Supplementary table S1: Interleukins involved in West Nile virus pathogenesis.

Cytokine	Model	Host	Expression	Source	Role in WNV pathogenesis	Reference
IL-1 α	*In vitro*	Horse	Upregulation	PBMCs	Unknown	[1]
	In vivo	Mouse	No change	Blood/Brain		[2–4]
			Upregulation	Blood/brain/ lung/ liver		[5–8]
			Strain-dependent	Brain		[9]
IL-1 β	*In vitro*	Human	No change	Astrocytes/ Resting MΦ/ U-937/ BMDCs	Unknown	[10–14]
			Upregulation	Neural stem cells/ U373/ LAN-2/MΦ/ SK-N-SH cells/ Activated MΦ/ NK cells	Direct neurotoxic effects in SK-N-SH cells	[11,12,15–18]
			Strain-dependent	THP-1/ THP-1-derived MΦ	Unknown	[19]
		Pig (*Sus domesticus*)	No change	BMDCs	Unknown	[13]
		Mouse	Upregulation	Primary BMECs and astrocytes	Mediates the ability of CXCR4 expressing lymphocytes to adhere to BMECs via CXCL12 expression.	[20]
				Peritoneal exudate cells	Expression may be induced by WNV envelope protein	[21]
				MΦ and BMDCs	Reduces WNV replication. Protective via the modulation of type I IFN responses dependent on the IRF3.	[22]
				BMDCs	Induced by WNV via ASC	[23]
				Cortical neurons	Reduces WNV replication. Synergizes with type I IFN to induce ISGs.	[2]
			Strain-dependent	MΦ	Unknown	[24]
	In vitro/ in vivo	Horse	Upregulation	PBMCs	Unknown	[1]
	In vivo	Horse	Upregulation	Lymphoid tissue	Unknown	[25]

		Mouse	-	-	Mediates langerhans cell migration and accumulation in the draining lymph nodes upon WNV cutaneous infection	[26]
			Variable	Popliteal lymph node/spleen	Unknown	[2,27]
			No change	Serum		
			Upregulation	Brain	Reduces WNV replication in the brain. Promotes CNS-Intrinsic Immune Control. Prevents synapse recovery and promotes spatial learning defects during WNV recovery	[2–4,27–29]
			Strain-dependent	Brain	Unknown	[9]
		Rabbit (*Oryctolagus cuniculus*)	Upregulation	Draining lymph nodes	Unknown	[30]
IL-1ra	*In vivo*	Mouse	Upregulation	Spleen/ Lung/ kidney	Unknown	[7]
		NHP (*Macaca mulatta)*	Upregulation	Brain/spinal cord	Unknown	[31]
IL-2	*In vivo*	Mouse	Upregulation	Brain	Unknown	[28,32]
	In vitro	Mouse	Upregulation	CD4+ T	Unknown	[33]
IL-3	*In vivo*	Mouse	Upregulation	Liver/kidney	Unknown	[7]
			Downregulation	Brain	Unknown	[28]
IL-4	*In vitro*	Human	-	BMDCs	No effect on viral replication	[34]
			No change	BMDCs	Unknown	[35]
			Downregulation	BMDCs	Unknown	[36]
	In vivo	Mouse	No change	Brain	Unknown	[27]
			Downregulation	Brain	Unknown	[28]
		Rabbit (*Oryctolagus cuniculus* and *Sylvilagus sp)*	Upregulation	Lymph nodes	Unknown	[37]
IL-5	*In vivo*	Mouse	No change	Brain	Unknown	[27]
			Upregulation	Brain	Unknown	[8]
			Downregulation	Brain	Unknown	[28]

