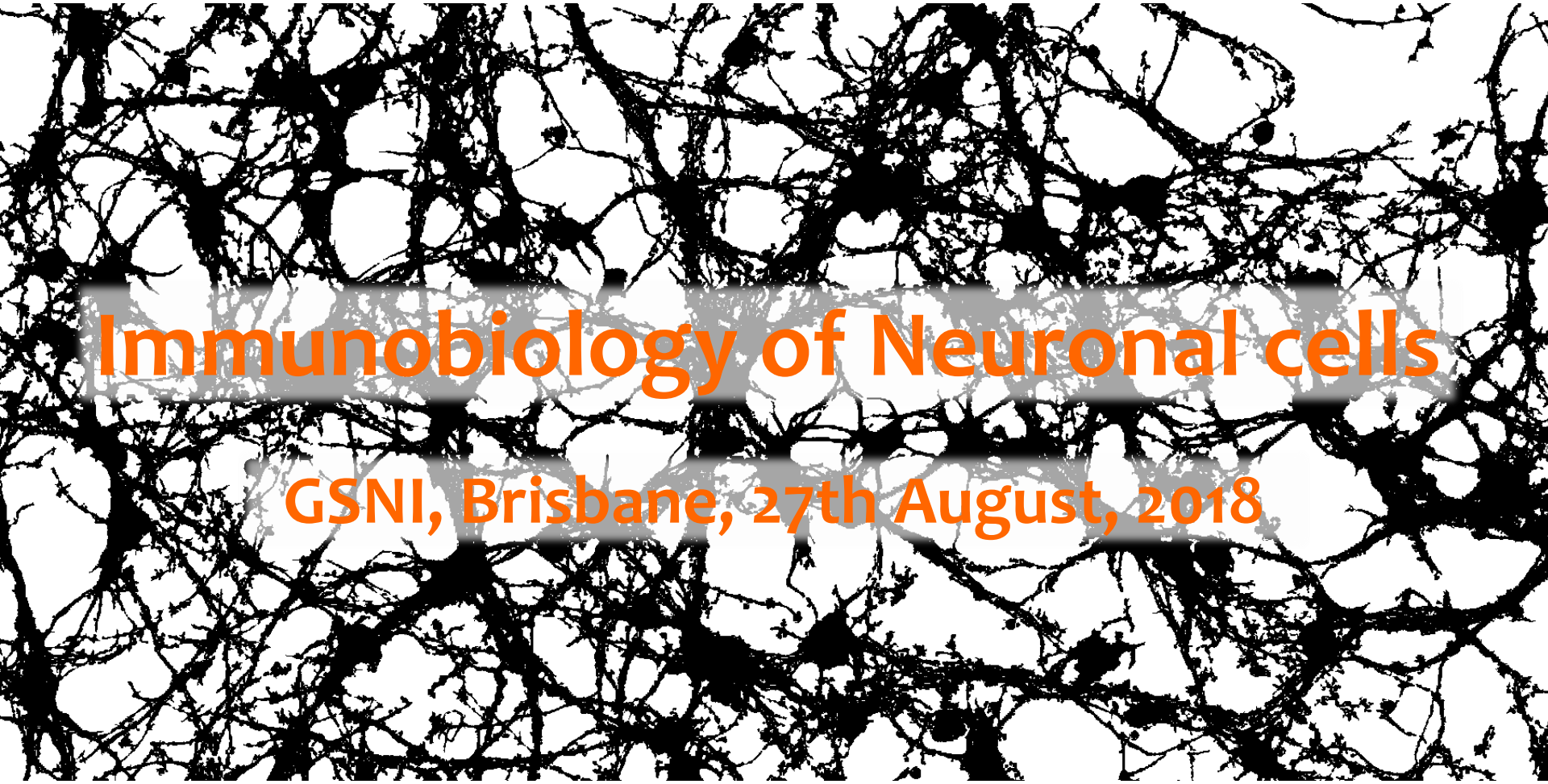
OSPEDALE SAN RAFFAELE

DIVISION OF NEUROSCIENCE

INSTITUTE OF EXPERIMENTAL NEUROLOGY



Immunobiology of Neuronal cells

GSNI, Brisbane, 27th August, 2018

Cinthia Farina, PhD
San Raffaele Scientific Institute, Milan, Italy
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Topics

- **Immune molecules in neurons**

Astrocytes are active players in cerebral innate immunity

Cinthia Farina[1], Francesca Aloisi[2] and Edgar Meinl[3,4]

Table 1. Innate immune pathways involved in CNS pathologies

PRR system	CNS disease	Refs
TLR	*Neisseria meningitides* meningitis	[8]
	Streptococcus pneumoniae meningitis	[9]
	Listeria monocytogenes meningitis	[9]
	Herpes simplex virus encephalitis	[11]
	West Nile virus encephalitis	[77]
	Multiple sclerosis or experimental autoimmune encephalitis	[22,78]
	Nerve injury	[79]
	Ischemia	[80]
Scavenger receptors	Alzheimer's disease	[48,81]
	N. meningitides meningitis	[50]
	Nerve injury	[82]
	Ischemia	[83]
Complement	Alzheimer's disease	[40,84]
	Parkinson's disease	[85]
	Huntington's disease	[40]
	Pick's disease	[40]
	Multiple sclerosis or experimental autoimmune encephalitis	[86,87]
	Rasmussen's encephalitis	[88]
	Prion disease	[85]
	N. meningitides meningitis	[8,44,89]
	HIV encephalitis	[89]
	Epstein-Barr virus encephalitis	[89]
	Measles virus encephalitis	[89]
	West Nile virus encephalitis	[46,47]
	Nerve injury	[90]
	Ischemia	[91]

Astrocytes are active players in cerebral innate immunity

Cinthia Farina[1], Francesca Aloisi[2] and Edgar Meinl[3,4]

Table 2. PRRs in astrocytes and microglia[a]

PRR	Astrocytes	Microglia
TLR	TLR2 [22,23], TLR3 [16], TLR4 [20,23], TLR5 [20,23], TLR9 [20,23]	TLR1 [24], TLR2 [13], TLR3 [24], TLR4 [15], TLR5 [24], TLR6 [24], TLR7 [24], TLR8 [24], TLR9 [24]
CD14	Not expressed	Expressed [92]
NOD	NOD1, NOD2 [36]	Unknown
PKR	Expressed [35]	Expressed [93]
Scavenger receptors	SR-BI [94], SR-MARCO [51], RAGE [95], SRCL [53]	SR-A [48], SR-BI [48], SR-MARCO [51], RAGE [51], CD36 [48], SRCL [53]
Mannose receptor	Expressed [38]	Expressed [3]
Complement factors	C1q, C1r, C1s, C4, C2, C3, factor B, factor D, C5, C6, C7, C8, C9 [40]	C1q, C3, C4 [40]
Complement receptors	CR1, CR2, C3aR, C5aR [40]	CR1, CR3/CD11b, CR4/CD11c, C3aR, C5aR, C1qRp [40]
Complement inhibitors	C1-INH, DAF/CD55, MCP/CD46, CD59, factor H, factor I, S protein, clusterin [40]	C1-INH, CD59, clusterin [40]

[a]Blue text indicates *in vitro* evidence (not yet supported by *in vivo* studies); red text indicates *in vivo* evidence (mostly supported by *in vitro* studies not cited in the table).

NATURE CELL BIOLOGY VOLUME 9 | NUMBER 9 | SEPTEMBER 2007

Toll-like receptors modulate adult hippocampal neurogenesis

Asya Rolls[1,*], Ravid Shechter[1,*], Anat London[1], Yaniv Ziv[1], Ayal Ronen[1], Rinat Levy[1] and Michal Schwartz[1,2]

TLR2 supports NPC differentiation into neurons
TLR4 inhibits NPC proliferation and differentiation into neurons

PNAS | August 31, 2010 | vol. 107 | no. 35 | 15625–15630

The Journal of Neuroscience, Novem

Neurobiology of Disease

Toll-Like Receptor 3 Is a Potent Negative Regula Axonal Growth in Mammals

Jill S. Cameron,[1] Lena Alexopoulou,[3] Jacob A. Sloane,[1] Allitia B. DiBernardo,[1] Yinghua Ma,[1] Bela Kosara Richard Flavell,[3,4] Stephen M. Strittmatter,[5] Joseph Volpe,[2] Richard Sidman,[1] and Timothy Vartanian[1]

Toll-like receptor 3 inhibits memory retention and constrains adult hippocampal neurogenesis

Eitan Okun[a], Kathleen Griffioen[a], Boaz Barak[b], Nicholas J. Roberts[a], Kamilah Castro[a], Mario A. Pita[a], Aiwu Cheng[a], Mohamed R. Mughal[a], Ruiqian Wan[a], Uri Ashery[b], and Mark P. Mattson[a,1]

The Journal of Neuroscience, July 10, 2013 • 33(28):11479–11493 • 11479

TLR7 Negatively Regulates Dendrite Outgrowth through the Myd88 – c-Fos–IL-6 Pathway

Hsin-Yu Liu,[1,3] Yun-Fen Hong,[2,3] Chiao-Ming Huang,[3] Chiung-Ya Chen,[3] Tzyy-Nan Huang,[3] and Yi-Ping Hsueh[1,3]
[1]Graduate Institute of Life Sciences, National Defense Medical Center, Taipei 114, Taiwan, Republic of China, [2]Faculty of Life Sciences, Institute of Genome Sciences, National Yang-Ming University, Taipei 112, Taiwan, Republic of China, and [3]Institute of Molecular Biology, Academia Sinica, Taipei 115, Taiwan, Republic of China

EMBO Reports (2017) 18: 169–183

TLR3 downregulates expression of schizophrenia gene *Disc1* via MYD88 to control neuronal morphology

Chiung-Ya Chen, Hsin-Yu Liu & Yi-Ping Hsueh*

NATURE NEUROSCIENCE VOLUME 15 | NUMBER 6 | JUNE 20

An unconventional role for miRNA: let-7 activates Toll-like receptor 7 and causes neurodegeneration

Sabrina M Lehmann[1], Christina Krüger[1], Boyoun Park[2], Katja Derkow[1], Karen Rosenberger[1], Jan Baumgart[3], Thorsten Trimbuch[4], Gina Eom[5], Michael Hinz[6], David Kaul[1], Piet Habbel[1], Roland Kälin[5], Eleonora Franzoni[7], Agnieszka Rybak[6], Duong Nguyen[7], Rüdiger Veh[8], Olaf Ninnemann[7], Oliver Peters[9], Robert Nitsch[3], Frank L Heppner[4,5], Douglas Golenbock[10], Eckart Schott[11], Hidde L Ploegh[12,13], F Gregory Wulczyn[7,13] & Seija Lehnardt[1,4,7]

Summary- Neuronal TLR

- **TLRs can be expressed by neurons and their precursors under physiological and pathological conditions.**
- **They may regulate NPC homeostasis and differentiation, neuronal survival and brain function.**

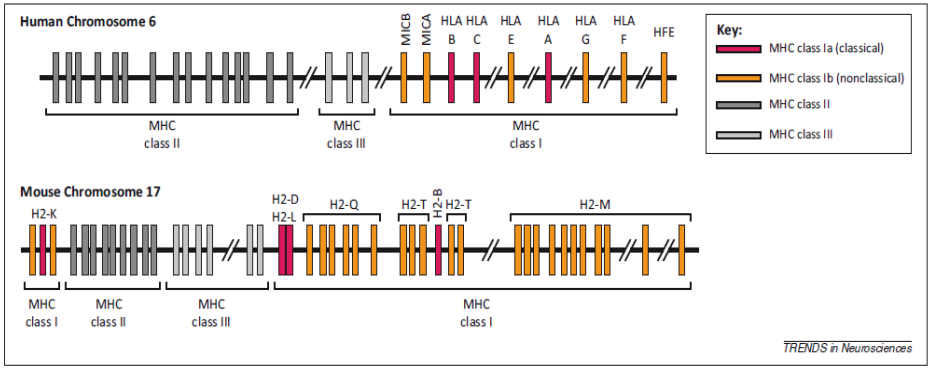
OPEN ISSUES

- **The lack of conditional mice limits the analysis about the role of PRR in specific CNS cell types and neuronal phenotypes.**
- **Unidentified ligands for PRR activation under physiological conditions**

Trends in Neurosciences November 2012, Vol. 35, No. 11

Major histocompatibility complex class I proteins in brain development and plasticity

