Inflammation and Immunity in Stroke

EUROPEAN STROKE NETWORK

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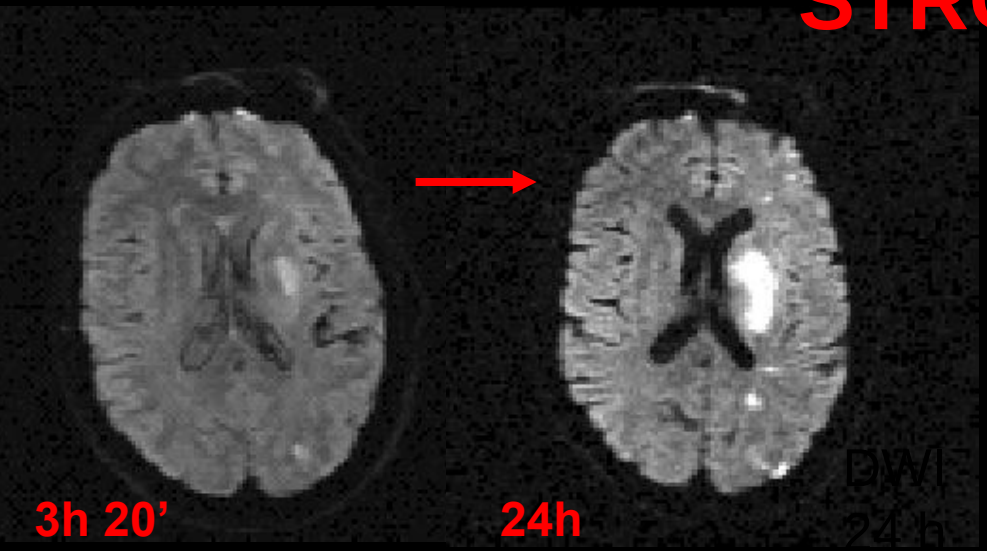
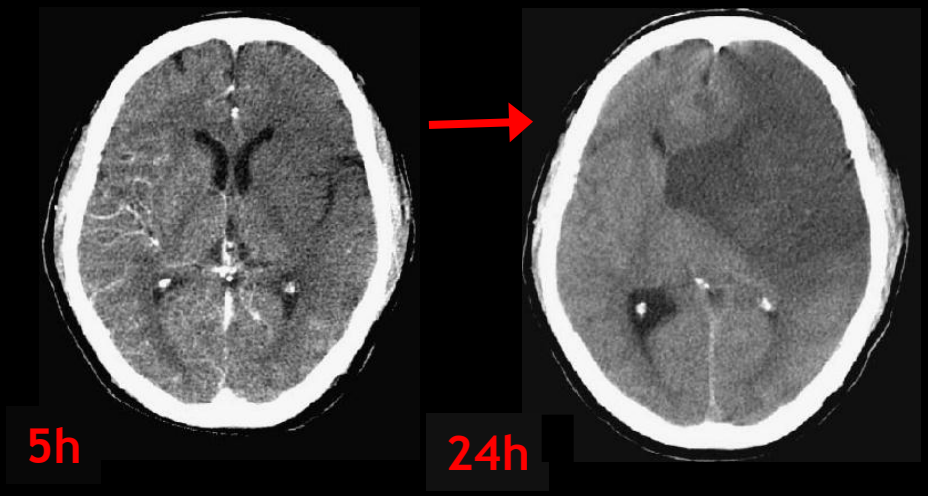
Anna M. Planas