IL-6	*In vitro*	Human	No change	Astrocytes/ BMDCs	Unknown	[10,35]
			Upregulation	Microglia/ SK-N-SH/ keratinocytes	Does not interfere with WNV-induced cytotoxicity in SK-N-SH.	[10,16,38]
		Human	Strain-dependent	THP-1/ THP-1-derived MΦ	Unknown	[19]
		Mouse	Upregulation	MΦ/H36.12j/ Renca/ Peritoneal exudate cells/ γδ T cells	Unknown	[21,24,39,40]
			-	N2a/ cortical neurons	Directly responsible for neuronal apoptosis.	[41]
	In vitro/ in vivo	Rabbit	Upregulation	PBMCs	Unknown	[42]
	In vivo	Mice	Upregulation	Blood/ brain	Does not impact mortality rates following lethal WNV-infection/ Production in plasma and brain mediated by Toll-like receptor 3.	[8,29,41,43]
		Rabbit (*Oryctolagus cuniculus* and *Sylvilagus sp)*	Upregulation	Brain/ spleen	Unknown	[37]
	Ex vivo	Mouse	Upregulation	Spinal cord slice	Unknown	[44]
IL-7	*In vivo*	Mouse	Upregulation	Brain	Unknown	[8]
			Strain-dependent	Brain	Unknown	[9]
IL-10	*In vitro*	Human	No change	BMDCs	Unknown	[14,34]
		Mouse	Upregulation	Peritoneal exudate cells/ MΦ	Negatively regulates TNF-α, IL-12/23p40 and type I interferon expression in MΦ.	[21,45]
			-	Splenocytes	Negatively regulates IL-12/23p40 and type I interferon expression in splenocytes.	[45]
	In vivo	Mouse	-	-	Promotes viral replication in the periphery and in the CNS via the I.P. and footpad route, not I.C. route. Decreases IL-12/23 p40 and TNF-α and increases mortality rates	[45]

			Upregulation	Serum/spleen/ lung/ liver/ brain	Unknown	[7,8,27,28,46]
		Rabbit (*Oryctolagus cuniculus* and *Sylvilagus sp)*	Upregulation	Brain/ spleen/ lymph nodes	Unknown	[37]
		Horse	Upregulation	Brain	Unknown	[25]
		NHP (*Macaca mulatta)*	Upregulation	Brain/spinal cord	Unknown	[31]
IL-11	*In vivo*	Mouse	Upregulation	Brain	Unknown	[27]
IL-12	*In vitro*	Human	No change	BMDCs	Unknown	[14,34,35]
			Strain-dependent	THP-1/ THP-1-derived MΦ	Unknown	[19]
		Mouse	Upregulation	Keratinocytes/ microglia	Unknown	[47,48]
		Rabbit (*Oryctolagus cuniculus)*	Upregulation	PBMCs	Unknown	[42]
	In vivo	Mouse	-	-	IL-12 p35 does not impact survival rate following WNV-challenge/ Does not interfere with brain infiltration or homing of leukocytes.	[49]
			Upregulation	Blood/ Spleen/ lung/ liver/ brain/DCs	Produced via TLR7-MyD88 signaling during WNV infection.	[7,43,50]
IL-13	*In vivo*	Mouse	No change	Brain	Unknown	[27]
			Upregulation	Serum/lung/kidney	Unknown	[7,8]
			Downregulation	Brain	Unknown	[28]
			Strain-dependent	Brain	Unknown	[8]
IL-15	*In vitro*	Human	No change	BMDCs	Unknown	[35]
	In vivo	Mouse	Upregulation	Spleen/ lung/ brain	Unknown	[7,27,32]
		Horse	Upregulation	Thalamus/ cerebrum	Unknown	[51]
IL-16	*In vivo*	Mouse	Downregulation	Brain	Unknown	[28]
IL-17A	*In vitro*	Human	Upregulation	PBMCs	Unknown	[52]
	In vivo	Mouse	Upregulation	Serum/ liver/ brain	Protects mice from lethal WNV infection and facilitates CD8+T cell cytotoxicity. IL-17A production during WNV infection in mice largely	[7,32,52]