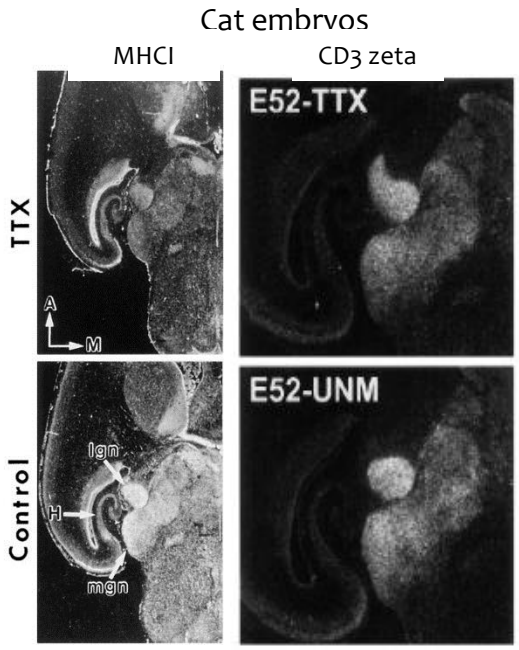
Bradford M. Elmer and A. Kimberley McAllister

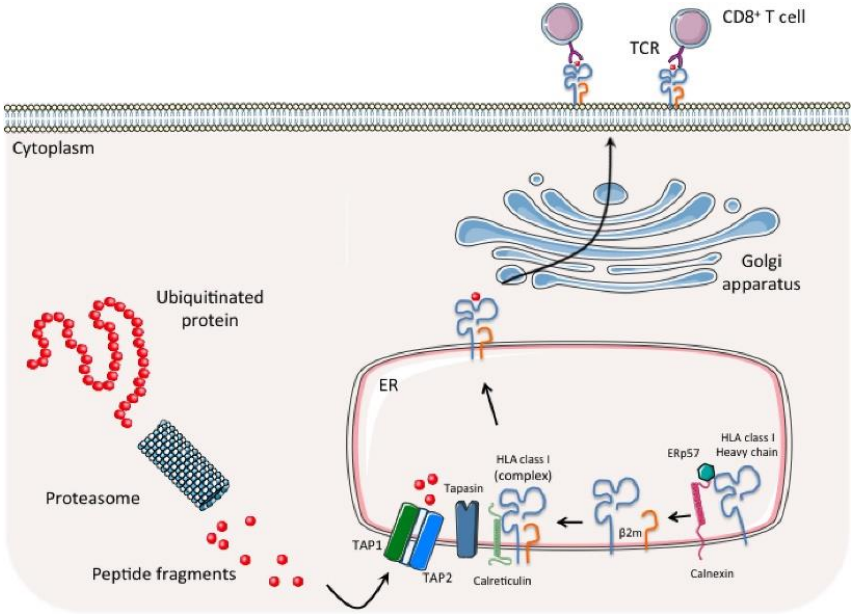


Neuron, Vol. 21, 505–520, September, 1998, Copyright ©1998 by Cell Press

Regulation of Class I MHC Gene Expression in the Developing and Mature CNS by Neural Activity

Roderick A. Corriveau,* Gene S. Huh,* and Carla J. Shatz†



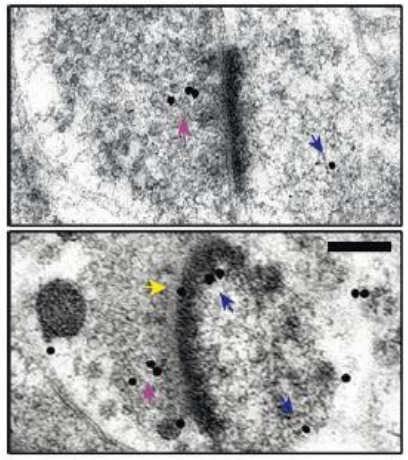


Trends in Neurosciences November 2012, Vol. 35, No. 11

Major histocompatibility complex class I proteins in brain development and plasticity

Bradford M. Elmer and A. Kimberley McAllister

- MHCI are found in an isoform- and region-specific manner throughout the CNS.
- Expressed in the visual and olfactory system, cerebral cortex, striatum, hippocampus, cerebellum and spinal cord.
- Present in the developing and adult mammalian CNS, with the highest levels occurring during early post-natal development.
- Expressed on the surface of axons and dendrites, and at synapses (both at pre- and post-synaptic level).



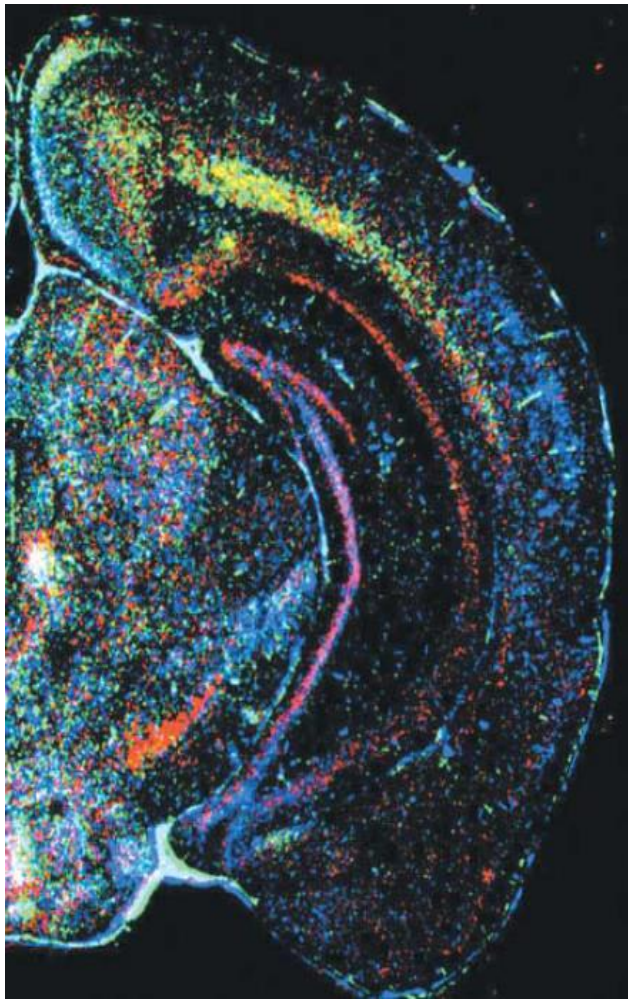


Figure 1 | **Expression of mRNA for three different major histocompatibility complex (MHC) class I molecules in a coronal section of adult mouse brain.** Blue, H-2D; red, T22; green, Qa-1. Image courtesy of G. S. Huh and C.J.S.

Major histocompatibility complex class I proteins in brain development and plasticity

Manipulation	Region	Phenotype (relative to WT or control)	Experimental details	Refs
MHCI				
$\beta2m^{-/-}$ (sMHCI deficient)	Retinogeniculate projection	Expanded ipsilateral projection, no change in LGN area	*In vivo*: P13	[40]
	Visual cortex	Increased synapse density (EM)	*In vivo*: P8, P11, P23, P60	[32]
		Increased glutamatergic synapse density (ICC: vGlut1, GluN2A/B)	Cultures: 8 div	
	Hippocampus	No change in neurite outgrowth	Cultures: 1 div	[52]
	Cerebellum	Normal CF-PC synapse elimination and CF-PC EPSC amplitude	Slices: 12–16 weeks old	[20]
$\beta2m^{-/-}TAP1^{-/-}$ (sMHCI deficient)	Retinogeniculate projection	Expanded ipsilateral projection, no change in LGN area or retinal waves	*In vivo*: P13	[40]
		Expanded ipsilateral projection and abnormal segregation of inputs	*In vivo*: P34	[47]
	Thalamocortical projection	Enhanced OD plasticity (Arc induction)	*In vivo*: P22–P31	
	Visual cortex	Increased mEPSC frequency, no change in amplitude	Slices: P19–P21, layer 4	[39]
	Hippocampus	Increased numbers of SVs at synapses, no change in PSD length, decreased perforated PSDs (EM)	*In vivo*: P44–P45	
		Enhanced LTP, absent LTD, no change in fEPSP slope (CA1)	Slices: P30–P44	[40]
		Increased mEPSC frequency, no change in amplitude	Cultures: 14 div	[39]
		Impaired synaptic scaling following TTX for 3–6 days		
		No change in synapse density (ICC: synapsin, tubulin)		
		Increased size of synapsin and vGlut1/2 puncta, no change in PSD-95 puncta		
		No change in protein levels of GluN1, GluN3A, GluA1, GluA2, or synaptophsyin (biochemistry)	Tissue: P28–P35	[55]
		Decreased GluA/GluN ratio, increased slope of GluN-mediated fEPSP, no change in proportion of silent synapses, GluN2A/B composition	Slices: P13–P16	
		No change in surface GluA1, GluA2, GluN1, GluN2B, or synapse density (ICC: SV2, GluN1)	Cultures: 16–20 div	
		Increased surface GluA1 following NMDA treatment (ICC), blockade of NMDA-induced decrease in surface GluA1 (biochemistry), increased surface GluA2 in response to NMDA (biochemistry)		
$Kb^{-/-}Db^{-/-}$	Retinogeniculate projection	Expanded ipsilateral projection, no change in LGN area	*In vivo*: P34	[47]
	Thalamocortical projection	Enhanced OD plasticity (Arc induction, transneuronal tracing)	*In vivo*: P22-31	
	Cerebellum	Normal CF-PC synapse elimination, PC dendritic arbors, and synapse density on CFs (ICC: vGlut2)	Slices: P19–P25, 12–16 weeks	[19,20]
		CF-PC EPSC amplitude normal, enhanced PF PPF and reduced PPD	Slices: P19, P19–P25	
		Lower induction threshold for LTD at PF-PC synapses	Slices: P19–P25	[19]
		Increased rotarod learning and retention	*In vivo*: 8–12 week males	
	Hippocampus	Reduced neurite outgrowth, delayed neuronal polarization	Cultures: 1–2 div	[52]
NSE-H2Db (neuronal MHCI overexpression)	Retinogeniculate projection	Smaller contralateral, but not ipsilateral, projection, and decreased LGN area	*In vivo*: P11	[51]
		Reduced RGC axonal outgrowth toward thalamic explants caused by secreted (shed) MHCI	Retinal–thalamic explants, 4–5 div	[53]
	Hippocampus	Reduced synapsin expression in DG and CA3, but not CA1	*In vivo*: P39	[51]
		No change in basal synaptic transmission (CA1)	Slices: P28–P42	
		No change in LTP (CA1)		
		Enhanced neurite outgrowth, increased numbers of neurites per cell	Cultures: 1–2 div	[52]

Manipulation	Region	Phenotype (relative to WT or control)	Experimental details	Refs
PIRB				
*PirB*TM (functionally PIRB deficient)	Retinogeniculate projection	Normal	*In vivo*: P15	[44]
	Thalamocortical projection	Normal refinement (Arc induction)	*In vivo*: P19, P34	
		Enhanced OD plasticity (Arc induction, transneuronal tracing)	*In vivo*, ME (P19–P25, P22–P31, P31–P36); MD (P19–P25, P25–P40)	
		Extended OD plasticity after critical period (Arc induction)	*In vivo*, ME (P100–P110)	
$PirB^{-/-}$	Hippocampus	fEPSP amplitude normal (CA3–CA1)	Slices: age not specified	[56]
		No change in CA3-CA1 LTP or LTD	Slices, LTP: P42–P56, LTD: P15–P20	
CD3ζ				
$CD3\zeta^{-/-}$	Retinogeniculate projection	Expanded ipsilateral projection, no change in retinal waves	*In vivo*: P13, P16	[40,48]
	Retina	Increased RGC dendritic branching	*In vivo*: P12, P33	[48]
		Altered dendritic stratification and segregation of ON/OFF inputs onto RGCs	*In vivo*: P33	
		Reduced frequency of retinal waves in second, but not in first, week	*In vivo*: P3, P10	
	Hippocampus	Enhanced LTP, absent LTD, no change in fEPSP slope	Slices: P30–P44	[40]
CD3ζ RNAi and DN	Cortex	Increased dendritic branching and width, reduced dendritic motility	Cultures: 5 div	[41]
CD3ζ antibody	Hippocampus	Decreased dendritic branching	Cultures: 5–7 div	[41]
CD3ε				
$CD3\varepsilon^{-/-}$	Cerebellum	Decreased PC dendritic branching and vGlut1 intensity, no change in PF-PC or CF-PC basal synaptic transmission or CF-PC synapse elimination, enhanced PF-PC PPF	Slices: P7	[42]
		Impaired rotarod performance at high speed	*In vivo*: adult	
Ly49				
Ly49 antibody	Cortex	Decreased neurite density, increased synapsin levels and neuron number	Cultures: 5 div	[45]