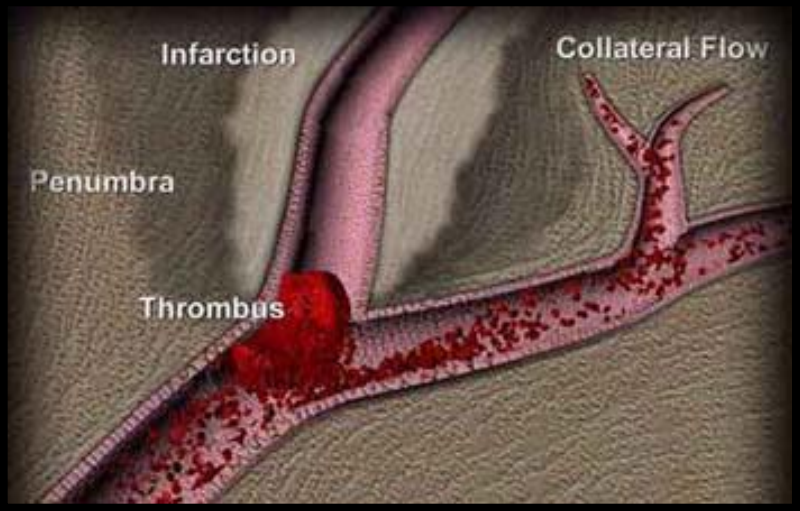
DISCLOSURES: none

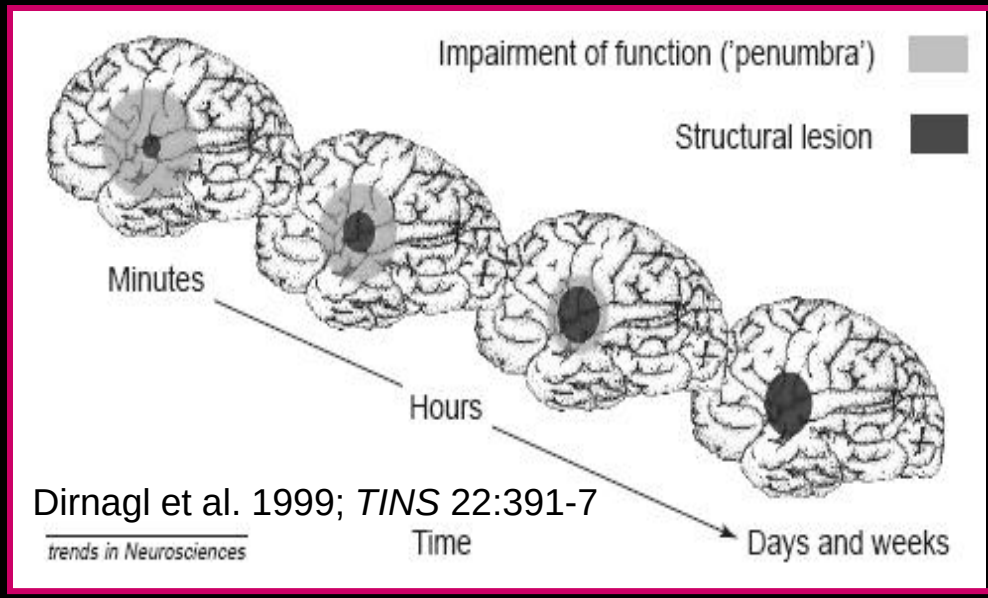
"In the last two years, I have not had a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation."