					depends on IL-23 signaling.	
			Strain-dependent	Brain	Unknown	[8]
IL-17B	*In vivo*	Mouse	Downregulation	Brain	Unknown	[28]
IL-18	*In vitro*	Human	No change	BMDCs/ SK-N-SH	Unknown	[14,16]
	In vivo	Mouse	Upregulation	Lung/ spleen	Unknown	[7]
IL-20	*In vivo*	Mouse	Downregulation	Brain	Unknown	[28]
IL-22	*In vivo*	Mouse	-	-	Enhances footpad WNV-lethal infection/ Facilitates WNV Entry into the CNS/ Promotes CXCL1, CXCL5 and Cxcr2 expression	[53]
			Upregulation	Lung/kidney	Unknown	[7]
		Horse	Upregulation	Peripheral blood leukocytes/ Thalamus/ cerebrum/ lymphoid tissue	Unknown	[25,51]
IL-23	*In vitro*	Human	No change	BMDCs	Unknown	[14]
	In vivo	Mouse	-	-	Protects mice from lethal WNV-challenge. Mediates brain infiltration and homing of leukocytes.	[49]
			Upregulation	Lung/kidney	Unknown	[7]
IL-33	*In vivo*	Mouse	Upregulation	Spleen MΦ	Unknown	[54]

Cell lines: H36.12j; *Mus musculus* (macrophage cell line) ATCC CRL-2449™; Renca *Mus musculus* (Kidney epithelial cells line) ATCC CRL-2947™; retinal pigment epithelium cell line (ARPE-19): L929 ATCC CCL-1™; LAN-2: *Mus musculus* neuroblastoma cell line (RRID:CVCL_1829); U-937: *Homo sapiens* Lymphoma cell line CRL-1593.2™; U373: *Homo sapiens* glioblastoma astrocytoma cell-line; SK-N-SH *Homo sapiens* neuroblastoma cell line ATCC HTB-11™; THP-1: Monocytic leukemia cells ATCC TIB-202 ; N2a : *Mus musculus* (neuroblastoma cell line) ATCC CCL-131™.

Abbreviations: ASC: Apoptosis-associated speck-like protein containing C-terminal caspase recruitment domain [CARD]; BMDCs: Bone marrow-derived dendritic cells; BMECs: Brain microvasculature endothelial cells; BMECs: Brain microvascular endothelial cells; CNS: Central nervous system; DCs: Dendritic cells; RPE: retinal pigment epithelium (RPE), ISGs: Interferon-stimulated genes; I.C. : Intracranial ; I.P.: Intra-peritoneal; IFN: Interferon, IRF: IFN regulatory factor 3; MΦ: Macrophages; NHP: Non-Human primate; PBMCs: Peripheral blood mononuclear cells.

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Supplementary table S2: Chemokines involved in West Nile virus pathogenesis.

Cytokine	Mode	Host	Expression	Source	Role in WNV pathogenesis	Reference
	CC- Chemokines					
CCL1	*In vivo*	Mouse	Downregulation	Brain	Unknown	[1]
CCL2	*In vitro*	Human	No change	LAN-2/ U-937/ MΦ/ BMDCs/ BMECs/ astrocytes	Unknown	[2–4]
			Upregulation	Microglia/ U373/ ARPE-19/RPE	Unknown	[2,5,6]
			Strain-dependent	SK-N-SH cells.	Unknown	[7]
		Mouse	Upregulation	Microglia/ neurons	Unknown	[8,9]
	In vivo	Mouse	-	-	Mediates monocytes migration and differentiation into DC in the skin and auricular lymph node	[10]
			Upregulation	Serum/ spleen/ lung/ liver/ brain	Not required for survival/ neutralization enhances survival Participates in monocytosis and monocytes trafficking to the brain	[1,9,11–20]
				Neurons/ astrocytes/ microglia/ inflammatory cells/ endothelial cells	Unknown	[21]
			Strain-dependent	Brain	Unknown	[22]
		NHP (*Macaca mulatta)*	Upregulation	Brain/spinal cord	Unknown	[23]
	In vivo	Mouse	Upregulation	Spinal cord slice	Unknown	[24]
CCL3	*In vitro*	Human	No change	BMDCs	Unknown	[3]
	In vivo	Mouse	Upregulation	Serum/ brain/spleen	Unknown	[1,9,11,12,14–16,25]
			Strain-dependent	Brain	Unknown	[22]
		NHP	Upregulation	Brain/spinal cord	Unknown	[23]