- Activity-dependent neuronal refinement and plasticity
- Axonal and dendritic growth
- Synapse density
- Synaptic transmission
- Synaptic plasticity

MHC class I in dopaminergic neurons suppresses relapse to reward seeking

Sci. Adv. 2018;4:eaap7388

Gen Murakami,[1,2,3]* Mitsuhiro Edamura,[1] Tomonori Furukawa,[4] Hideya Kawasaki,[2] Isao Kosugi,[2] Atsuo Fukuda,[4] Toshihide Iwashita,[2] Daiichiro Nakahara[1,5]*

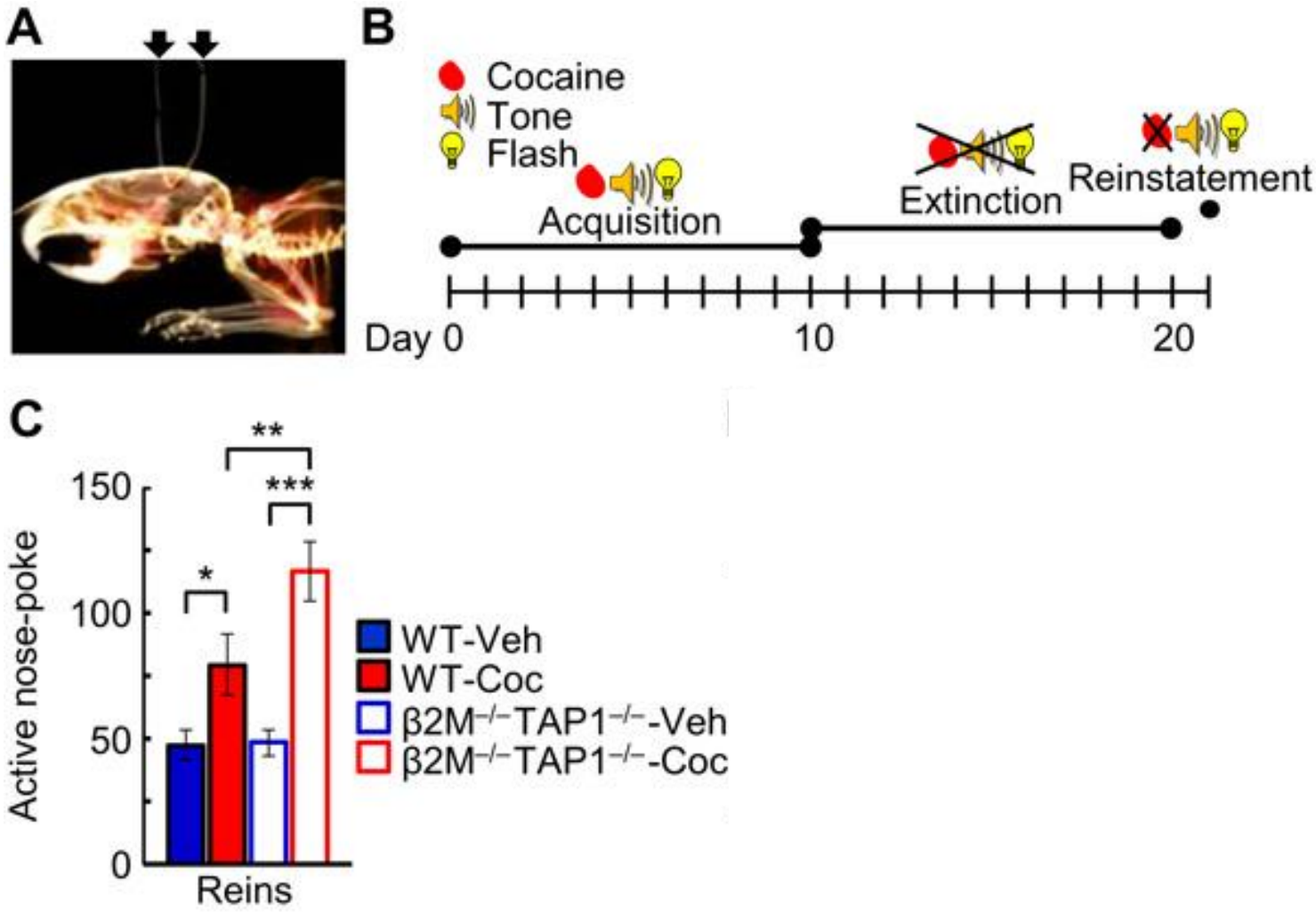


Fig. 1 Cocaine-seeking behavior in WT and functional MHCI knockout (KO) mice.

Fig. 3 Immunohistochemical analysis of MHCI localization in the VTA.

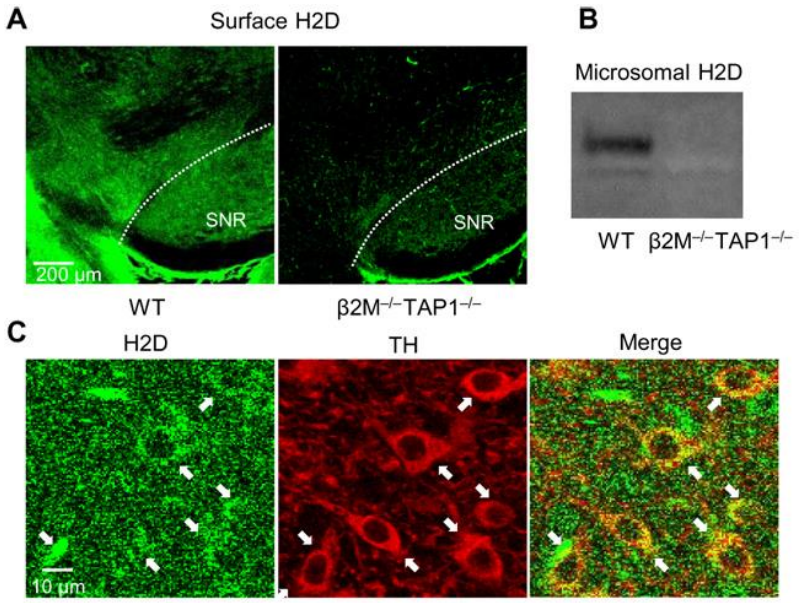


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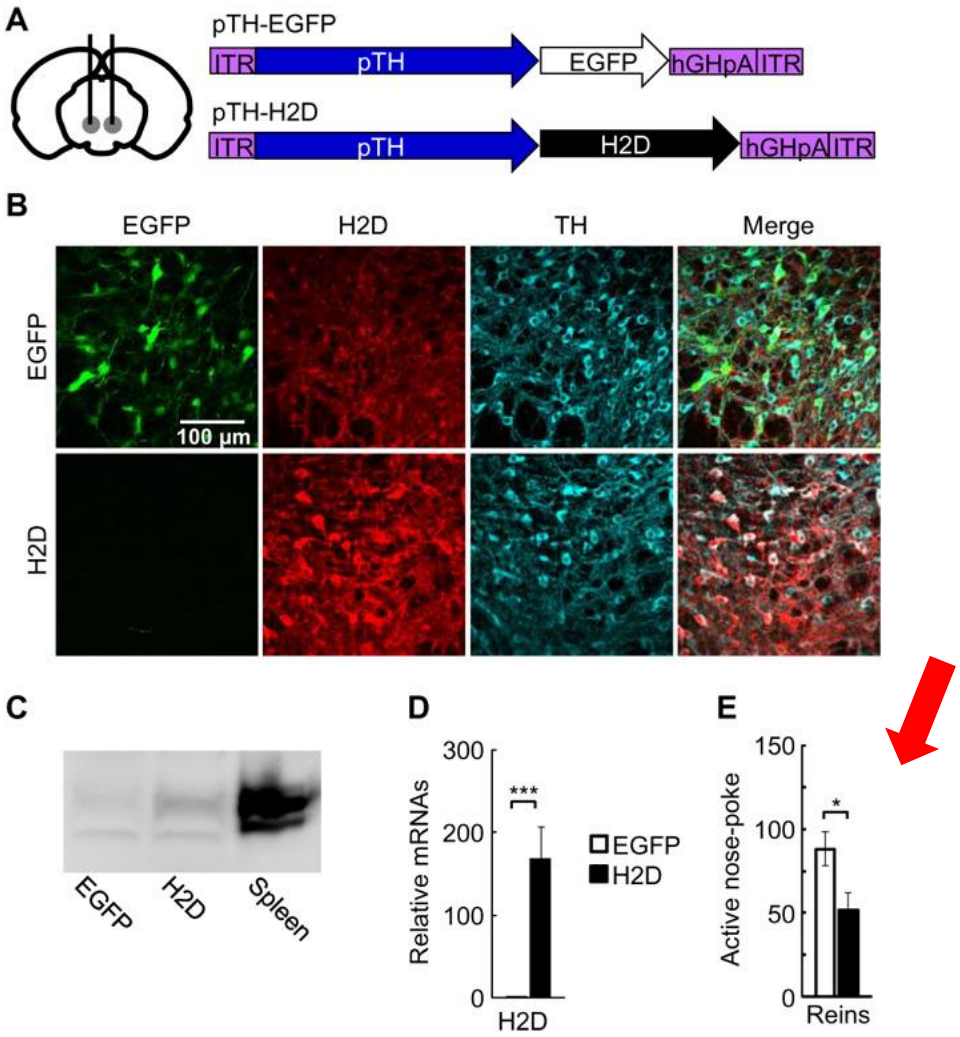
Fig. 5 Cocaine-seeking behavior in WT mice overexpressing H2D in VTA dopaminergic neurons.

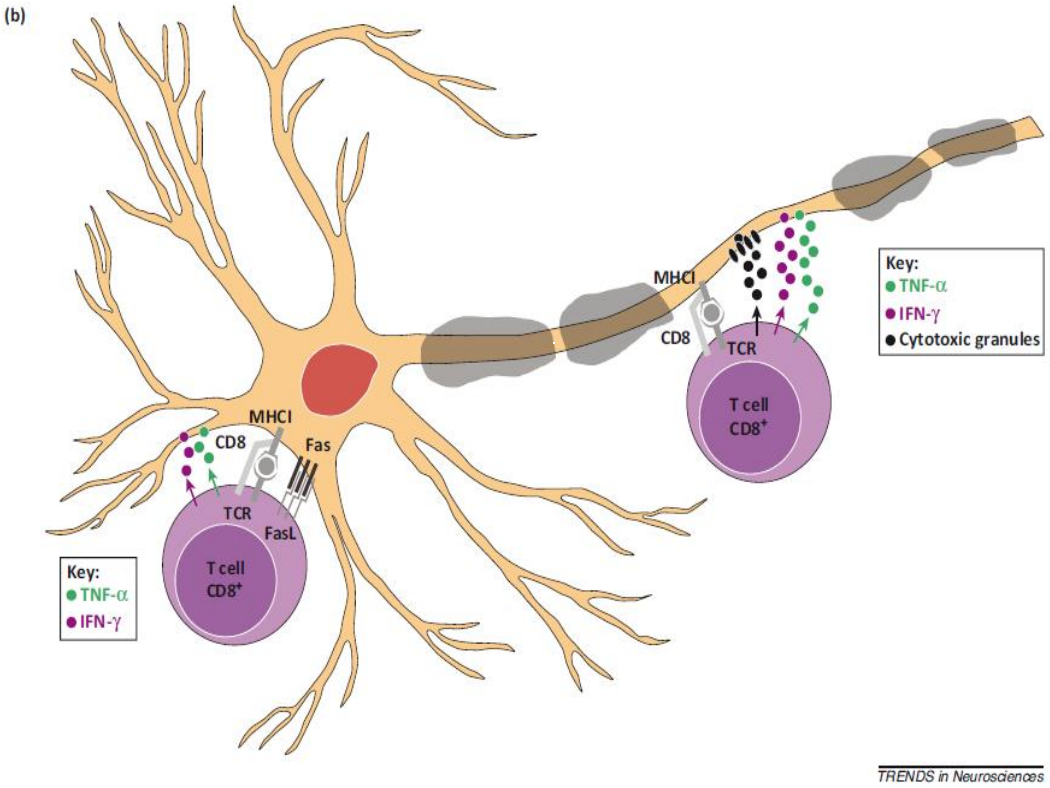


Gen Murakami et al. Sci Adv 2018;4:eaap7388

ScienceAdvances
AAAS

Neurons as targets for T cells in the nervous system

Roland S. Liblau[1,2,3], Daniel Gonzalez-Dunia[1,2], Heinz Wiendl[4], and Frauke Zipp[5]