STROKE


3h 20’
24h
DWI
24 h


5h
24h

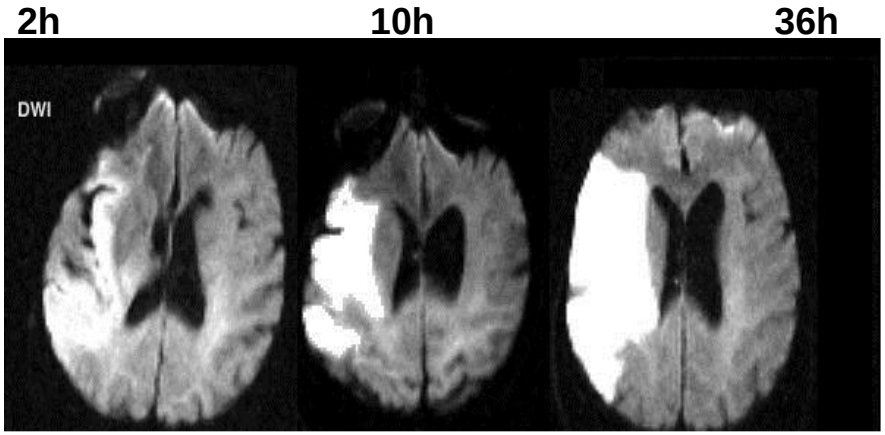

Infarction
Collateral Flow
Penumbra
Thrombus

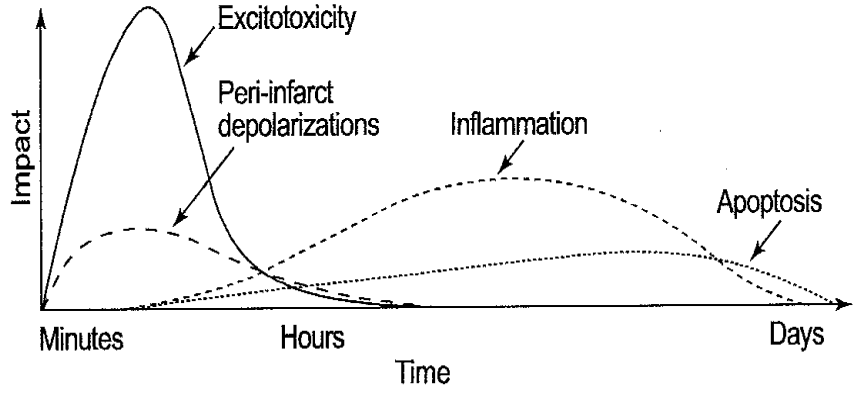

Impairment of function (‘penumbra’)
Structural lesion
Minutes
Hours
Days and weeks
Time
Dirnagl et al. 1999; *TINS* 22:391-7
trends in Neurosciences

The inflammatory cascade after brain ischemia

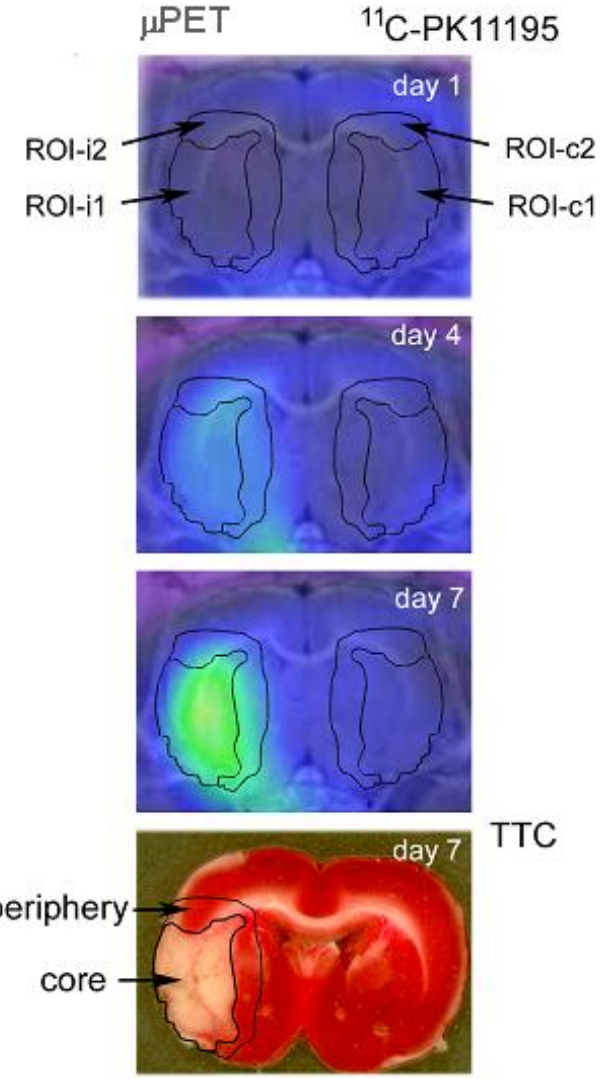
1) Reaction of resident cells: glial reaction
2) Adhesion and infiltration of leukocytes
3) Molecular players: cytokines, chemokines, adhesion molecules, TLR, complement…

