W.C., Li L., Suderman M.T., Barrett A.D., West Nile virus strains differ in mouse neurovirulence and binding to mouse or human brain membrane receptor preparations, *Ann. NY Acad. Sci.* (2001) 951:332–335.
- [10] Beasley D.W.C., Li L., Suderman M., Barrett A., Mouse neuroinvasive phenotype of West Nile virus strains varies depending upon virus genotype, *Virology* (2002) 296:17–23.
- [11] Beasley D.W.C., Davis C.T., Guzman H., Vanlandingham D.L., Travassos da Rosa A.P.A., Parsons R.E., et al., Limited evolution of West Nile virus has occurred during its southwesterly spread in the United States, *Virology* (2003) 309:190–195.
- [12] Beasley D.W.C., Whiteman M.C., Zhang S., Huang C.Y.-H., Schneider B.S., Smith D.R., et al., Envelope protein glycosylation status influences mouse neuroinvasion phenotype of genetic lineage 1 West Nile virus strains, *J. Virol.* (2005) 79:8339–8347.
- [13] Bernard K.A., Kramer L.D., West Nile virus activity in the United States, 2001, *Viral Immunol.* (2001) 14:319–338.
- [14] Bernard K.A., Maffei J.G., Jones S.A., Kauffman E.B., Ebel G., Dupuis A.P., et al., West Nile virus infection in birds and mosquitoes, New York State, 2000, *Emerg. Infect. Dis.* (2001) 7:679–685.
- [15] Bernkopf H., Levine S., Nerson R., Isolation of West Nile virus in Israel, *J. Infect. Dis.* (1953) 93:207–218.
- [16] Berthet F.X., Zeller H.G., Drouet M.T., Rauzier J., Digoutte J.P., Deubel V., Extensive nucleotide changes and deletions within the envelope glycoprotein gene of Euro-African West Nile viruses, *J. Gen. Virol.* (1997) 78:2293–2297.
- [17] Bin H., Grossman Z., Pokamunski S., Malkinson M., Weiss L., Duvdevani P., et al., West Nile fever in Israel 1999–2000: from geese to humans, *Ann. NY Acad. Sci.* (2001) 951:127–142.
- [18] Blitvich B.J., Fernandez-Salas I., Contreras-Cordero J.F., Marlenee N.L., Gonzalez-Rojas J.I., Komar N., et al., Serologic evidence of West Nile virus infection in horses, Coahuila State, Mexico, *Emerg. Infect. Dis.* (2003) 9:853–856.
- [19] Bondre V.P., Jadhav R.S., Mishra A.C., Yergolkar P.N., Arankalle V.A., West Nile virus isolates from India: evidence for a distinct genetic lineage, *J. Gen. Virol.* (2007) 88:875–884.
- [20] Bosch I., Herrera F., Navarro J.-C., Lentino M., Dupuis A., Maffei J., et al., West Nile virus, Venezuela, *Emerg. Infect. Dis.* (2007) 13:651–653.
- [21] Botha E.M., Markotter W., Wolfaardt M., Paweska J.T., Swanepoel R., Palacios G., et al., Genetic determi-

- nants of virulence in pathogenic lineage 2 West Nile virus strains, *Emerg. Infect. Dis.* (2008) 14:222–230.
- [22] Brault A., Huang C., Langevin S., Kinney R., Bowen R., Ramey W., et al., A single positively selected West Nile viral mutation confers increased virogenesis in American crows, *Nat. Genet.* (2007) 39:1162–1166.
- [23] Brault A.C., Changing patterns of West Nile virus transmission: altered vector competence and host susceptibility, *Vet. Res.* (2009) 40:1–19.
- [24] Briese T., Jia X.Y., Huang C., Grady L.J., Lipkin W.I., Identification of a Kunjin/West Nile-like flavivirus in brains of patients with New York encephalitis, *Lancet* (1999) 354:1261–1262.
- [25] Brinton M., The molecular biology of West Nile virus: a new invader of the Western Hemisphere, *Annu. Rev. Microbiol.* (2002) 56:371–402.
- [26] Calisher C.H., Gould E.A., Taxonomy of the virus family Flaviviridae, *Adv. Virus Res.* (2003) 59:1–19.
- [27] Campbell G.L., Ceianu C.S., Savage H.M., Epidemic West Nile encephalitis in Romania: waiting for history to repeat itself, *Ann. NY Acad. Sci.* (2001) 951:94–101.
- [28] CDC, Outbreak of West Nile-like viral encephalitis – New York, 1999, *MMWR Morb. Mortal. Wkly Rep.* (1999) 48:845–849.
- [29] CDC, Update: surveillance for West Nile virus in overwintering mosquitoes – New York, 2000, *MMWR Morb. Mortal. Wkly Rep.* (2000) 49:178–179.