Summary- Neuronal MHCI

- **MHCI and its interaction partners can be expressed by neurons under physiological and pathological conditions.**
- **They may regulate activity-dependent refinement and plasticity, axonal and dendritic outgrowth, synaptic transmission and behavior.**
- **MHCI makes neurons susceptible to interaction with T cells.**

OPEN ISSUES

- **The lack of inducible conditional mice limits the analysis about the role of MHCI and its receptors in specific CNS cell types and neuronal phenotypes.**
- **Binding partners for MHCI in specific functions.**
- **Role of antigen presentation by MHCI in CNS physiology.**

Topics

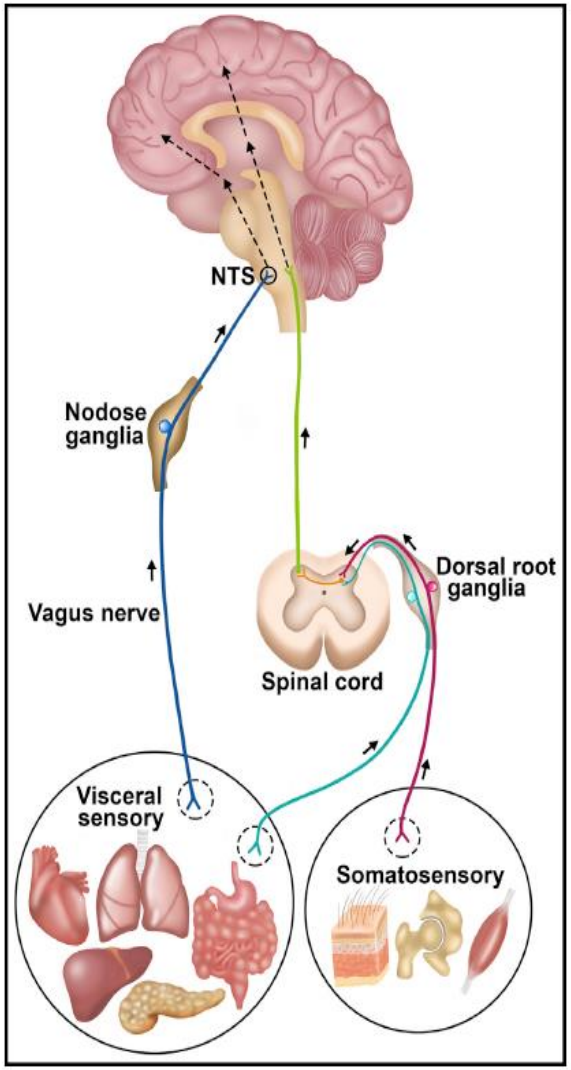
- Immune molecules in neurons (TLRs and MHCI)
- Neuronal circuits and immunomodulation

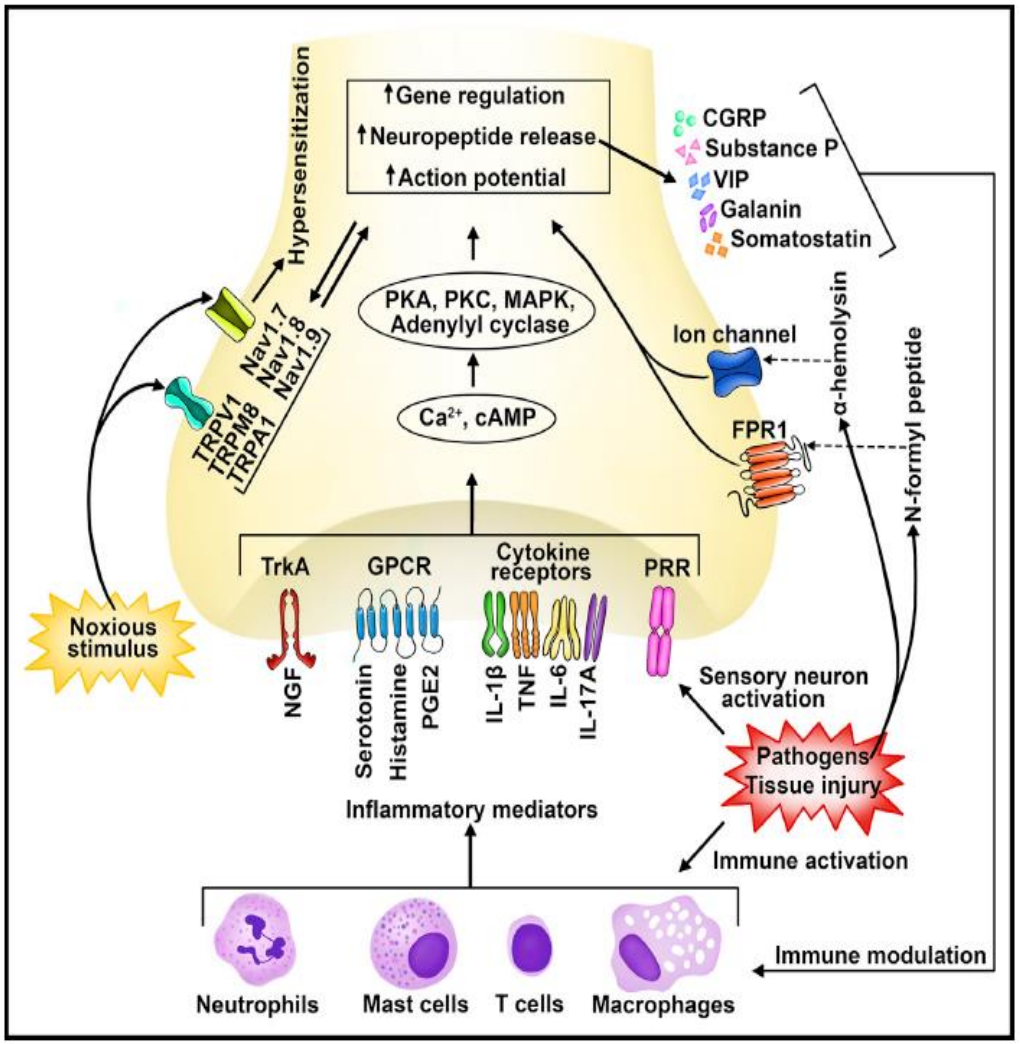
Immunity 46, June 20, 2017

Mechanisms and Therapeutic Relevance of Neuro-immune Communication

Sangeeta S. Chavan,[1,2,*] Valentin A. Pavlov,[1,2,*] and Kevin J. Tracey[1,2,*]

The Afferent neuronal circuit



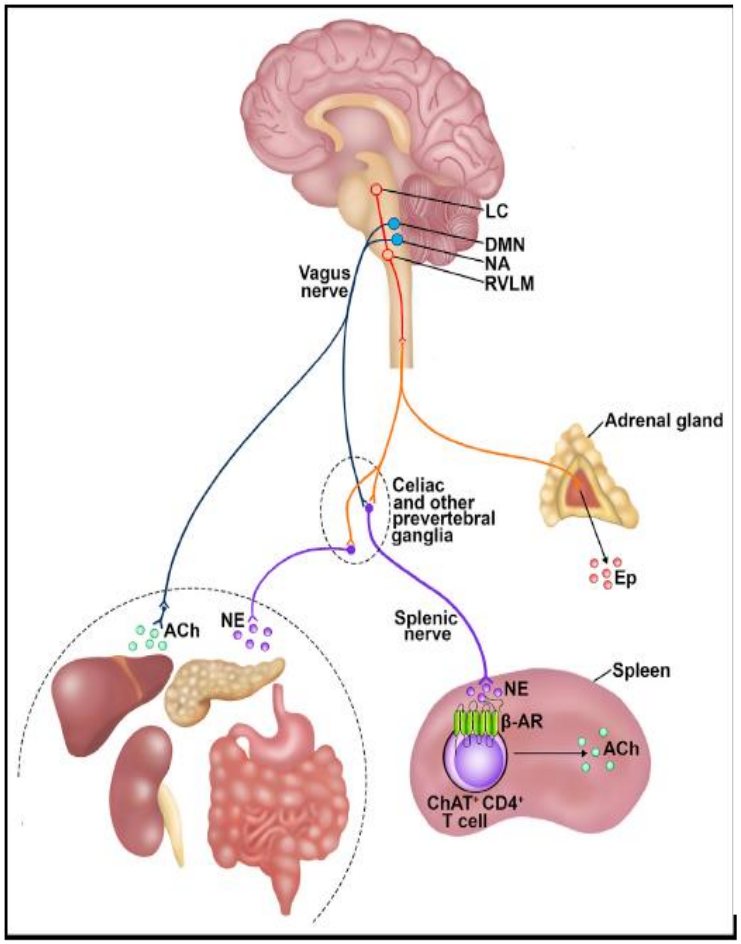


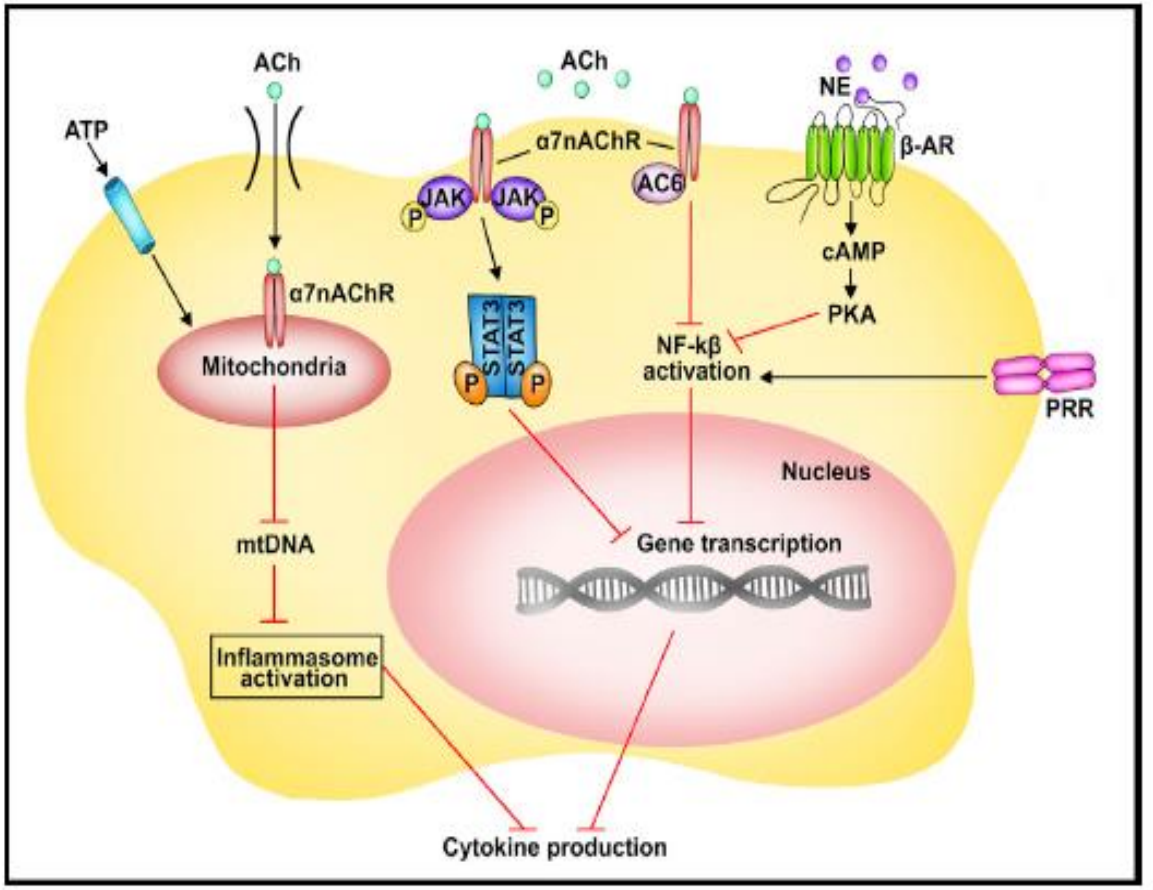
Immunity 46, June 20, 2017

Mechanisms and Therapeutic Relevance of Neuro-immune Communication

Sangeeta S. Chavan,[1,2,*] Valentin A. Pavlov,[1,2,*] and Kevin J. Tracey[1,2,*]