		(*Macaca mulatta)*				
	In vivo	Mouse	Upregulation	Spinal cord slice	Unknown	[24]
CCL4	*In vitro*	Human	No change	BMDCs	Unknown	[3]
			Upregulation	NK cells	Unknown	[26]
		Mouse	Upregulation	Microglia	Unknown	[8]
	In vivo	Mouse	Upregulation	Brain/ spleen/ lung	Unknown	[9,11–14,16,25]
			Strain-dependent	Brain	Unknown	[22]
CCL5	*In vitro*	Human	No change	BMDCs	Unknown	[3]
			Upregulation	Astrocytes/ Microglia/ ARPE-19/RPE/ SK-N-SH/ MΦ/ BMECs	Unknown	[4–7,27]
			Strain-dependent	THP-1/ THP-1-derived MΦ	Unknown	[28]
		Mouse	Upregulation	MΦ/ neurons	Unknown	[9,29]
	In vivo	Mouse	Upregulation	Serum/brain/spleen/ lung	Unknown	[1,9,11–16,25]
				Astroglia	Unknown	[21]
			Strain-dependent	Brain	Unknown	[22]
		NHP (*Macaca mulatta)*	Upregulation	Brain/spinal cord	Unknown	[23]
		Rabbit (*Oryctolagus cuniculus*)	Upregulation	Draining lymph nodes	Unknown	[30]
	In vivo	Mouse	Upregulation	Spinal cord slice	Unknown	[24]
CCL6[1]	*In vivo*	Mouse	Upregulation	Brain	Unknown	[13]
CCL7	*In vivo*	Mouse	Upregulation	Blood/ spleen/ lung/ liver/ brain	Required for efficient monocytosis, recruitment of neutrophils and CD8+ T cells into the CNS, survival after lethal challenge and viral clearance from the brain, not blood or spleen.	[1,9,11,15,17,18,20]
			Strain-dependent	Brain	Unknown	[22]

CCL8	*In vitro*	Human	Upregulation	MΦ	Unknown	[27]
	In vivo	Mouse	Upregulation	Brain	Unknown	[1]
			Strain-dependent	Brain	Unknown	[22]
		NHP (*Macaca mulatta)*	Upregulation	Brain/spinal cord	Unknown	[23]
CCL9	*In vivo*	Mouse	Upregulation	Brain	Unknown	[1]
CCL11	*In vivo*	Mouse	Upregulation	Lung/ Brain	Unknown	[11,12]
CCL12[1]	*In vivo*	Mouse	Upregulation	Brain	Unknown	[1,13,18]
CCL13	*In vivo*	Mouse	Upregulation	Brain	Unknown	[16]
CCL15	*In vivo*	Rabbit (*Oryctolagus cuniculus*)	Downregulation	Draining lymph nodes	Unknown	[30]
CCL17	*In vivo*	Mouse	Upregulation	Lung	Unknown	[11]
		Rabbit (*Oryctolagus cuniculus*)	Downregulation	Draining lymph nodes	Unknown	[30]
CCL18	*In vivo*	Mouse	Upregulation	Brain	Unknown	[18]
CCL19	*In vivo*	Mouse	No change	Brain	Unknown	[9]
			Upregulation	Spleen/ lung/ brain	Unknown	[1,11]
			Strain-dependent	Brain	Unknown	[22]
CCL20	*In vitro*	Human	Upregulation	ARPE-19/RPE/ keratinocytes	Unknown	[6,31]
	In vivo	Mouse	Downregulation	Brain	Unknown	[1]
CCL21	*In vivo*	Mouse	No change	Brain	Unknown	[9]
			Upregulation	Lung	Unknown	[11]
		Rabbit (*Oryctolagus cuniculus*)	Downregulation	Draining lymph nodes	Unknown	[30]
CCL22	*In vivo*	Mouse	Upregulation	Lung/kidney	Unknown	[11]
CCL24	*In vivo*	Mouse	Upregulation	Spleen/ lung/ liver	Unknown	[11]
			Downregulation	Brain	Unknown	[1]
CC- Chemokines receptors						