- [30] CDC, Possible West Nile virus transmission to an infant Through breast-feeding – Michigan, 2000, *MMWR Morb. Mortal. Wkly Rep.* (2002) 51:877–878.
- [31] CDC, Intrauterine West Nile virus infection – New York, 2002, *MMWR Morb. Mortal. Wkly Rep.* (2002) 51:1135–1136.
- [32] Chambers T.J., Halevy M., Nestorowicz A., Rice C.M., Lustig S., West Nile virus envelope proteins: nucleotide sequence analysis of strains differing in mouse neuroinvasiveness, *J. Gen. Virol.* (1998) 79:2375–2380.
- [33] Chambers T.J., Nickells M., Neuroadapted yellow fever virus 17D: genetic and biological characterization of a highly mouse-neurovirulent virus and its infectious molecular clone, *J. Virol.* (2001) 75:10912–10922.
- [34] Chambers T.J., Diamond M.S., Pathogenesis of flavivirus encephalitis, *Adv. Virus Res.* (2003) 60:273–342.
- [35] Charatan F., Organ transplants and blood transfusions may transmit West Nile virus, *BMJ* (2002) 325:566.
- [36] Charrel R.N., Brault A.C., Gallian P., Lemasson J.-J., Murgue B., Murri S., et al., Evolutionary relationship between Old World West Nile virus strains. Evidence for viral gene flow between Africa, the Middle East, and Europe, *Virology* (2003) 315:381–388.
- [37] Chaturvedi U.C., Dhawan R., Khanna M., Mathur A., Breakdown of the blood-brain barrier during dengue virus infection of mice, *J. Gen. Virol.* (1991) 72:859–866.
- [38] Chowers M.Y., Lang R., Nassar F., Ben-David D., Giladi M., Rubinshtein E., et al., Clinical characteristics of the West Nile fever outbreak, Israel, 2000, *Emerg. Infect. Dis.* (2001) 7:675–678.
- [39] Cruz L., Cardenas V.M., Abarca M., Rodriguez T., Reyna R.F., Serpas M.V., et al., Short report: serological evidence of West Nile virus activity in El Salvador, *Am. J. Trop. Med. Hyg.* (2005) 72:612–615.
- [40] Davis C., Beasley D., Guzman H., Siirin M., Parsons R., Tesh R., Barrett A., Emergence of attenuated West Nile virus variants in Texas, 2003, *Virology* (2004) 330:342–350.
- [41] Davis C., Ebel G., Lanciotti R., Brault A., Guzman H., Siirin M., et al., Phylogenetic analysis of North American West Nile virus isolates, 2001–2004: evidence for the emergence of a dominant genotype, *Virology* (2005) 342:252–265.
- [42] Davis L.E., DeBiasi R., Goade D.E., Haaland K.Y., Harrington J.A., Harnar J.B., et al., West Nile virus neuroinvasive disease, *Ann. Neurol.* (2006) 60:286–300.
- [43] Desprès P., Frenkiel M.P., Ceccaldi P.E., Duarte Dos Santos C., Deubel V., Apoptosis in the mouse central nervous system in response to infection with mouse-neurovirulent dengue viruses, *J. Virol.* (1998) 72:823–829.
- [44] Diamond M., Madhani H., Virus and host determinants of West Nile virus pathogenesis, *PLoS Pathog.* (2009) 5:e1000452.
- [45] Diaz A., Komar N., Visintin A., West Nile virus in birds, Argentina, *Emerg. Infect. Dis.* (2008) 14:689–691.
- [46] Drebot M.A., Lindsay R., Barker I.K., Buck P.A., Fearon M., Hunter F., et al., West Nile virus surveillance and diagnostics: a Canadian perspective, *J. Can. Infect. Dis.* (2003) 14:105–114.
- [47] Dupuis A.P., Marra P.P., Kramer L.D., Serologic evidence of West Nile virus transmission, Jamaica, West Indies, *Emerg. Infect. Dis.* (2003) 9:860–863.
- [48] Ebel G.D., Carricaburu J., Young D., Bernard K., Kramer L.D., Genetic and phenotypic variation of West Nile virus in New York, 2000–2003, *Am. J. Trop. Med. Hyg.* (2004) 71:493–500.
- [49] Fagbami A., Human arthropod-borne virus infections in Nigeria. Serological and virological

- investigations and Shaki, Oyo State, J. Hyg. Epidemiol. Microbiol. Immunol. (1978) 22:184–189.
- [50] Fredericksen B.L., Smith M., Katze M.G., Shi P.-Y., Gale M., The host response to West Nile virus infection limits viral spread through the activation of the interferon regulatory factor 3 pathway, J. Virol. (2004) 78:7737–7747.
- [51] German A., Myint K., Mai N., Pomeroy I., Phu N., Tzartos J., et al., A preliminary neuropathological study of Japanese encephalitis in humans and a mouse model, Trans. R. Soc. Trop. Med. Hyg. (2006) 100:1135–1145.