The Efferent neuronal circuit

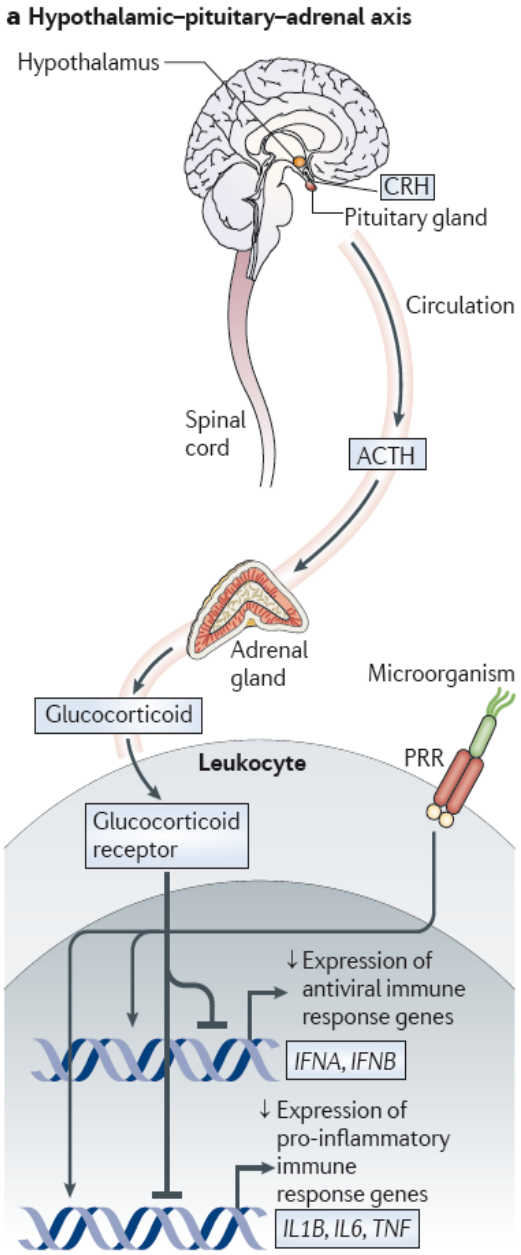




NATURE REVIEWS | IMMUNOLOGY VOLUME 11 | SEPTEMBER 2011

Reciprocal regulation of the neural and innate immune systems

Michael R. Irwin and Steven W. Cole



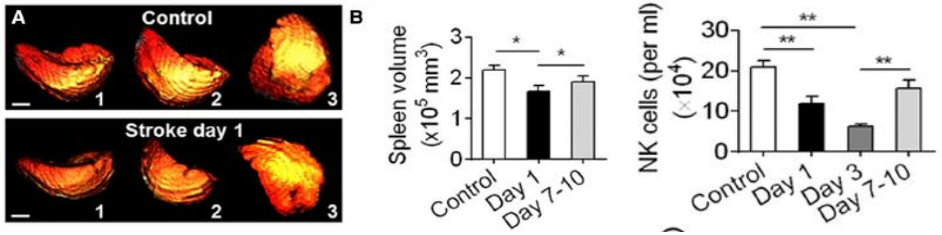
CRH, corticotropin-releasing hormone
ACTH, adrenocorticotropic hormone

Immunity 46, 474–487, March 21, 2017

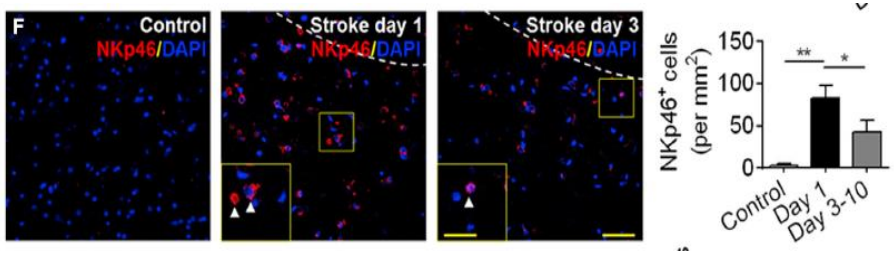
Brain Ischemia Suppresses Immunity in the Periphery and Brain via Different Neurogenic Innervations

Qiang Liu,[1,2,6,*] Wei-Na Jin,[1,2,6] Yaou Liu,[1] Kaibin Shi,[1,2] Haoran Sun,[1] Fang Zhang,[1] Chao Zhang,[1] Rayna J. G
Kevin N. Sheth,[4] Antonio La Cava,[5] and Fu-Dong Shi[1,2,7,*]

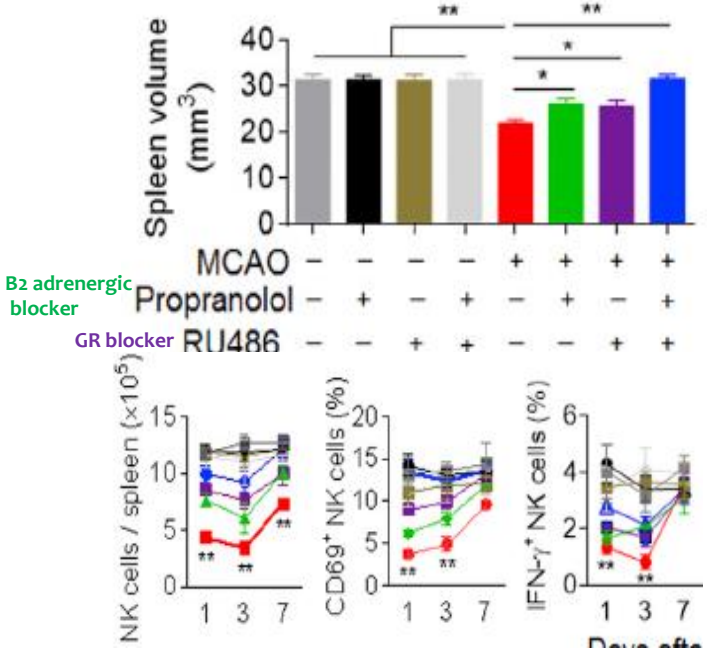
Splenic atrophy and peripheral NK cell contraction after stroke



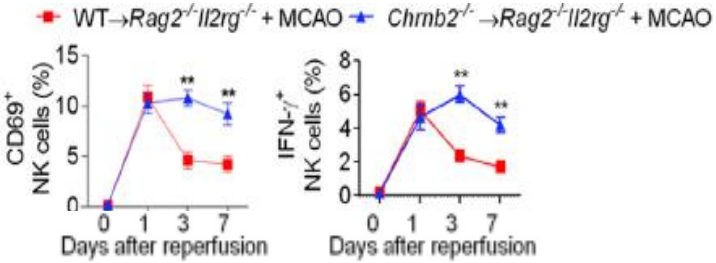
NK cells in the brain peak immediately after stroke and then decrease



Adrenergic and HPA axes act synergistically to induce splenic atrophy and NK cell deficiency in the periphery



Cholinergic signaling through B2-nAChR is responsible for NK cell loss in the ischemic brain

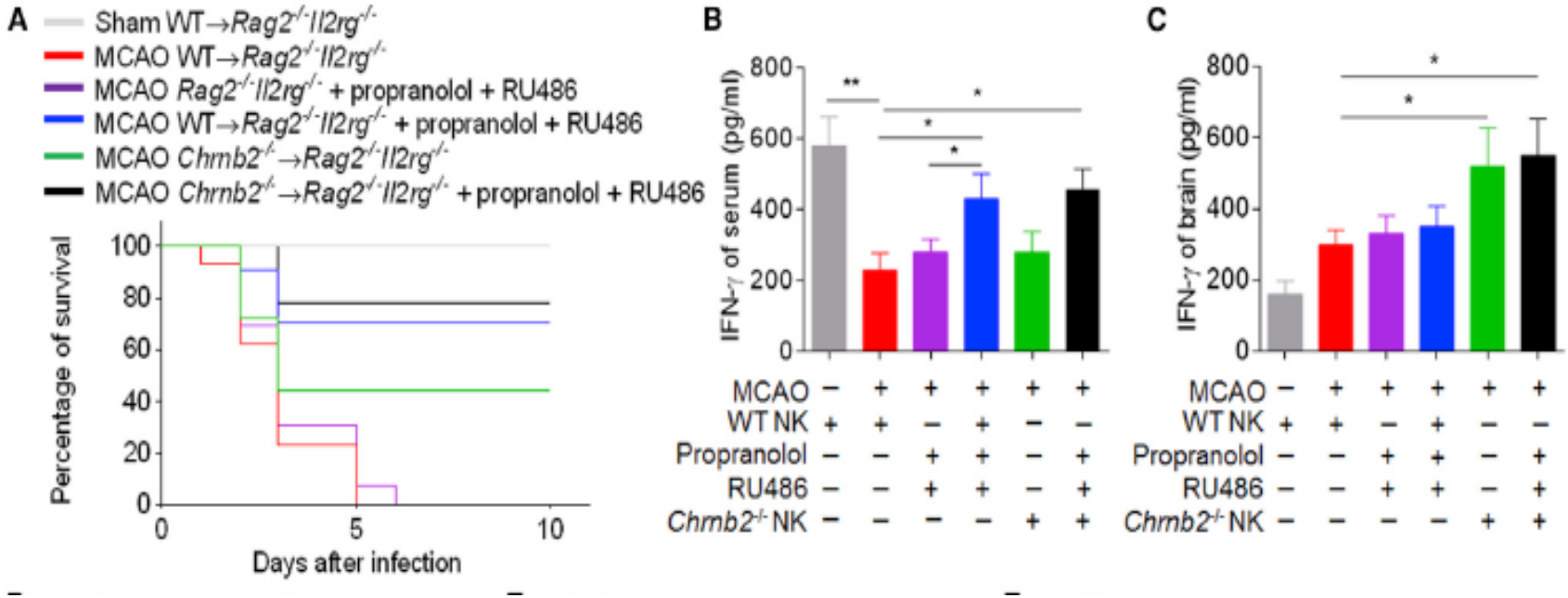


Immunity 46, 474–487, March 21, 2017

Brain Ischemia Suppresses Immunity in the Periphery and Brain via Different Neurogenic Innervations

Qiang Liu,[1,2,6,*] Wei-Na Jin,[1,2,6] Yaou Liu,[1] Kaibin Shi,[1,2] Haoran Sun,[1] Fang Zhang,[1] Chao Zhang,[1] Rayna J. Gonzales,[3] Kevin N. Sheth,[4] Antonio La Cava,[5] and Fu-Dong Shi[1,2,7,*]

MCAO predisposes to LM infection and blockade of adrenergic and HPA signalling gives some protection.
Blockade of cholinergic signalling in NK cells protects also from infection.
Blockade of systemic adrenergic+HPA axis plus cholinergic signalling in NK cells further increases survival.