Ccr1	*In vivo*	Mouse	Upregulation	Lung/brain	Unknown	[10, 14]14]
Ccr2	*In vivo*	Mouse	Upregulation	Lung/brain	Protects from lethal challenge and promotes viral clearance from the CNS. Required for monocytosis and accumulation of monocytes in the brain by regulating blood monocyte levels, not trafficking from blood to brain.	[1,11,18]
Ccr3	*In vitro*	Human	Upregulation	MΦ	Restricts viral replication	[27]
	In vivo	Mouse	Upregulation	Brain	Unknown	[1]
Ccr4	*In vivo*	Mouse	Downregulation	Brain	Unknown	[1]
		Rabbit (*Oryctolagus cuniculus*)	Downregulation	Draining lymph nodes	Unknown	[30]
Ccr5	*In vivo*	Mouse	-	-	Enhances survival following WNV challenge Controls viral loads in the brain and the BBB permeability	[32]
			-	CD4+ and CD8+ T cells, NK, MΦ	Crucial for survival and viral clearance in the brain not the spleen Promotes leukocyte trafficking to the CNS	[14]
			Upregulation	Brain	Unknown	[14,18]
		Rabbit (*Oryctolagus cuniculus*)	Upregulation	Draining lymph nodes	Unknown	[30]
Ccr6	*In vivo*	Mouse	Downregulation	Brain	Unknown	[1]
Ccr7	*In vivo*	Mouse	-	Brain	Required for survival DC and T cell trafficking to the lymph nodes Does not impact leukocyte accumulation or T cell priming in the spleen Limits the infiltration of WNV-infected myeloid cells into the CNS.	[14,32][14,
Ccr8	*In vivo*	Mouse	Downregulation	Brain	Unknown	[1]
		Rabbit (*Oryctolagus*	Downregulation	Draining lymph nodes	Unknown	[30]

		cuniculus)				
Ccr9	*In vivo*	Mouse	Upregulation	Brain	Unknown	[1]
	CX-Chemokines					
CXCL1	*In vitro*	Human	Upregulation	MΦ/ keratinocytes	Unknown	[31,34]
		Mouse	Upregulation	Neutrophils/ MΦ	Unknown	[34]
	In vivo	Mouse	Upregulation	Serum/ brain	Unknown	[1,12,14,20]
			Strain-dependent	Brain	Unknown	[22]
		NHP (*Macaca mulatta)*	Upregulation	Brain/spinal cord	Unknown	[23]
	Ex vivo	Mouse	Upregulation	Spinal cord slice	Unknown	[24]
CXCL2	*In vitro*	Human	Upregulation	MΦ/ keratinocytes	Unknown	[31,34]
		Mouse	Upregulation	Neutrophils/ MΦ	Unknown	[34]
	In vivo	Mouse	Upregulation	Lung/ liver/ brain	Unknown	[11–14,16,20]
CXCL3	*In vivo*	Mouse	Upregulation	Spleen/ kidney	Unknown	[11]
CXCL4	*In vivo*	Mouse	Upregulation	Brain	Unknown	[14]
CXCL5	*In vivo*	Mouse	Upregulation	Spleen/ brain	Unknown	[11,12]
CXCL8/IL-8[2]	*In vitro*	Human	No change	Activated MΦ	Unknown	[35]
			Upregulation	MΦ/ SK-N-SH/ ARPE-19/RPE/ keratinocytes/ BMDCs/ plasmacytoid DCs	Not responsible for WNV-induced cell death in SK-N-SH	[6,27,31,35–37]
			Strain-dependent	SK-N-SH	Unknown	[7]
	In vivo	NHP (*Macaca mulatta)*	Upregulation	Brain/spinal cord	Unknown	[23]
CXCL9	*In vitro*	Human	No change	BMDCs	Unknown	[3]
		Mouse	Upregulation	Neurons	Unknown	[9]
	In vivo	Mouse	-	-	Not required for survival after lethal challenge	[38]
			Upregulation	Spleen/ lung/ liver/ brain	Unknown	[9,11–16,20]
		Horse	Upregulation	Thalamus/ cerebrum	Unknown	[39]
		Rabbit	Upregulation	Draining lymph nodes	Unknown	[30]