- [52] Giladi M., Metzker-Cotter E., Martin D.A., Siegman-Igra Y., Korczyn A.D., Rosso R., et al., West Nile encephalitis in Israel, 1999: the New York connection, Emerg. Infect. Dis. (2001) 7:659–661.
- [53] Granwehr B., Lillibridge K., Higgs S., Mason P., Aronson J., Campbell G., Barrett A., West Nile virus: where are we now?, Lancet Infect. Dis. (2004) 4: 547–556.
- [54] Gubler D.J., Emerging infections: the continuing spread of West Nile virus in the Western Hemisphere, Clin. Infect. Dis. (2007) 45:1039–1046.
- [55] Guo J.-T., Hayashi J., Seeger C., West Nile virus inhibits the signal transduction pathway of alpha interferon, J. Virol. (2005) 79:1343–1350.
- [56] Hall R.A., Scherret J.H., Mackenzie J.S., Kunjin virus: an Australian variant of West Nile?, Ann. NY Acad. Sci. (2001) 951:153–160.
- [57] Hayes E.B., Gubler D., West Nile virus: epidemiology and clinical features of an emerging epidemic in the United States, Annu. Rev. Med. (2006) 57: 181–194.
- [58] Hayes E.B., Komar N., Nasci R.S., Montgomery S.P., O’Leary D.R., Campbell G.L., Epidemiology and transmission dynamics of West Nile virus disease, Emerg. Infect. Dis. (2005) 11:1167–1173.
- [59] Hayes E.B., Sejvar J.J., Zaki S.R., Lanciotti R.S., Bode A.V., Campbell G.L., Virology, pathology, and clinical manifestations of West Nile virus disease, Emerg. Infect. Dis. (2005) 11:1174–1179.
- [60] Higgs S., Schneider B.S., Vanlandingham D.L., Klingler K.A., Gould E.A., Nonviremic transmission of West Nile virus, Proc. Natl. Acad. Sci. USA (2005) 102:8871–8874.
- [61] Hubálek Z., Halouzka J., West Nile fever – a reemerging mosquito-borne viral disease in Europe, Emerg. Infect. Dis. (1999) 5:643–650.
- [62] Hubálek Z., Mosquito-borne viruses in Europe, Parasitol. Res. (2008) 103:Suppl. 1:S29–S43.
- [63] Hunsperger E., Roehrig J., Temporal analyses of the neuropathogenesis of a West Nile virus infection in mice, J. Neurovirol. (2006) 12:129–139.
- [64] Hurlbut H., West Nile virus infection in arthropods, Am. J. Trop. Med. Hyg. (1956) 5:76–85.
- [65] Hutcheson H.J., Gorham C.H., Machain-Williams C., Loroño-Pino M.A., James A.M., Marlenee N.L., et al., Experimental transmission of West Nile virus (Flaviviridae: Flavivirus) by *Carios capensis* ticks from North America, Vector Borne Zoonotic Dis. (2005) 5:293–295.
- [66] Ilkal M.A., Mavale M.S., Prasanna Y., Jacob P.G., Geevarghese G., Banerjee K., Experimental studies on the vector potential of certain *Culex* species to West Nile virus, Indian J. Med. Res. (1997) 106:225–228.
- [67] Jia X.Y., Briese T., Jordan I., Rambaut A., Chi H.C., MacKenzie J.S., et al., Genetic analysis of West Nile New York 1999 encephalitis virus, Lancet (1999) 354:1971–1972.
- [68] Jones M., Davidson A., Hibbert L., Gruenwald P., Schlaak J., Ball S., et al., Dengue virus inhibits alpha interferon signaling by reducing STAT2 expression, J. Virol. (2005) 79:5414–5420.
- [69] Joubert L., Oudar J., Hannoun C., Beytout D., Corniou B., Guillon G.C., Panthier R., Epidemiology of the West Nile virus: study of a focus in Camargue. IV. Meningo-encephalomyelitis of the horse, Ann. Inst. Pasteur (Paris) (1970) 118:239–247.
- [70] Jupp P.G., The ecology of West Nile virus in South Africa and the occurrence of outbreaks in humans, Ann. NY Acad. Sci. (2001) 951:143–152.
- [71] Kajaste-Rudnitski A., Mashimo T., Frenkiel M.-P., Guénet J.-L., Lucas M., Desprès P., The 2',5'-oligoadenylate synthetase 1b is a potent inhibitor of West Nile virus replication inside infected cells, J. Biol. Chem. (2006) 281:4624–4637.
- [72] Kanamitsu M., Taniguchi K., Urasawa S., Ogata T., Wada Y., Wada Y., Saroso J.S., Geographic distribution of arbovirus antibodies in indigenous human populations in the Indo-Australian Archipelago, Am. J. Trop. Med. Hyg. (1979) 28:351–363.