Summary- Neuronal circuits and immunomodulation

- **HPA axis and the circuitry between central and peripheral nervous system may regulate local and systemic immunity.**
- **The expression of receptors for neurotransmitters, including acetilcoline receptors and adrenergic receptors, has been identified on macrophages, dendritic cells, T cells and other immune cells, facilitating neural regulation of immune responses. Immune cells synthetize and release substances classically reputed as neurotransmitters and neuromodulators, including acetylcholine.**

OPEN ISSUES

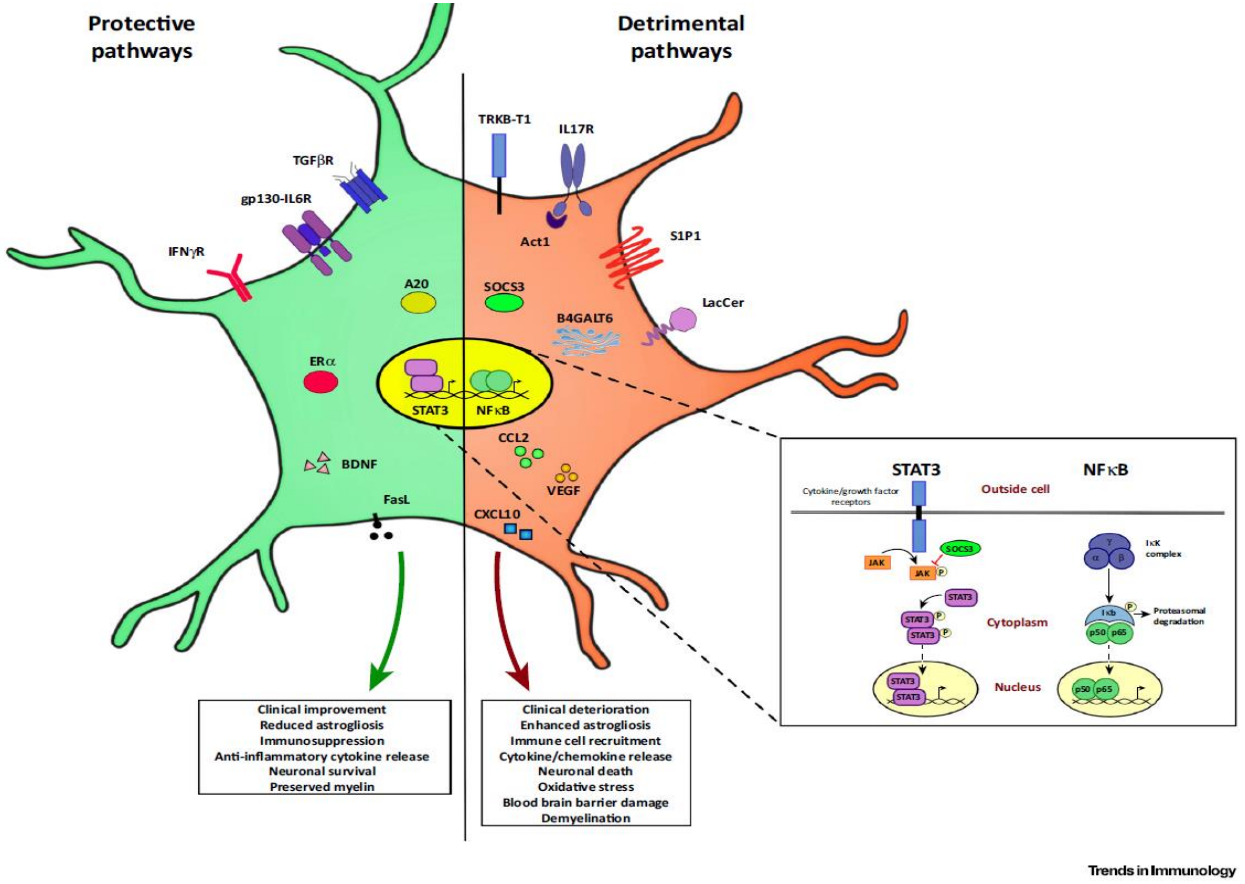
- **Definition of complex, integrated neuro-immune reflexes and therapeutic applications.**

Topics

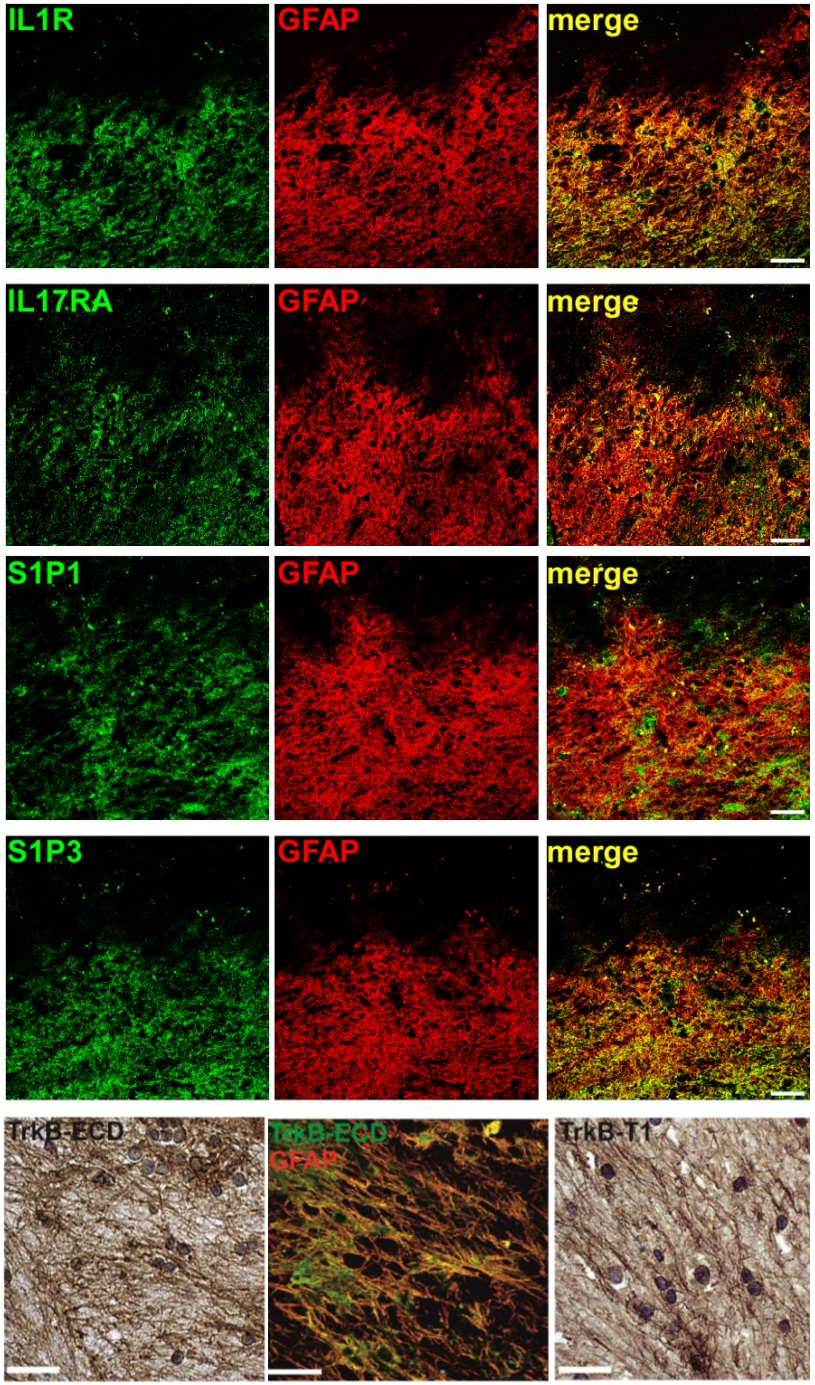
- Immune molecules in neurons
- Neuronal circuits and immunomodulation
- Astrocytes and neuroinflammation

Astrocytes: Key Regulators of Neuroinflammation

Emanuela Colombo[1] and Cinthia Farina[1,*]

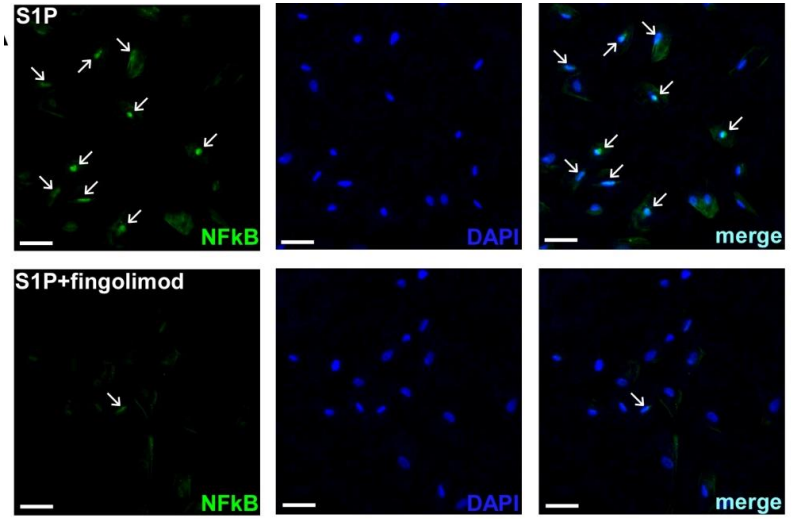


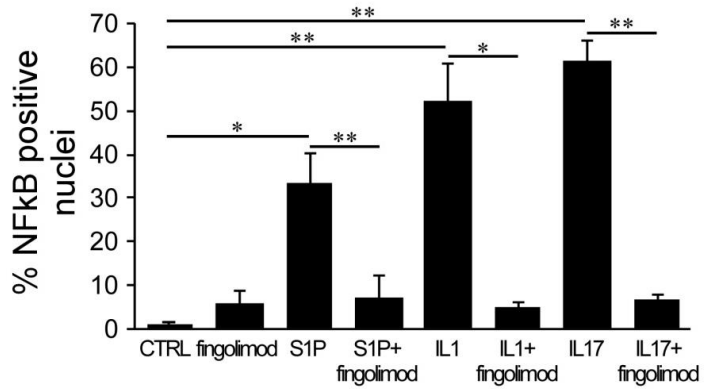
Trends in Immunology, September 2016, Vol. 37, No. 9

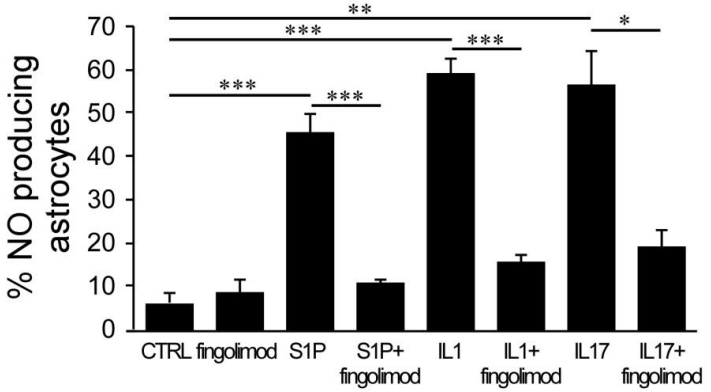


Colombo et al. Annals Neurol. 2014

Colombo et al. J.Exp.Med. 2012

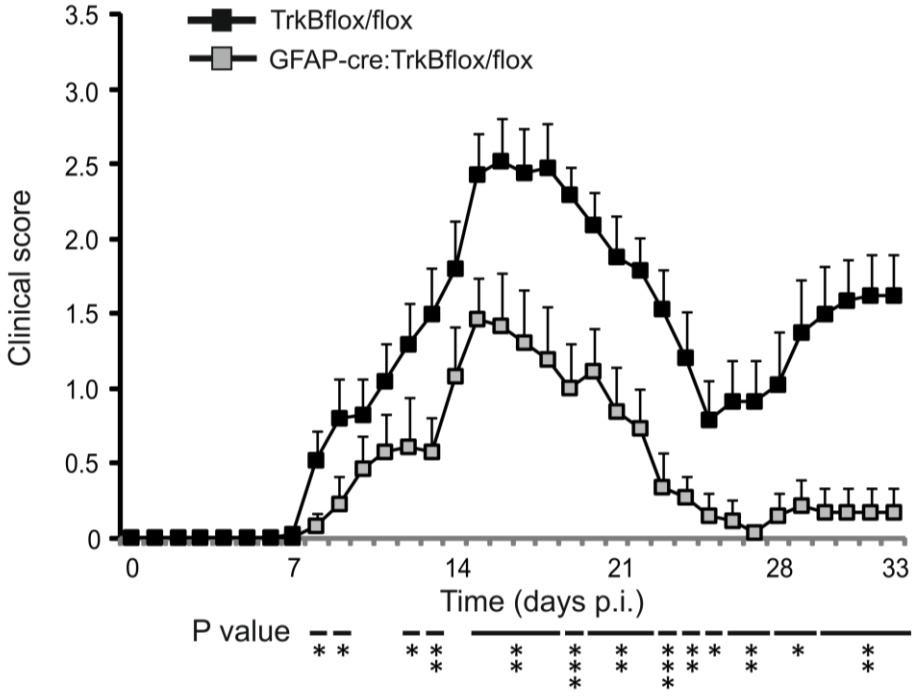


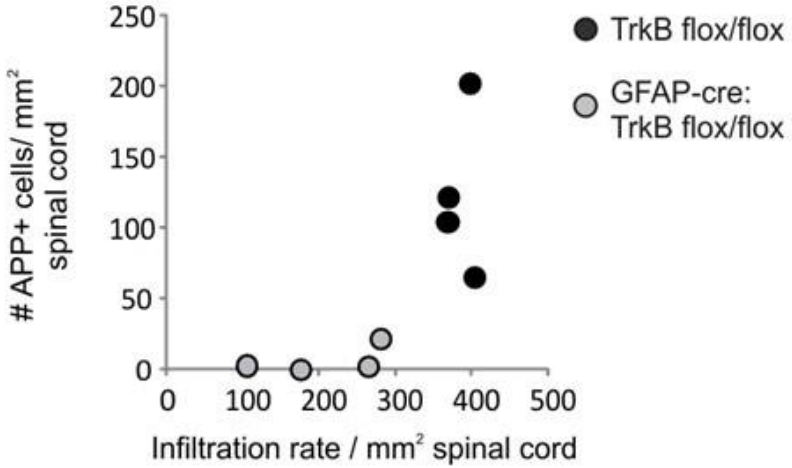




Colombo et al. Annals Neurol. 2014

GFAP-TrkB mice develop milder EAE





	TrkBflox/flox	GFAP-cre:TrkBflox/flox	P value
Incidence	100% (20/20)	68% (13/19)	<0.01
Max weight loss (%)	14.4 ± 4	11 ± 4	n.s.
Onset (days p.i.)	9 ± 1.7	12 ± 1.3	<0.01
Max Score	2.8 ± 0.3	2.1 ± 0.3	<0.001
Score at peak	2.5 ± 0.5	1.5 ± 0.5	<0.01
C.D.I.	29.2 ± 7.2	13.8 ± 5	<0.001

