Theiler`s murine encephalomyelitis virus (TMEV)

Host species

- natural hosts: wild mice (Lipton et al. 2001), laboratory mice (Miyata & Sato 1990), water, bank and meadow voles (family Microtinae) (Descoteaux & Mihok 1986, Descoteaux 1992)
- positive serological reactions in laboratory rats (Hemelt et al. 1974, Lussier & Descoteaux 1986); only one report on clinical signs and lesions in rats (infected with the MHG virus strain) (McConnell et al. 1964); a genetically divergent theilovirus was isolated from clinically healthy, TMEV-seropositive rats and designated rat Theiler-like virus (Oshawa et al. 2003)
- guinea pigs: the presence of antibodies to TMEV in guinea pigs suffering from lameness indicates that the causative agent of guinea pig lameness may be a cardiovirus (Hansen et al. 1997)
- mice, rats, hamsters and cotton rats but not guinea pigs are susceptible to intracerebrally inoculated virus (GDVII strain) (Thompson et al. 1951, Downs 1982)

serological prevalence of TMEV in laboratory mice and rats:

- antibodies to TMEV were detected in 2.2% of mouse samplings and 2.3% of rat samplings from Western European institutions (Schoondermark-van de Ven et al. 2006)
- about 9% of US institutions reported TMEV infection in their mouse colonies (Carty 2008)
- large surveys in North America and Western Europe revealed antibodies in 0.09–0.26% of mice and 0.14–1.43% of rats monitored (Livingston & Riley 2003, Mähler & Köhl 2009, Pritchett-Corning et al. 2009)

Properties of the virus

RNA virus, family Picornaviridae, genus Cardiovirus; all TMEV strains (see below) are of the same serotype and cross-neutralize with polyclonal antisera (Rohon et al. 1982, Ohara & Roos 1987)

- different subgroups exist:
  - subgroup TO (DA, BeAn 8386, WW, TO, Yale) may produce chronic persistent infection of the central nervous system (CNS), accompanied by demyelinating lesions of the spinal cord; small plaques in cell culture
  - subgroup GDVII (FA, GDVII) produces acute fulminant encephalomyelitis; large plaques in cell culture (Lipton & Dal Canto 1979, Yamada et al. 1991)
- virus can be stored for a long period at –60 °C
- optimal stability of the virus in the vicinity of pH 8 and pH 3,3
- exposure to air has little influence on the stability of the virus
- TMEV is rapidly destroyed at temperatures above 50°C
- virus is completely inactivated by 1% H₂O₂ at 37°C and by 50% acetone or alcohol (Theiler 1940)
Strain susceptibility

- different susceptibilities of various mouse strains to TMEV-induced demyelinating disease after experimental intracerebral inoculation (Lipton & Dal Canto 1979, Dal Canto et al. 1995):
  - high susceptibility: SJL/J, DBA/2, SWR, PL/J and NZW mice
  - intermediate susceptibility: C3H/He, CBA, AKR, C57BR mice
  - resistant: BALB/C substrains, C57BL/6, C57BL/10, C57/L, 129/J and $H-2D^b$ mice; resistance to DA virus in $H-2^d$ mice maps to the $H-2D$ gene and is associated with a potent antiviral cytotoxic T-lymphocyte response (Azoulay-Cayla et al. 2001)
  - mice can be made susceptible with cyclophosphamide (cy) but resistance was restored by adoptive transfer of splenic cells from non cy-treated donors, only C57BL/6 could not be made susceptible; high doses of gamma irradiation increase susceptibility of mice (Dal Canto et al. 1995)
  - C57BL/6J mice are prone to develop acute encephalitic seizures (epilepsy) after intracerebral infection with the DA strain of TMEV (Stewart et al. 2010)
  - ABY/SnJ, BALB/cByJSmn-Prkdcscid/J, C3H/HeNTac and C3H/HeJ mice are prone to develop myocarditis after intraperitoneal infection with the DA strain of TMEV (Gómez et al. 1996, Sato et al. 2014)

Organotropism

- replication of the virus in gastrointestinal mucosa (Olitzky & Schlesinger 1941, Theiler & Gard 1940); natural infection rarely spreads from intestine to spinal cord or brain; macrophages are a reservoir of the virus (DA, TO, WW, BeAn) (Dal Canto & Rabinowitz 1982, Clatch et al. 1985) as well as oligodendrocytes, astrocytes and microglia (Rodriguez et al. 1983, Aubert & Ozden 1993); placentas and foetuses (only in early gestation) can be infected (Abzug 1993)