		(*Oryctolagus cuniculus*)				
CXCL10/IP10	*In vitro*	Human	Upregulation	Astrocytes/ Microglia/ THP-1-derived MΦ/ MΦ/ LAN-2/ PBMCs/U373/ U-937/ ARPE-19/RPE/ SK-N-SH/ keratinocytes/ BMDCs/ Plasmacytoid DCs	Unknown	[2,5–7,27,28,31,34,37,40]
			Strain-dependent	THP-1	Unknown	[28]
		Mouse	Upregulation	Neutrophils/ MΦ/ microglia	Unknown	[8,29,34]
		Rabbit (*Oryctolagus cuniculus*)	Upregulation	Draining Lymph nodes/ PBMCs	Unknown	[30,41]
	In vivo	Mouse	Upregulation	Serum/ spleen/ lung/ liver/ brain	Required for T-lymphocyte recruitment into the CNS, control of viral infection, and survival after WNV lethal challenge	[1,9,11–16,20,25,38,42]
				Neurons/ neutrophils/ astroglia	Unknown	[21]
			Strain-dependent	Brain	Unknown	[22]
		Rabbit (*Oryctolagus cuniculus* and *Sylvilagus sp)*	Upregulation	Spleen/LNs/ Brain	Unknown	[43]
		NHP (*Macaca mulatta)*	Upregulation	Brain/spinal cord	Unknown	[23]
		Horse	Upregulation	Lymphoid tissue/ brain	Unknown	[44]
	In vivo	Mouse	Upregulation	Spinal cord slice	Unknown	[24]
CXCL11	*In vitro*	Mouse	Upregulation	Neurons	Unknown	[9]
	In vivo	Mouse	Upregulation	Brain	Unknown	[1,15]
		NHP	Upregulation	Brain/spinal cord	Unknown	[23]

		(*Macaca mulatta)*				
		Rabbit (*Oryctolagus cuniculus*)	Upregulation	Draining lymph nodes	Unknown	[30]
CXCL12	*In vitro*	Mouse	-	BMECs	IL-1β mediates the ability of Cxcr4 expressing lymphocytes to adhere to BMECs via CXCL12 expression on their basolateral surface	[45]
	*I*n vivo	Mouse	No change	Brain	Unknown	[20,46]
			Downregulation (β isoform)	Brain	Unknown	[45,46]
			Upregulation	Brain	Unknown	[22]
	In vivo	Mouse	Upregulation	Primary BMECs and astrocytes	CXCL12 expression at the CNS microvasculature is IL-1- mediated and regulates the efficient parenchymal entry of T lymphocytes.	[45]
CXCL13	*In vivo*	Mouse	No change	Brain/spleen	Unknown	[25]
			Upregulation	Brain	Unknown	[1,15]
			Strain-dependent	Brain	Unknown	[22]
		NHP (*Macaca mulatta)*	Upregulation	Brain/spinal cord	Unknown	[23]
CXCL14	*In vivo*	Mouse	Upregulation	Brain	Unknown	[25]
			Strain dependent	Spleen	Unknown	[25]
CXCL15	*In vivo*	Mouse	Downregulation	Brain	Unknown	[1]
CXCL16	*In vivo*	Mouse	Strain-dependent	Brain	Unknown	[22]
CX-Chemokines receptors						
Cxcr2	*In vivo*	Mouse	-	-	Enhances viremia and death	[34]
Cxcr3	*In vitro*	Human	Upregulation	MΦ	Restricts viral replication	[27]
		Mouse	No change	Microglia	Unknown	[47]

			Downregulation	Neurons	Does not influence viral replication. Leads to cell death at early time-points. Expression on neurons via TNFR1 signaling.	[47]
	In vivo	Mouse	-	-	Required for survival after lethal WNV-challenge and for CD8+ T cells control of WNV infection within the cerebellum.	[38]
			Downregulation during early phase	Neurons/ CD8+ T cells	Unknown	[47]
			Upregulation	Brain	Unknown	[14,18]
Cxcr4	*In vivo*	Mouse	-	Macrophage/ microglia/ CD8+ T cells	Enhances mortality and viral loads in the brain via downregulating T cells trafficking Increases glial cells activation	[46]
			Upregulation	Lung/ brain	Unknown	[11,14,16]
CX3C Chemokine and its receptor						
CX3CL1	*In vivo*	Mouse	Upregulation	Brain (microglia/monocytes)	Does not impact survival following WNV challenge. Monocytes (microglial precursor) recruitment to the brain.	[14]
		NHP (*Macaca mulatta)*	Upregulation	Spinal cord	Unknown	[23]
Cx3cr1	*In vivo*	Mouse	Upregulation	-	Does not impact survival following WNV challenge.	[14,19,33]
		NHP (*Macaca mulatta)*	Downregulation	Cerebrum/ spinal cord	Unknown	[23]
XC chemokine receptor						
Xcr1	*In vivo*	Mouse	Downregulation	Brain	Unknown	[1]