- [73] Kilpatrick A.M., Meola M.A., Moudy R.M., Kramer L.D., Buchmeier M.J., Temperature, viral genetics, and the transmission of West Nile virus by *Culex pipiens* mosquitoes, PLoS Pathog. (2008) 4:e1000092.
- [74] King N.J.C., Getts D.R., Getts M.T., Rana S., Shrestha B., Kesson A.M., Immunopathology of flavivirus infections, Immunol. Cell Biol. (2007) 85:33–42.
- [75] Klee A.L., Maidin B., Edwin B., Poshni I., Mostashari F., Fine A., et al., Long-term prognosis for clinical West Nile virus infection, Emerg. Infect. Dis. (2004) 10:1405–1411.
- [76] Klein R.S., Lin E., Zhang B., Luster A.D., Tollett J., Samuel M.A., et al., Neuronal CXCL10 directs CD8+ T-cell recruitment and control of West Nile virus encephalitis, J. Virol. (2005) 79:11457–11466.

- [77] Klenk K., Snow J., Morgan K., Bowen R., Stephens M., Foster F., et al., Alligators as West Nile virus amplifiers, *Emerg. Infect. Dis.* (2004) 10:2150–2155.
- [78] Koh W.-L., Ng M.-L., Molecular mechanisms of West Nile virus pathogenesis in brain cell, *Emerg. Infect. Dis.* (2005) 11:629–632.
- [79] Komar N., Langevin S., Hinten S., Nemeth N., Edwards E., Hettler D., et al., Experimental infection of North American birds with the New York 1999 strain of West Nile virus, *Emerg. Infect. Dis.* (2003) 9:311–322.
- [80] Komar N., Clark G.G., West Nile virus activity in Latin America and the Caribbean, *Rev. Panam. Salud Publica* (2006) 19:112–117.
- [81] Kong K., Delroux K., Wang X., Qian F., Arjona A., Malawista S., et al., Dysregulation of TLR3 impairs the innate immune response to West Nile virus in the elderly, *J. Virol.* (2008) 82:7613–7623.
- [82] Krisztalovics K., Ferenczi E., Molnar Z., Csohan A., Ban E., Zoldi V., Kaszas K., West Nile virus infections in Hungary, August–September 2008, *Euro Surveill.* (2008) 13:pii: 19030.
- [83] Kulasekera V.L., Kramer L., Nasci R.S., Mostashari F., Cherry B., Trock S.C., et al., West Nile virus infection in mosquitoes, birds, horses, and humans, Staten Island, New York, 2000, *Emerg. Infect. Dis.* (2001) 7:722–725.
- [84] Kumar D., Prasad G., Zaltzman J., Levy G., Humar A., Community-acquired West Nile virus infection in solid-organ transplant recipients, *Transplantation* (2004) 77:399–402.
- [85] Lanciotti R.S., Roehrig J.T., Deubel V., Smith J., Parker M., Steele K., et al., Origin of the West Nile virus responsible for an outbreak of encephalitis in the Northeastern United States, *Science* (1999) 286:2333–2337.
- [86] Le Guenno B., West Nile: a deadly virus?, *Lancet* (1996) 348:1315.
- [87] Lefrançois T., Blitvich B.J., Pradel J., Molia S., Vachiéry N., Pallavicini G., et al., West Nile virus surveillance, Guadeloupe, 2003–2004, *Emerg. Infect. Dis.* (2005) 11:1100–1103.
- [88] Li J., Loeb J.A., Shy M.E., Shah A.K., Tselis A.C., Kupski W.J., Lewis R.A., Asymmetric flaccid paralysis: a neuromuscular presentation of West Nile virus infection, *Ann. Neurol.* (2003) 53:703–710.
- [89] Liao C.L., Lin Y.L., Shen S.C., Shen J.Y., Su H.L., Huang Y.L., et al., Antiapoptotic but not antiviral function of human bcl-2 assists establishment of Japanese encephalitis virus persistence in cultured cells, *J. Virol.* (1998) 72:9844–9854.
- [90] Licon Luna R.M., Lee E., Müllbacher A., Blanden R.V., Langman R., Lobigs M., Lack of both Fas ligand and perforin protects from flavivirus-mediated encephalitis in mice, *J. Virol.* (2002) 76:3202–3211.
- [91] Lim J., Lisco A., McDermott D., Huynh L., Ward J., Johnson B., et al., Genetic variation in OAS1 is a risk factor for initial infection with West Nile virus in man, *PLoS Pathog.* (2009) 5:e1000321.
- [92] Lin R.-J., Liao C.-L., Lin E., Lin Y.-L., Blocking of the alpha interferon-induced Jak-Stat signaling pathway by Japanese encephalitis virus infection, *J. Virol.* (2004) 78:9285–9294.