Rojas et al, 07
JCBF 27:1975





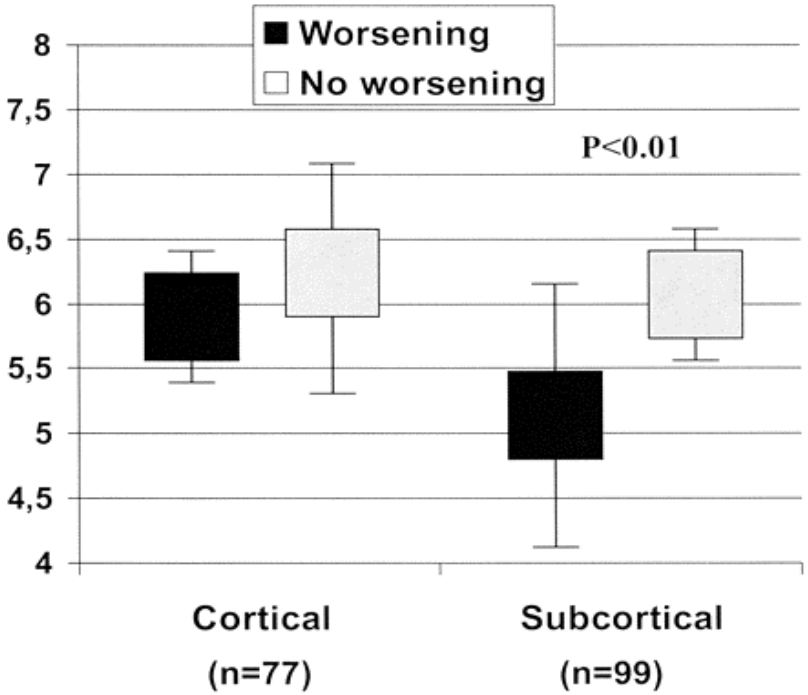
Dirnagl et al. 1999; *TINS* 22:391-7



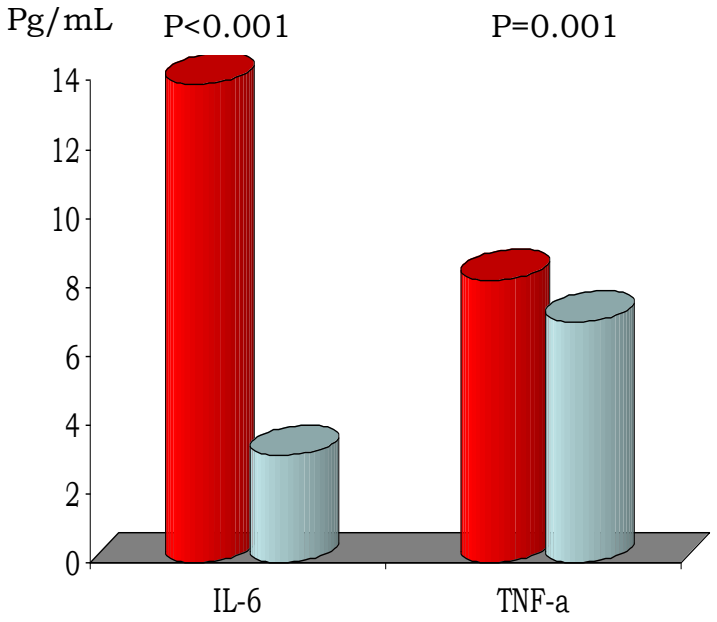
Inflammatory markers as clinical predictors of outcome

-Eritrocyte sedimentation rate
-C Reactive protein (CRP)
-Interleukin-6 (IL-6)
-Tumor necrosis fator (TNF)
-Intercellular adhesion molecule (ICAM-1)

Low plasma levels of IL-10 predict bad outcome and neurological impairment
Vila et al. (2003) *Stroke*



High plasma levels of IL-6 and TNF-α predict bad outcome and neurological impairment
Castellanos et al. (2002) *Stroke*