Clinical disease

- mice, natural infection, subgroup TO: in mice asymptomatic gastrointestinal infection (except immunodeficient mice) (Rozengurt & Sanchez 1992), the virus rarely spreads to the CNS (Theiler 1937, Thompson et al. 1951), symptoms are flaccid posterior paralysis and seldom anterior paralysis in mice that are otherwise clinically normal; incubation period: 7-30 days
- mice, natural infection, subgroup GDVII: encephalomyelitic form may be expressed clinically by excitability, circling, rolling, tremor and convulsions on noise stimulation (incubation time: 2-9 days); most of the infected mice die soon after onset of clinical signs (Theiler & Gard 1940)
- rats, MHG virus strain: case report of symptoms in 3 rats of a colony with symptoms like circling, incoordination, tremor, torticollis (McConnell et al. 1964)
- experimental infections in mice and rats (intracerebrally, intranasally or footpad inoculation), subgroup TO: wobbling gait about 2 to 4 weeks p.i., followed by weakness of the posterior limbs, spastic paralysis, urinary incontinence and priapism (Lipton 1975, Dal Canto et al. 1996); weanling rats die within 2-3 days without paralytic symptoms (Downs 1982); subgroup GDVII: hyperexcitability, circling, and flaccid paralysis which lead to death within one week (Theiler & Gard 1940, Rodriguez et al. 1987, Martinat et al. 1999)
Pathology

• mice, natural infection, subgroup TO: non-suppurative encephalomyelitis with gliosis and necrosis of ventral horn neurons of the spinal cord and neuronal necrosis in posterior regions of the brain, satellitosis, Cowdry type B intranuclear inclusion bodies in neurons are not a consistent feature of the disease (Olitzky & Schlesinger 1941), inflammation may persist for several months after necrosis subsides and is then accompanied by astrocytosis and focal mineralization (Jacoby 1988)

• mice, natural infection, subgroup GDVII (Prkdcscid mice): severe degeneration (often spongiform) and necrosis of neurons and glial cells of the ventral horns (lesser involvement of the dorsal horns of the spinal cord (Rozengurt & Sanchez 1992)

• experimental infection in mice (intracerebral inoculation), subgroup TO: acute neuronal degenerative changes and microglial proliferation primarily in the spinal cord anterior horn, brain stem and thalamus and perivascular inflammation also in the spinal cord leptomeninges, followed after 1 month p.i. by persistent viral infection of the spinal cord (white matter) with varying degrees of chronic progressive demyelination and inflammation and remyelination after a few months (resembles multiple sclerosis in man) (Lipton 1975, Downs 1982, Rodriguez et al. 1987); hydrocephalus and pachymeningitis in mice after inoculation of a DA virus variant (H101 virus), without viral persistence, no demyelination (Tsunoda et al. 1999); subgroup GDVII: acute polioencephalomyelitis with necrosis of ganglion cells and neuronophagia of hippocampus, cortex and spinal cord anterior horn and nonsuppurative inflammation, high apoptosis rate in neurons, little if any demyelination, no viral persistence in the CNS (Lipton 1980, Tsunoda et al. 1997, Obuchi & Ohara 1999)

Morbidity and mortality

• natural infection, subgroup TO: low morbidity, little or no mortality (except immunodeficient mice with high morbidity and mortality) (Rozengurt & Sanchez 1992); subgroup GDVII: high morbidity and mortality

• experimental infection (intracerebral inoculation), subgroup TO: high morbidity, low mortality; subgroup GDVII: high morbidity (100%) and mortality

Zoonotic potential

• none

Interference with research

Physiology

• electrophysiologic abnormalities and reduced motor coordination in SJL/J mice infected with the DA strain of TMEV (McGavern et al. 2000)

• restraint stress has an effect on CBA mice infected with the BeAn strain (increased mortality, increased viral titres, decreased number of lymphocytes, alterations in chemokine expression) (Campbell et al. 2001, Mi et al. 2004)

• DA-infected C57BL/6J mice show disrupted spatial memory formation (Buenz et al. 2006)

• DA-infected SJL/J mice display neurological deficits (using Rotarod analysis) and exhibit thermal hyperalgesia and mechanical allodynia (Lynch et al. 2008)
• seized C57BL/6 mice inoculated with the DA strain display impaired cognitive ability and anxiety-like behaviour (Umpierre et al. 2014)

Pathology
• lesions of demyelination in the CNS of mice with clinically inapparent, chronic TMEV infection may interfere with studies that require evaluation of the CNS (Krinke & Zurbriggen 1997)