- [93] Lin R.-J., Chang B.-L., Yu H.-P., Liao C.-L., Lin Y.-L., Blocking of interferon-induced Jak-Stat signaling by Japanese encephalitis virus NS5 through a protein tyrosine phosphatase-mediated mechanism, *J. Virol.* (2006) 80:5908–5918.
- [94] Lindenbach B., Thiel H.J., Rice C.M., Flaviviridae: The viruses and their replication, in: Knipe D.M., Howley P.M. (Eds.), *Fields virology*, Lippincott Williams & Wilkins, Philadelphia, 2007, pp. 1101–1152.
- [95] Liou M.L., Hsu C.Y., Japanese encephalitis virus is transported across the cerebral blood vessels by endocytosis in mouse brain, *Cell Tissue Res.* (1998) 293:389–394.
- [96] Liu W.J., Chen H.B., Wang X.J., Huang H., Khromykh A., Analysis of adaptive mutations in Kunjin virus replicon RNA reveals a novel role for the flavivirus nonstructural protein NS2A in inhibition of beta interferon promoter-driven transcription, *J. Virol.* (2004) 78:12225–12235.
- [97] Liu W.J., Wang X.J., Mokhonov V.V., Shi P.-Y., Randall R., Khromykh A.A., Inhibition of interferon signaling by the New York 99 strain and Kunjin subtype of West Nile virus involves blockage of STAT1 and STAT2 activation by nonstructural proteins, *J. Virol.* (2005) 79:1934–1942.
- [98] Liu W.J., Wang X.J., Clark D., Lobigs M., Hall R., Khromykh A., A single amino acid substitution in the West Nile virus nonstructural protein NS2A disables its ability to inhibit alpha/beta interferon induction and attenuates virus virulence in mice, *J. Virol.* (2006) 80:2396–2404.
- [99] Lucas M., Mashimo T., Frenkiel M.-P., Simon-Chazottes D., Montagutelli X., Ceccaldi P.-E., et al., Infection of mouse neurones by West Nile virus is modulated by the interferon-inducible 2'–5' oligoadenylate synthetase 1b protein, *Immunol. Cell Biol.* (2003) 81:230–236.
- [100] Lvov D.K., Butenko A.M., Gromashevsky V.L., Larichev V.P., Gaidamovich S.Y., Vyshemirsky O.I., et al., Isolation of two strains of West Nile virus during an outbreak in southern Russia, 1999, *Emerg. Infect. Dis.* (2000) 6:373–376.
- [101] Macdonald J., Tonry J., Hall R.A., Williams B., Palacios G., Ashok M.S., et al., NS1 protein secretion during the acute phase of West Nile virus infection, *J. Virol.* (2005) 79:13924–13933.

- [102] Mackenzie J.S., Barrett A.D., Deubel V., The Japanese encephalitis serological group of flaviviruses: a brief introduction to the group, *Curr. Top. Microbiol. Immunol.* (2002) 267:1–10.
- [103] Marfin A.A., Bleed D.M., Lofgren J.P., Olin A.C., Savage H.M., Smith G.C., et al., Epidemiologic aspects of a St. Louis encephalitis epidemic in Jefferson County Arkansas, 1991, *Am. J. Trop. Med. Hyg.* (1993) 49:30–37.
- [104] Mashimo T., Lucas M., Simon-Chazottes D., Frenkiel M., Montagutelli X., Ceccaldi P., et al., A nonsense mutation in the gene encoding 2'-5'-oligoadenylate synthetase/L1 isoform is associated with West Nile virus susceptibility in laboratory mice, *Proc. Natl. Acad. Sci. USA* (2002) 99:11311–11316.
- [105] Matthews V., Robertson T., Kendrick T., Abdo M., Papadimitriou J., McMinn P., Morphological features of Murray Valley encephalitis virus infection in the central nervous system of Swiss mice, *Int. J. Exp. Pathol.* (2000) 81:31–40.
- [106] McIntosh B., Epidemics of West Nile and Sindbis viruses in South Africa with *Culex (Culex) univittatus* Theobald as vector, *S. Afr. J. Sci.* (1976) 72:295–300.
- [107] McMinn P.C., Dalgarno L., Weir R.C., A comparison of the spread of Murray Valley encephalitis viruses of high or low neuroinvasiveness in the tissues of Swiss mice after peripheral inoculation, *Virology* (1996) 220:414–423.
- [108] McMinn P.C., The molecular basis of virulence of the encephalitogenic flaviviruses, *J. Gen. Virol.* (1997) 78:2711–2722.
- [109] Melian E., Hinzman E., Nagasaki T., Firth A., Wills N., Nouwens A., et al., NS1' of flaviviruses in the Japanese encephalitis serogroup is a product of ribosomal frameshifting and plays a role in viral neuro-invasiveness, *J. Virol.* (2009) 84:1641–1647.