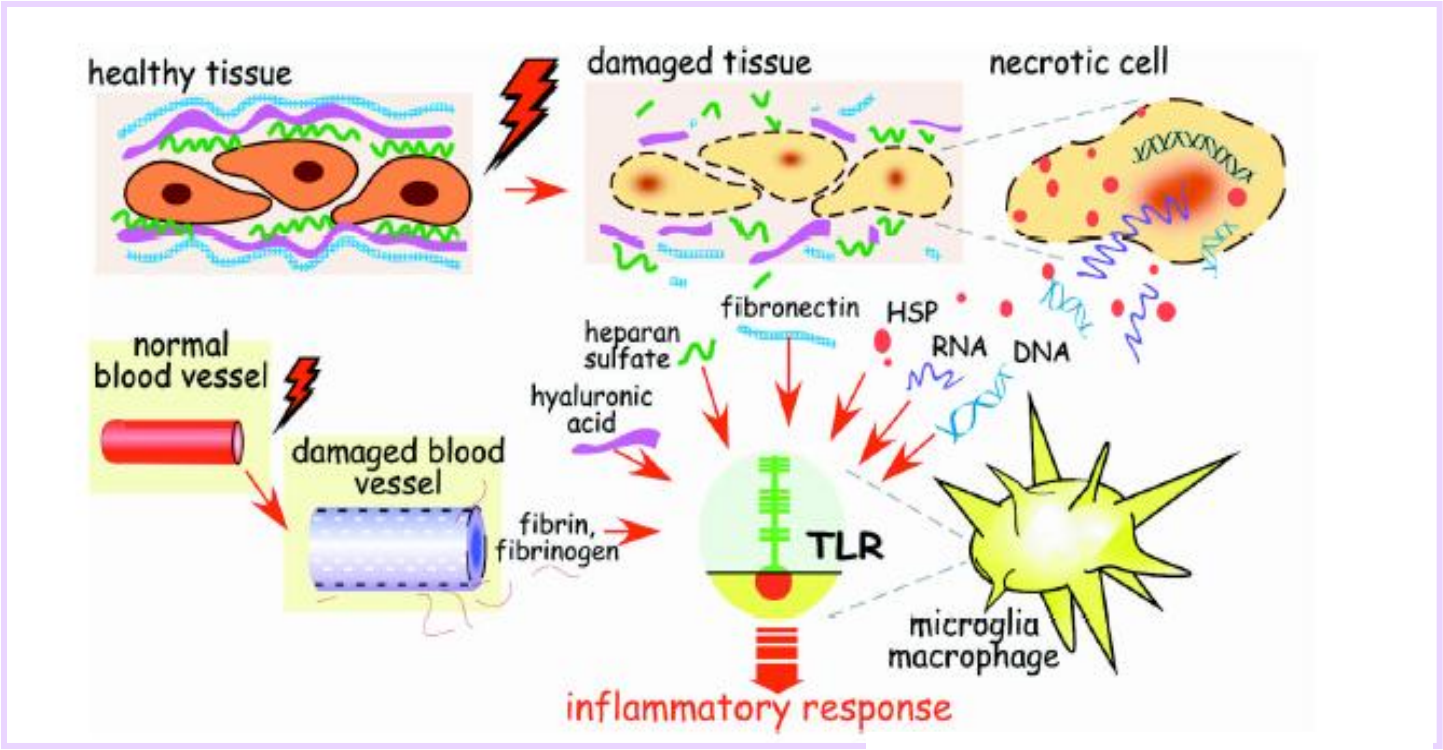


Mean ± SD delay to sampling 8.2 ± 5.7 hrs

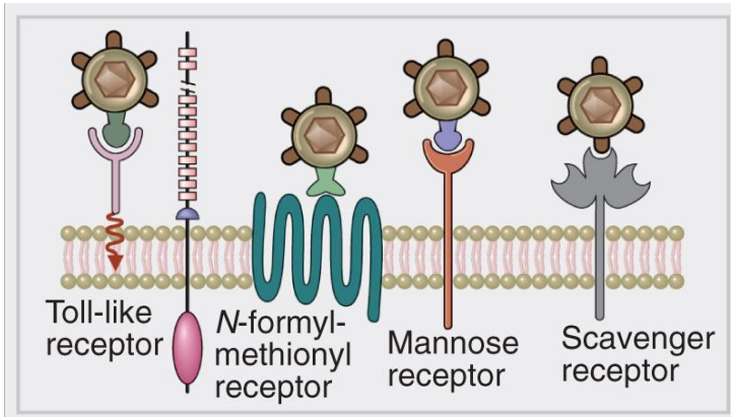
Lacunar stroke (n=113) Controls (n=43)

How is inflammation triggered after stroke??

Matzinger P, 2007
Nat Immunol



Kariko et al 2004 *JCBF* 24:1288