Colombo et al. J.Exp Med. 2012

Topics

- Immune molecules in neurons
- Neuronal circuits and immunomodulation
- Astrocytes and neuroinflammation
- Brain function and immunomodulation

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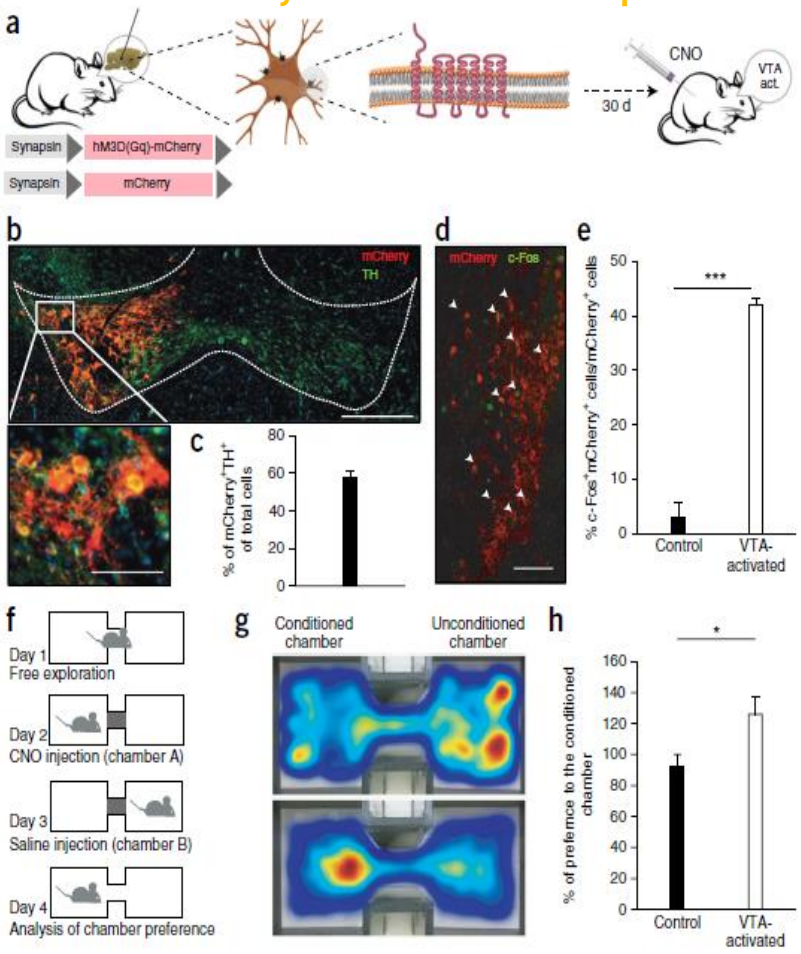
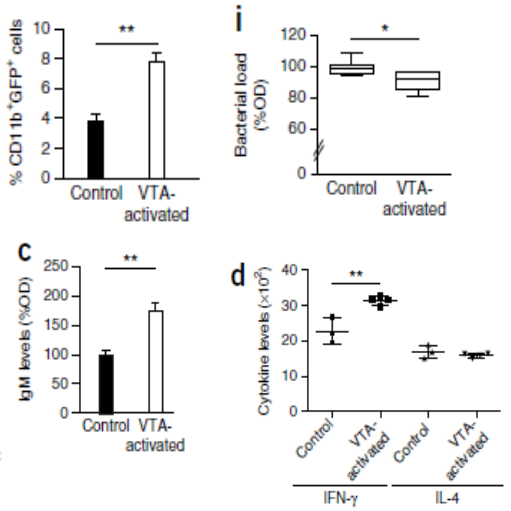
Activation of the reward system boosts innate and adaptive immunity

Tamar L Ben-Shaanan[1,2], Hilla Azulay-Debby[1,2], Tania Dubovik[1], Elina Starosvetsky[1], Ben Korin[1,2], Maya Schiller[1,2], Nathaniel L Green[1,2], Yasmin Admon[1], Fahed Hakim[1,3], Shai S Shen-Orr[1,4,5] & Asya Rolls[1,2,5]

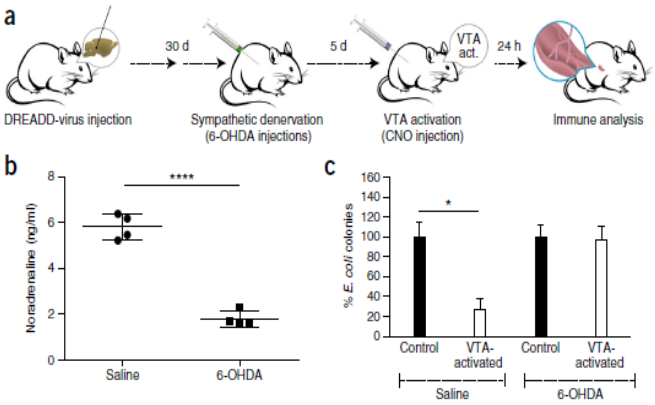
Activation of VTA neurons with DREADDs stimulates reward circuitry and behavioural responses



Activation of VTA neurons improves innate and adaptive immune responses to E. Coli



The effects of VTA activation on the immune system are partially mediated by catecholaminergic neurons of the sympathetic nervous system



Topics

- Immune molecules in neurons
- Neuronal circuits and immunomodulation
- Astrocytes and neuroinflammation
- Brain function and immunomodulation
- Immunity in Neurological Disorders

Journal of Autoimmunity 38 (2012) J144–J155

Contents lists available at SciVerse ScienceDirect

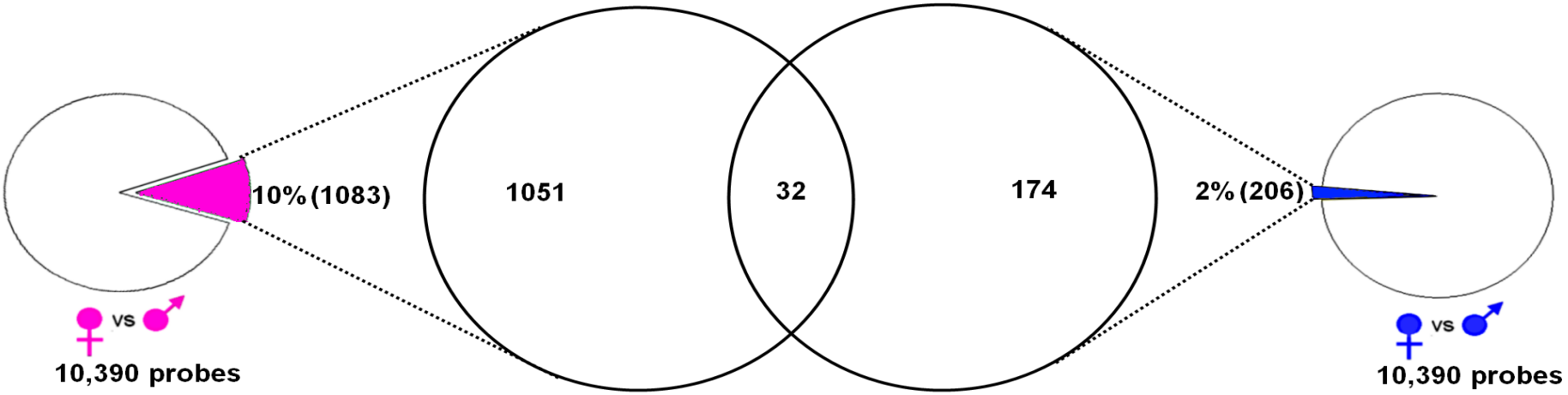
Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Multiple Sclerosis presents alterations in the expression of sexually dimorphic genes

Gender-based blood transcriptomes and interactomes in multiple sclerosis: Involvement of SP1 dependent gene transcription

Ramesh Menon [a,b,1], Marco Di Dario [a,b,1], Chiara Cordiglieri [a,b], Silvia Musio [b], Loredana La Mantia [b], Clara Milanese [b], Anna Luisa Di Stefano [c], Massimo Crabbio [c], Diego Franciotta [d], Roberto Bergamaschi [c], Rosetta Pedotti [b], Enzo Medico [e], Cinthia Farina [a,b,*]



In diseased subjects almost all natural sex-specific genes are not differentially expressed between women and men any more, while a new (smaller) subset of genes performs as sex-specific.

Gender-based transcriptomics profiles in relapsing-remitting MS

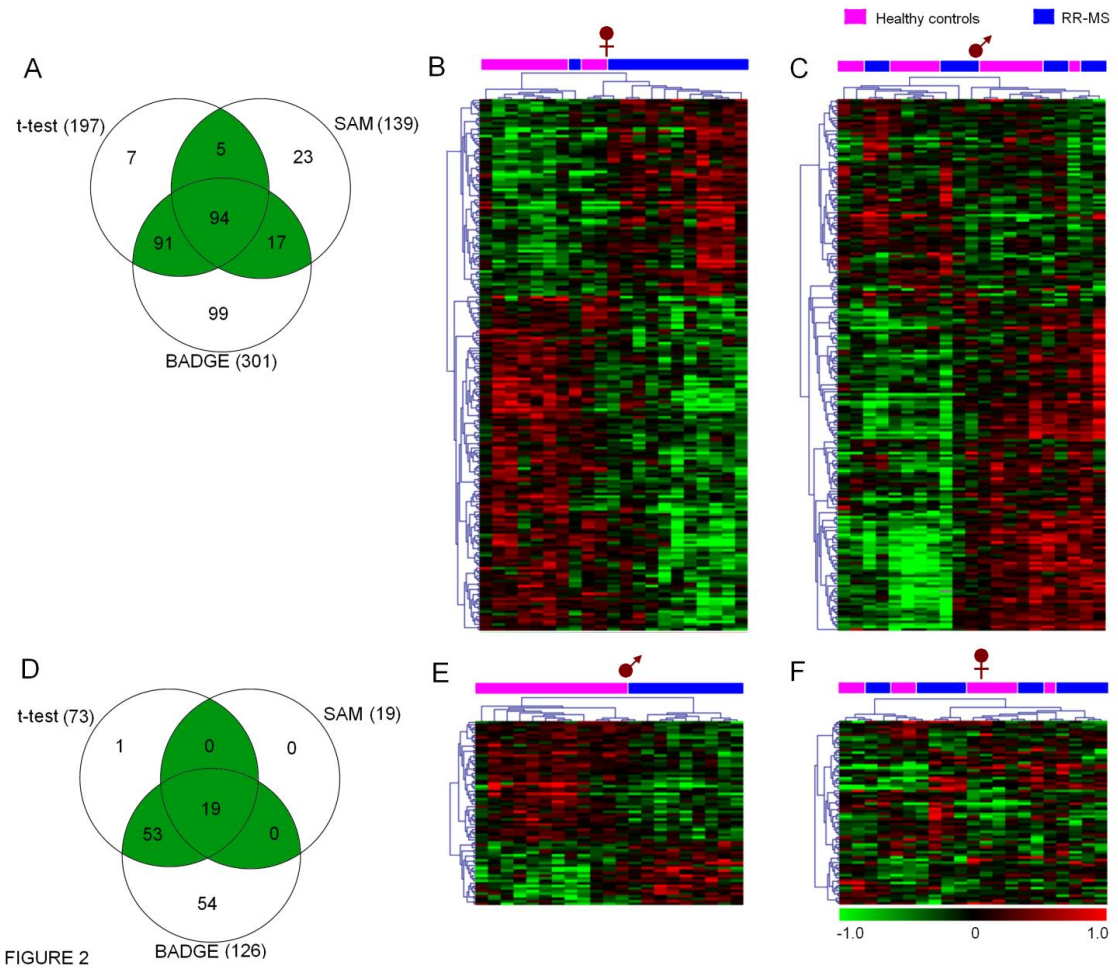


FIGURE 2

Menon et al. J. Autoimmunity 2012

Journal of Autoimmunity 38 (2012) J144–J155

Gender-based blood transcriptomes and interactomes in multiple sclerosis: Involvement of SP1 dependent gene transcription