- [110] Mertens E., Kajaste-Rudnitski A., Torres S., Funk A., Frenkiel M.-P., Iteman I., et al., Viral determinants in the NS3 helicase and 2K peptide that promote West Nile virus resistance to antiviral action of 2',5'-oligoadenylate synthetase 1b, *Virology* (2010) 399:1–10.
- [111] Miller B.R., Nasci R.S., Godsey M.S., Savage H.M., Lutwama J.J., Lanciotti R.S., Peters C.J., First field evidence for natural vertical transmission of West Nile virus in *Culex univittatus* complex mosquitoes from Rift Valley province, Kenya, *Am. J. Trop. Med. Hyg.* (2000) 62:240–246.
- [112] Miller D.L., Mauel M.J., Baldwin C., Burtle G., Ingram D., Hines M.E., Frazier K.S., West Nile virus in farmed alligators, *Emerg. Infect. Dis.* (2003) 9:794–799.
- [113] Monath T., Cropp C., Harrison A., Mode of entry of a neurotropic arbovirus into the central nervous system. Reinvestigation of an old controversy, *Lab. Invest.* (1983) 48:399–410.
- [114] Morales M.A., Barrandeguy M., Fabbri C., Garcia J.B., Vissani A., Trono K., et al., West Nile virus isolation from equines in Argentina, 2006, *Emerg. Infect. Dis.* (2006) 12:1559–1561.
- [115] Mostashari F., Bunning M., Kitsutani P., Singer D., Nash D., Cooper M., et al., Epidemic West Nile encephalitis, New York, 1999: results of a household-based seroepidemiological survey, *Lancet* (2001) 358:261–264.
- [116] Moudy R., Meola M., Morin L.L., Ebel G.D., Kramer L.D., A newly emergent genotype of West Nile virus is transmitted earlier and more efficiently by *Culex* mosquitoes, *Am. J. Trop. Med. Hyg.* (2007) 77:365–370.
- [117] Müllbacher A., Lobigs M., Lee E., Immunobiology of mosquito-borne encephalitic flaviviruses, *Adv. Virus Res.* (2003) 60:87–120.
- [118] Munoz-Jordan J., Sanchez-Burgos G., Laurent-Rolle M., Garcia-Sastre A., Inhibition of interferon signaling by dengue virus, *Proc. Natl. Acad. Sci. USA* (2003) 100:14333–14338.
- [119] Muñoz-Jordán J.L., Laurent-Rolle M., Ashour J., Martínez-Sobrido L., Ashok M., Lipkin W.I., García-Sastre A., Inhibition of alpha/beta interferon signaling by the NS4B protein of flaviviruses, *J. Virol.* (2005) 79:8004–8013.
- [120] Murgue B., Murri S., Triki H., Deubel V., Zeller H.G., West Nile in the Mediterranean Basin: 1950–2000, *Ann. NY Acad. Sci.* (2001) 951:117–126.
- [121] Murray K.O., Baraniuk S., Resnick M., Arafat R., Kilborn C., Cain K., et al., Risk factors for encephalitis and death from West Nile virus infection, *Epidemiol. Infect.* (2006) 134:1325–1332.
- [122] Murray K.O., Resnick M., Miller V., Depression after infection with West Nile virus, *Emerg. Infect. Dis.* (2007) 13:479–481.
- [123] Murray K.O., Baraniuk S., Resnick M., Arafat R., Kilborn C., Shallenberger R., et al., Clinical investigation of hospitalized human cases of West Nile virus infection in Houston, Texas, 2002–2004, *Vector Borne Zoonotic Dis.* (2008) 8:167–174.
- [124] Murray K.O., Koers E., Baraniuk S., Herrington E., Carter H., Sierra M., et al., Risk factors for encephalitis from West Nile virus: a matched case-control study using hospitalized controls, *Zoonoses Public Health* (2009) 56:370–375.
- [125] Murray K.O., Walker C., Herrington E., Lewis J.A., McCormick J., Beasley D.W.C., et al., Persistent infection with West Nile virus years after initial infection, *J. Infect. Dis.* (2010) 201:2–4.
- [126] Nasci R.S., Savage H.M., White D.J., Miller J.R., Cropp B.C., Godsey M.S., et al., West Nile virus in overwintering *Culex* mosquitoes, New York City, 2000, *Emerg. Infect. Dis.* (2001) 7:742–744.
- [127] Nasci R.S., White D.J., Stirling H., Oliver J.A., Daniels T.J., Falco R.C., et al., West Nile virus isolates

- from mosquitoes in New York and New Jersey, 1999, *Emerg. Infect. Dis.* (2001) 7:626–630.
- [128] Nash D., Mostashari F., Fine A., Miller J., O’Leary D., Murray K., et al., The outbreak of West Nile virus infection in the New York City area in 1999, *N. Engl. J. Med.* (2001) 344:1807–1814.