Cell biology
• high apoptosis rate in neurons in GDVII-infected SJL/J mice, high apoptosis rate in oligodendrocytes in DA-infected SJL/J mice (Tsunoda et al. 1997)
• GDVII infection induces apoptosis in cultured murine astrocytes through TNF-receptor and TNF-related apoptosis-inducing ligand (Rubio et al. 2003)
• BeAn infection induces upregulation of the programmed death-1 pathway in bone marrow-derived dendritic cells in vitro and in the spinal cord of SJL/J mice (Takizawa et al. 2014)
• BeAn infection of cultured murine macrophages induces apoptosis through the intrinsic pathway (Son & Lipton 2015)
• multiple matrix metalloproteinases (e.g. MMP-3 and -12), inhibitors of MMPs (e.g. TIMP-1) and extracellular matrix molecules are upregulated in the spinal cord of BeAn-infected SJL/J mice (Ulrich et al. 2006, Haist et al. 2012)
• multiple matrix metalloproteinases (MMP-3, -9, -10, -12 and -13) and TIMP-1 are upregulated in mouse astrocytes infected with the BeAn strain in culture; in contrast, BeAn infection is associated with downregulation of MMPs and TIMPs in cultured microglia (Kumnok et al. 2008)
• BeAn infection of cultured mouse astrocytes results in stimulation of the GTP-binding activity and the GTPase activity (Rubio et al. 2008)
• TMEV blocks oligodendrocytic differentiation in vitro (Pringproa et al. 2010)
• Ca²⁺ channels are upregulated in mouse astrocytes infected with the BeAn strain in culture (Rubio et al. 2013)
• retinoic acid inducible gene-I and melanoma differentiation-associated gene 5 are upregulated in mouse cochlear sensory epithelial cells ex vivo infected with GDVII (Hayashi et al. 2013)
• changes of microglia/macrophage M1 and M2 polarisation in BeAn-infected SJL mice (Herder et al. 2014)

Immunology
• chronic CD4+ response which is initially directed at viral determinants but persists in the CNS and is directed against multiple myelin autoepitopes; T cell proliferative response in the spleen (Dal Canto et al. 1996)
• increase of CD4+ Th1-cells producing IFN-γ (DA strain) (Monteyne et al. 1999)
• high mRNA expression of proinflammatory cytokines in the brain and spinal cord of SJL/J mice beginning at day 5 post infection for TNF-α and INF-γ; high chemokine (RANTES, MCP-1, IP-10, MIP-1β, MIP-1α, MIP-2) mRNA expression after DA, GDVII and H101 virus infections; in addition, high IFN-β and IL-6 mRNA expression during GDVII infection and high LT-α mRNA expression during DA infection (Hoffman et al. 1999, Murray et al. 2000, Theil et al. 2000)
interleukin-1 receptor declines in the hippocampus of DA-infected SJL/J mice (Lledo et al. 1999)

inhibition of IFN-α/β synthesis in infected L929 cells (van Pesch et al. 2001)

BeAn infection upregulates microglial expression of various cytokines (type I interferons, TNF-α, IL-1β, IL-6, IL-10, IL-12, IL-18, GM-CSF), chemokines (MIP1α, MCP-1, RANTES), MHC class II, costimulatory molecules (B7-1, B7-2, CD40, ICAM-1) and toll-like receptors (TLRs 2, 3, 5, 9) in vitro (Olson et al. 2001, Olson & Miller 2004)

infection of cultured murine astrocytes with TMEV results in a time-dependent phosphorylation of IκBα, degradation of IκBα and IκBβ, activation of NF-κB, and expression of NOS-2, COX-2 and PGE₂ (Molina-Holgado et al. 2002a, 2002b, Palma et al. 2003)

BeAn infection induces expression of type I interferons and IFN-γ in cultured dendritic cells (Hou et al. 2007)

upregulation of B-lymphocyte chemoattractant, G-CSF, IL-10, IFN-α4, IFN-β and IFN-γ in cultured murine macrophages infected with the DA strain (Himeda et al. 2010)

BeAn infection induces the development of Th17 cells in vitro and in vivo in an IL-6-dependent manner (Hou et al. 2009)

multiple Toll-like receptors and kallikreins (in particular Klk6 and Klk8) are upregulated in the CNS of TMEV-infected mice (Turrin 2008, Panos et al. 2014)

increased numbers of CD3+ T cells, Foxp3+ regulatory T cells, CD45R+ B cells and GFAP+ astrocytes and elevated transcription levels of TNF, IFN-γ, IL-1, IL-2, IL-10, IL-12 and TGF-β1 in the brain of SJL/J and/or C57BL/6 mice during the acute phase of DA infection (Herder et al. 2012)

increased expression of the T-cell immunoglobulin and mucin domain-3 (TIM-3) in the spinal cord of mice with TMEV-induced demyelinating disease (Kaneyama et al. 2014)

**Interactions with other infectious agents**

infection with mouse cytomegalovirus attenuates the disease course in the TMEV-induced model of multiple sclerosis (Pirko et al. 2012)

**References**

Aubert C and Ozden S. Comparison of the sensitivities of ribonucleic acid and oligonucleotide probes for in situ detection of Theiler's virus mRNA. *J Histochem Cytochem* 1993; 41: 1099–1103.


Lipton HL, Kim BS, Yahikozawa H, et al. Serological evidence that Mus musculus is the natural host of Theiler's murine encephalomyelitis virus. Virus Res 2001; 76: 79–86.


**Authors:** Bettina Kränzlin (Mannheim) / Michael Mähler (Hannover) (revised 2015)