[1] Present only in mice

[2] Present only in humans

Cell Lines: H36.12j; *Mus musculus* (macrophage cell line) ATCC CRL-2449™; Renca *Mus musculus* (Kidney epithelial cells line) ATCC CRL-2947 ™; retinal pigment epithelium cell line (ARPE-19): L929 ATCC CCL-1™; LAN-2: *Mus musculus* neuroblastoma cell line (RRID:CVCL_1829); U-937: *Homo sapiens* Lymphoma cell line CRL-1593.2 ™; U373: *Homo sapiens* glioblastoma astrocytoma cell-line; SK-N-SH *Homo sapiens* neuroblastoma cell line ATCC HTB-11™; THP-1: Monocytic leukemia cells ATCC TIB-202™.

Abbreviations: ASC: Apoptosis-associated speck-like protein containing C-terminal caspase recruitment domain [CARD]; BBB: Blood-brain barrier; BMDCs: Bone marrow-derived dendritic cells; BMECs: Brain microvasculature endothelial cells; BMECs: Brain microvascular endothelial cells; CNS: Central nervous system; DCs: Dendritic cells; NHP: Non-Human primate; RPE: retinal pigment epithelium (RPE); IFN: Interferon, IRF: IFN regulatory factor 3; MΦ: Macrophages; PBMCs: Peripheral blood mononuclear cells.

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Supplementary table S3: Tumor necrosis factor superfamily ligands involved in West Nile virus pathogenesis.

Cytokine	Model	Host	Expression	Source	Role in WNV pathogenesis	Reference
TNF- α	*In vitro*	Human	No change	Astrocytes/	Unknown	[1]
			Upregulation	Microglia/ Neural stem cells/ BMDCs/ SK-N-SH/ MΦ/ ARPE-19/RPE/ keratinocytes	WNV infection induces antiviral indoleamine via TNFα. Neurotoxic	[1–9]
			Strain-dependent	THP-1/ THP-1-derived MΦ	Unknown	[10]
		Pig (*Sus domesticus*)	Upregulation	BMDCs	Unknown	[3]
		Mouse	Upregulation	Splenic and brain CD8+ T cell /neurons/ MΦ/ DCs/ H36.12j/ Renca/ γδ T cells/ microglia	Downregulates CXCR3 expression on neurons via TNFR1 signaling. Enhances neurons survival at early time-points. Reduces viral replication in MΦ and fibroblasts, not neurons and DCs. Not required to upregulate MHC-I in fibroblasts/ Does not activate NF-κB during WNV infection of fibroblasts	[11–17]
				Peritoneal exudate cells	Expression may be induced by WNV envelope protein	[18]
			Strain-dependent	MΦ	Unknown	[19]
			-	Microglia/ N2a and primary cultures of murine cortical neurons	Production in microglia mediated by TLR3. Direct neuronal injury.	[20]
	In vivo	Mouse	Upregulation	Blood/liver/ spleen/ kidney/ brain	Variable effects on viral replication and survival after WNV challenge. Controls leukocyte infiltration in the CNS/ down-regulates neuronal CXCR3 and subsequent neuronal apoptosis/ enhances BBB permeability. Expression positively regulated by SARM and TLR3 in the brain. Does not affect the early antibody responses and CD8+ T cells priming in the spleen after WNV infection.	[13,18,20–29]