- [129] Nunes Duarte Dos Santos C., Determinants in the envelope E protein and viral RNA helicase NS3 that influence the induction of apoptosis in response to infection with dengue type 1 virus, *Virology* (2000) 274:292–308.
- [130] Oesterle P., Nemeth N., Young G., Mooers N., Elmore S., Bowen R., et al., Cliff swallows, swallow bugs, and West Nile virus: an unlikely transmission mechanism, *Vector Borne Zoonotic Dis.* (2010) 10:507–513.
- [131] Panthier R., Hannoun C., Beytout D., Mouchet J., Epidemiology of West Nile virus. Study of a center in Camargue. 3.-Human diseases, *Ann. Inst. Pasteur (Paris)* (1968) 115:435–445.
- [132] Parquet M.C., Kumatori A., Hasebe F., Morita K., Igarashi A., West Nile virus-induced bax-dependent apoptosis, *FEBS Lett.* (2001) 500:17–24.
- [133] Perelygin A., Scherbik S.V., Zhulin I.B., Stockman B.M., Li Y., Brinton M.A., Positional cloning of the murine flavivirus resistance gene, *Proc. Natl. Acad. Sci. USA* (2002) 99:9322–9327.
- [134] Petersen L.R., Roehrig J.T., West Nile virus: a reemerging global pathogen, *Emerg. Infect. Dis.* (2001) 7:611–614.
- [135] Petersen L.R., Hayes E.B., West Nile virus in the Americas, *Med. Clin. North Am.* (2008) 92:1307–1322.
- [136] Platonov A.E., Shipulin G.A., Shipulina O.Y., Tyutyunnik E.N., Frolochkina T.I., Lanciotti R.S., et al., Outbreak of West Nile virus infection, Volgograd Region, Russia, 1999, *Emerg. Infect. Dis.* (2001) 7:128–132.
- [137] Platt K., Tucker B., Halbur P., Blitvich B., Fabiosa F., Mullin K., et al., Fox squirrels (*Sciurus niger*) develop West Nile virus viremia sufficient for infecting select mosquito species, *Vector Borne Zoonotic Dis.* (2008) 8:225–234.
- [138] Poidinger M., Hall R.A., MacKenzie J.S., Molecular characterization of the Japanese encephalitis serocomplex of the flavivirus genus, *Virology* (1996) 218:417–421.
- [139] Pupo M., Guzmán M.G., Fernández R., Llop A., Dickinson F.O., Pérez D., et al., West Nile virus infection in humans and horses, Cuba, *Emerg. Infect. Dis.* (2006) 12:1022–1024.
- [140] Rappole J.H., Derricksen S.R., Hubálek Z., Migratory birds and spread of West Nile virus in the Western Hemisphere, *Emerg. Infect. Dis.* (2000) 6:319–328.
- [141] Rappole J.H., Hubálek Z., Migratory birds and West Nile virus, *J. Appl. Microbiol.* (2003) 94 Suppl:47S–58S.
- [142] Reisen W., Fang Y., Lothrop H., Martinez V., Wilson J., Oconnor P., et al., Overwintering of West Nile virus in Southern California, *J. Med. Entomol.* (2006) 43:344–355.
- [143] Rios J.J., Fleming J.G.W., Bryant U.K., Carter C.N., Huber J.C., Long M.T., et al., OAS1 polymorphisms are associated with susceptibility to West Nile encephalitis in horses, *PLoS ONE* (2010) 5:e10537.
- [144] Sampson B.A., Armbrustmacher V., West Nile encephalitis: the neuropathology of four fatalities, *Ann. NY Acad. Sci.* (2001) 951:172–178.
- [145] Samuel C.E., Host genetic variability and West Nile virus susceptibility, *Proc. Natl. Acad. Sci. USA* (2002) 99:11555–11557.
- [146] Samuel M., Diamond M.S., Pathogenesis of West Nile virus infection: a balance between virulence, innate and adaptive immunity, and viral evasion, *J. Virol.* (2006) 80:9349–9360.
- [147] Schneider B., Higgs S., The enhancement of arbovirus transmission and disease by mosquito saliva is associated with modulation of the host immune response, *Trans. R. Soc. Trop. Med. Hyg.* (2008) 102:400–408.
- [148] Schneider B.S., Soong L., Girard Y.A., Campbell G., Mason P., Higgs S., Potentiation of West Nile encephalitis by mosquito feeding, *Viral Immunol.* (2006) 19:74–82.
- [149] Sejvar J.J., Leis A.A., Stokic D.S., Van Gerpen J.A., Marfin A.A., Webb R., et al., Acute flaccid paralysis and West Nile virus infection, *Emerg. Infect. Dis.* (2003) 9:788–793.