Ramesh Menon [a,b,1], Marco Di Dario [a,b,1], Chiara Cordiglieri [a,b], Silvia Musio [b], Loredana La Mantia [b], Clara Milanese [b], Anna Luisa Di Stefano [c], Massimo Crabbio [c], Diego Franciotta [d], Roberto Bergamaschi [c], Rosetta Pedotti [b], Enzo Medico [e], Cinthia Farina [a,b,*]

1) Identification of female and male specific expression signatures for RRMS

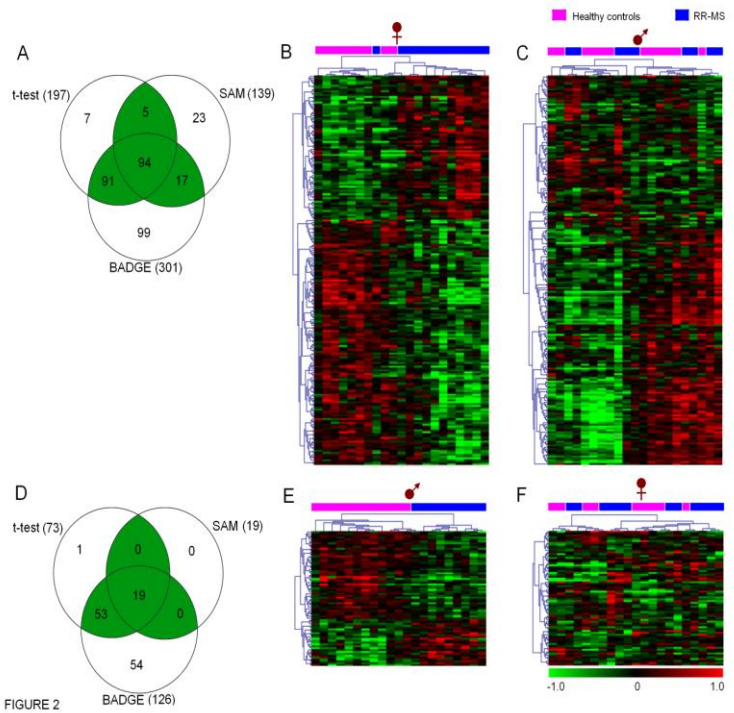
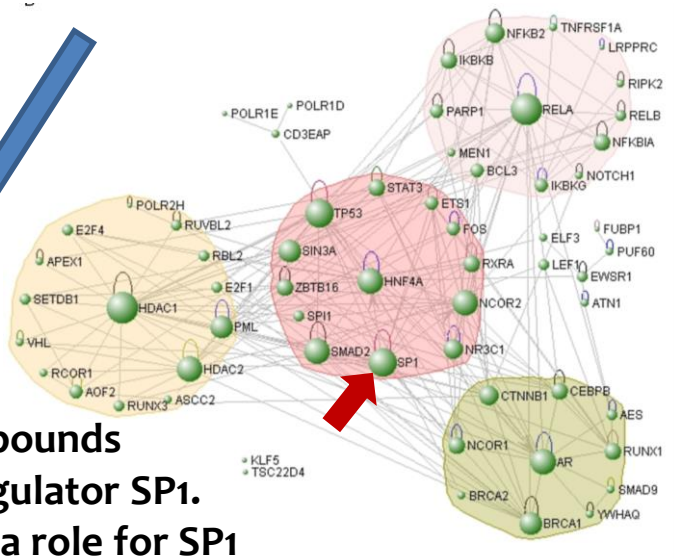


FIGURE 2

Bioinformatics,
Network Biology,
In silico

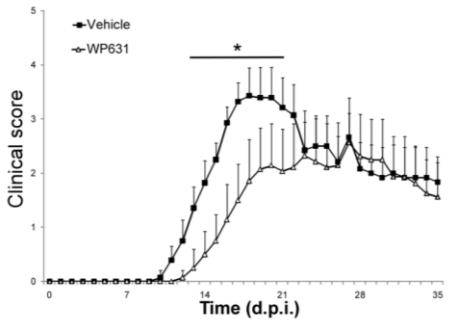
2) Search for candidate master regulators of transcription in MS



Immunology,
In vitro

3) Identification of compounds targeting the master regulator SP1. Functional validation of a role for SP1 In human and mouse blood cells.

Animal model of disease
In vivo



4) In vivo validation for SP1 as a regulator of neuroinflammation.

fondazione cariplo

Transcriptional profiling to dissect MS stages

SCIENTIFIC REPORTS | 7: 8981 | DOI:10.1038/s41598-017-09286-y

Transcriptional dysregulation of Interferome in experimental and human Multiple Sclerosis

Sundararajan Srinivasan[1,2], Martina Severa[3], Fabiana Rizzo[3], Ramesh Menon[1], Elena Brini[1], Rosella Mechelli[4], Vittorio Martinelli[1], Paul Hertzog[5], Marco Salvetti[4,6], Roberto Furlan[1], Gianvito Martino[1,2], Giancarlo Comi[1,2], Eliana Coccia[3] & Cinthia Farina[1]

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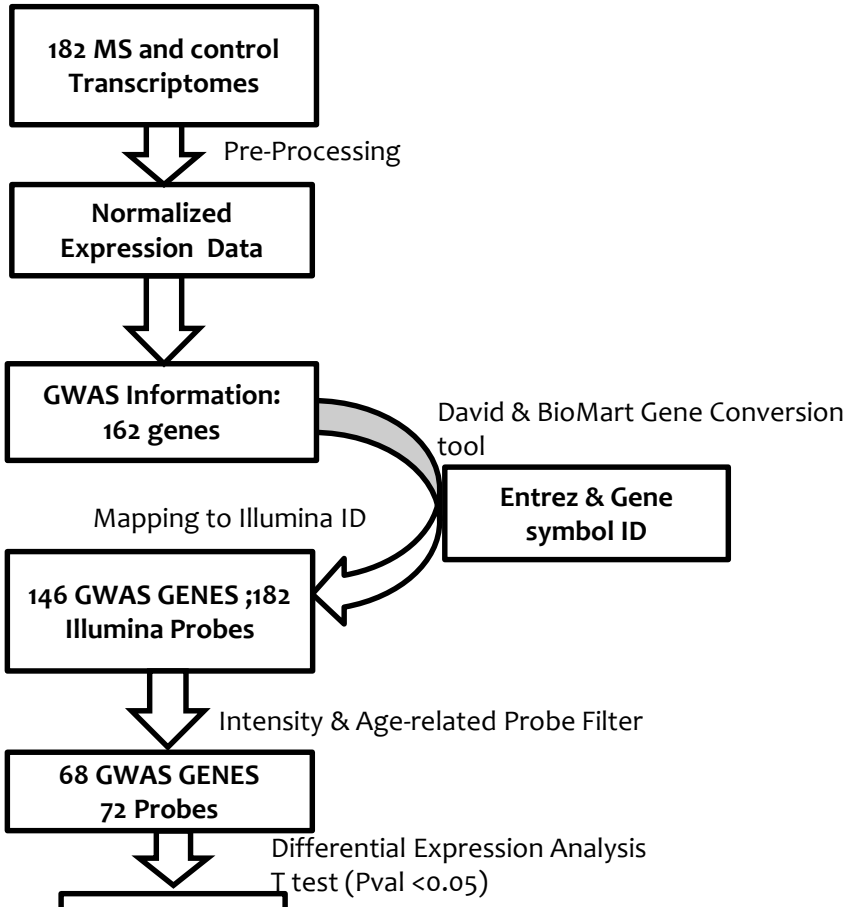
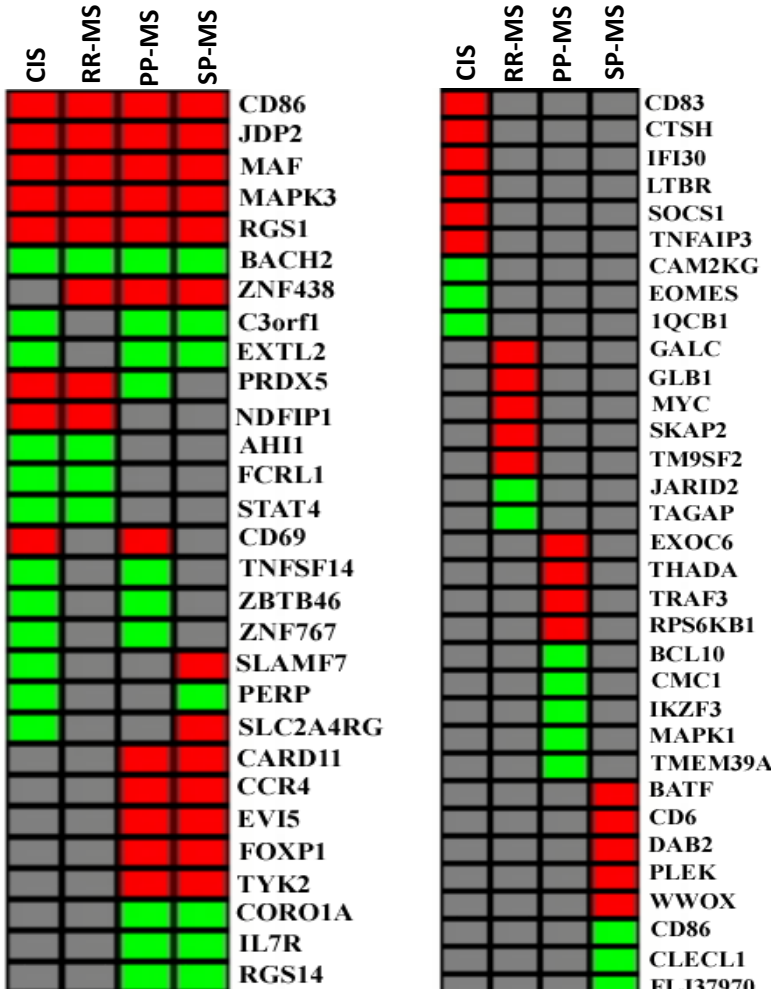
Marco Di Dario, MSc
Alessandra Russo, MSc
Ramesh Menon, PhD
Elena Brini, PhD
Marzia Romeo, MD
Francesca Sangalli, MD
Gloria Dalla Costa, MD
Mariaemma Rodegher, MD
Marta Radaelli, MD
Lucia Moiola, MD
Daniela Cantarella, MSc
Enzo Medico, PhD
Gianvito Martino, MD
Roberto Furlan, MD, PhD
Vittorio Martinelli, MD
Giancarlo Comi, MD
Cinthia Farina, PhD

Neurol Neuroimmunol Neuroinflamm 2017;4:e337; doi: 10.1212/NXI.0000000000000337

Dysregulation of MS risk genes and pathways at distinct stages of disease

Dysregulation of MS GWAS Genes at distinct stages of disease





Alteration in the expression of MS risk genes is not a stable feature reproduced throughout the distinct phases and forms of disease, but is a selective event for each disease stage

Summary- Immunity in MS

- **Dissection of MS through blood transcriptomics uncovers distinct changes in gene expression and pathways in MS subjects depending on sex and disease stage.**
- **It emphasizes epigenetic events as basis for MS, with SP1 as key transcriptional master regulator of differential expression in human and experimental MS.**
- **Machine learning approaches for biomarker selection may allow the identification of transcriptional signatures predictive of MS stages.**