			-	-	TNF-/- mice developed severe limbic seizures like wild type mice. Does not affect Langerhans cell migration and accumulation in the draining lymph nodes and viral entry into the CNS	[30–32]
			Strain-dependent	Brain	Unknown	[33]
		Rabbit (*Oryctolagus cuniculus* and *Sylvilagus sp.)*	Upregulation	PBMCs/ brain/ lymph nodes	Unknown	[34,35]
		Horse	Upregulation	Lymphoid tissue	Unknown	[36]
		NHP (*Macaca mulatta)*	Upregulation	Brain/spinal cord	Unknown	[37]
	In vivo	Mouse	Upregulation	Spinal cord slice	Unknown	[38]
TRAIL	***In vitro***	Mouse	-	Cortical neurons	CD8+ T cells require TRAIL to optimally control WNV infection in neurons.	[39]
			Negatively correlated to replication rate	L929	Unknown	[40]
	In vivo	Mouse	-	-	Protected mice from lethal infection and enhanced viral clearance from the CNS. Reduced viral replication in the CNS and not in the serum or spleen when footpad- infected, not intracranially-infected. Did not affect trafficking of leukocytes to the brain neither adaptive B nor T cell responses induction after WNV infection.	[39]
			Upregulation	Brain	Unknown	[28]
			Strain-dependent	Brain	Unknown	[33]
			Negatively correlated to replication rate	L929	Unknown	[40]
		Rabbit (*Oryctolagus cuniculus*)	Upregulation	Draining lymph nodes	Unknown	[30]
	In vivo	Mouse	Upregulation	Spinal cord slice	Unknown	[38]

FasL	*In vitro*	Mouse	Upregulation	Cortical neurons	Used by CD8+ T cells to control neuronal infection.	[41]
	In vivo	Mouse	Upregulation	Lung/brain	Protects mice from lethal WNV infection Required for the clearance of WNV infection from the CNS	[23,33,41]
			-	-	Does not protect mice from lethal infection	[42]
		NHP (*Macaca mulatta)*	Upregulation	Brain/spinal cord	Unknown	[37]
CD40L	*In vivo*	Mouse	-	-	Protects from lethal WNV infection Required for efficient production of neutralizing antibodies, trafficking of CD8+ T cells into the brain, and control of WNV replication in the CNS not the serum and spleen.	[43]
			Upregulation	Brain	Unknown	[28]
OX40L	*In vitro*	Human	Upregulation	BMDCs	Unknown	[44]
TWEAK	*In vivo*	Mouse	Upregulation	Brain	Unknown	[45]
LIGHT	*In vitro*	Human	Upregulation	A172	Unknown	[46]
	In vivo	Mouse	Upregulation	Lung/brain	Unknown	[23]
BAFF	*In vivo*	Mouse	-	-	Not essential to control virus replication at early stages of WNV infection, but they are critical for viral clearance from sera, spleen and brain	[47]
			Upregulation	Neutrophils/ DCs	BAFF from DCs, not neutrophils, is required for protective immunity to WNV	[48]

Cell Lines: H36.12j; *Mus musculus* macrophage cell line ATCC CRL-2449; Renca *Mus musculus* Kidney epithelial cells line ATCC CRL-2947; ARPE-19 : *Homo sapiens* Retinal pigment epithelium cell line CRL-2302; L929 : *Mus musculus* fibroblastic cell line ATCC CCL-1; LAN-2: *Mus musculus* neuroblastoma cell line (RRID:CVCL_1829); U-937: *Homo sapiens* Lymphoma cell line CRL-1593.2; U373: *Homo sapiens* glioblastoma astrocytoma cell-line; SK-N-SH *Homo sapiens* neuroblastoma cell line ATCC HTB-11; THP-1: Monocytic leukemia cells ATCC TIB-202.

Abbreviations: BAFF: B-cell activating factor; BBB: Blood-brain barrier; BMDCs: Bone marrow-derived dendritic cells; BMECs: Brain microvasculature endothelial cells; BMECs: Brain microvascular endothelial cells; CNS: Central nervous system; DCs: Dendritic cells; RPE: retinal pigment epithelium (RPE), IFN: Interferon, IRF: IFN regulatory factor 3; MΦ: Macrophages; NF-κB: Nuclear factor Kappa B; NHP: Non-Human primate; PBMCs: Peripheral blood mononuclear cells; SARM: Sterile alpha and HEAT/Armadillo motif; TLR: Toll-like receptor 3; TRAIL: TNF-related apoptosis-inducing ligand; TWEAK: TNF-related weak inducer of apoptosis.

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