- [150] Shirato K., Miyoshi H., Goto A., Ako Y., Ueki T., Kariwa H., Takashima I., Viral envelope protein glycosylation is a molecular determinant of the neuroinvasiveness of the New York strain of West Nile virus, *J. Gen. Virol.* (2004) 85:3637–3645.
- [151] Shrestha B., Gottlieb D., Diamond M.S., Infection and injury of neurons by West Nile encephalitis virus, *J. Virol.* (2003) 77:13203–13213.
- [152] Shrestha B., Zhang B., Purtha W., Klein R., Diamond M., Tumor necrosis Factor Alpha protects against lethal West Nile virus infection by promoting trafficking of mononuclear leukocytes into the central nervous system, *J. Virol.* (2008) 82:8956–8964.
- [153] Siegel-Itzkovich J., Twelve die of West Nile virus in Israel, *BMJ* (2000) 321:724.
- [154] Silverman R.H., Viral encounters with 2',5'-oligoadenylate synthetase and RNase L during the interferon antiviral response, *J. Virol.* (2007) 81:12720–12729.
- [155] Smithburn K.C., Hughs T.P., Burke A.W., Paul J.H., A neurotropic virus isolated from the blood of a

- native of Uganda, *Am. J. Trop. Med. Hyg.* (1940) 20:471–492.
- [156] Snapinn K.W., Holmes E.C., Young D.S., Bernard K.A., Kramer L.D., Ebel G.D., Declining growth rate of West Nile virus in North America, *J. Virol.* (2006) 81:2531–2534.
- [157] Suthar M., Gale Jr M., Owen D., Evasion and disruption of innate immune signalling by hepatitis C and West Nile viruses, *Cell. Microbiol.* (2009) 11:880–888.
- [158] Tatsumi R., Sekiya S., Nakanishi R., Mizutani M., Kojima S.-I., Sokawa Y., Function of ubiquitin-like domain of chicken 2'-5'-oligoadenylate synthetase in conformational stability, *J. Interferon Cytokine Res.* (2003) 23:667–676.
- [159] Taylor R., Work T., Hurlbut H., Risk F., A study of the ecology of West Nile virus in Egypt, *Am. J. Trop. Med. Hyg.* (1956) 5:579–620.
- [160] Tsai T.F., Popovici F., Cernescu C., Campbell G.L., Nedelcu N.I., West Nile encephalitis epidemic in southeastern Romania, *Lancet* (1998) 352:767–771.
- [161] Turell M.J., O'Guinn M., Oliver J., Potential for New York mosquitoes to transmit West Nile virus, *Am. J. Trop. Med. Hyg.* (2000) 62:413–414.
- [162] Venter M., Myers T.G., Wilson M.A., Kindt T.J., Paweska J.T., Burt F.J., et al., Gene expression in mice infected with West Nile virus strains of different neurovirulence, *Virology* (2005) 342:119–140.
- [163] Wachter C., Muller M., Hofer M.J., Getts D.R., Zabarar R., Ousman S.S., et al., Coordinated regulation and widespread cellular expression of interferon-stimulated genes (ISG) ISG-49, ISG-54, and ISG-56 in the central nervous system after infection with distinct viruses, *J. Virol.* (2006) 81:860–871.
- [164] Wang J.J., Liao C.L., Chiou Y.W., Chiou C.T., Huang Y.L., Chen L.K., Ultrastructure and localization of E proteins in cultured neuron cells infected with Japanese encephalitis virus, *Virology* (1997) 238:30–39.
- [165] Wicker J., Whiteman M., Beasley D., Davis C., Zhang S., Schneider B., et al., A single amino acid substitution in the central portion of the West Nile virus NS4B protein confers a highly attenuated phenotype in mice, *Virology* (2006) 349:245–253.
- [166] Wilson J.R., de Sessions P.F., Leon M.A., Scholle F., West Nile virus nonstructural protein 1 inhibits TLR3 signal transduction, *J. Virol.* (2008) 82:262–8271.
- [167] Wojnarowicz C., Olkowski A., Schwean-Lardner K., First Canadian outbreak of West Nile virus disease in farmed domestic ducks in Saskatchewan, *Can. Vet. J.* (2007) 48:1270–1271.
- [168] Work T., Hurlbut H., Taylor R., Indigenous wild birds of the Nile Delta as potential West Nile virus circulating reservoirs, *Am. J. Trop. Med. Hyg.* (1955) 4:872–888.
- [169] Xiao S.Y., Guzman H., Zhang H., Travassos da Rosa A.P., Tesh R.B., West Nile virus infection in the golden hamster (*Mesocricetus auratus*): a model for West Nile encephalitis, *Emerg. Infect. Dis.* (2001) 7:714–721.
- [170] Zeller H.G., Schuffenecker I., West Nile virus: an overview of its spread in Europe and the Mediterranean Basin in contrast to its spread in the Americas, *Eur. J. Clin. Microbiol. Infect. Dis.* (2004) 23: 147–156.