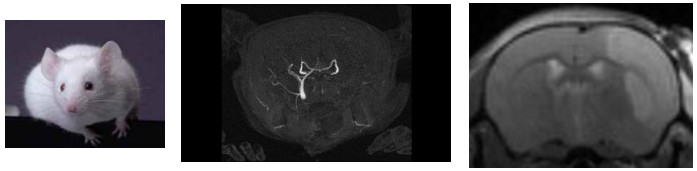


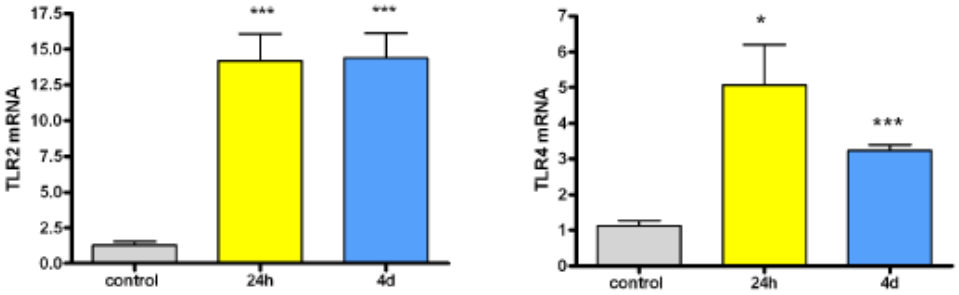
Ischemia induces danger signals activating the innate immune system

Innate Immunity
Cell Associated Receptors

TLR expression increases after ischemia

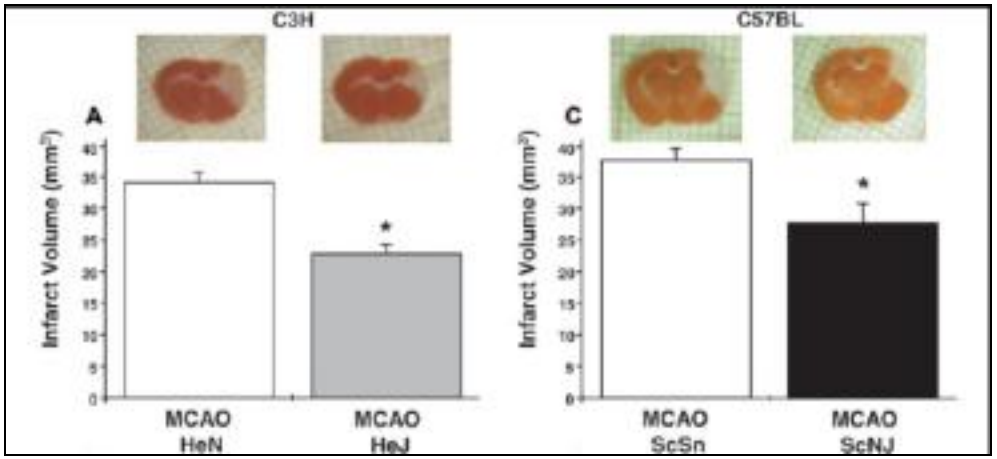
(Perez-de Puig et al., unpublished)





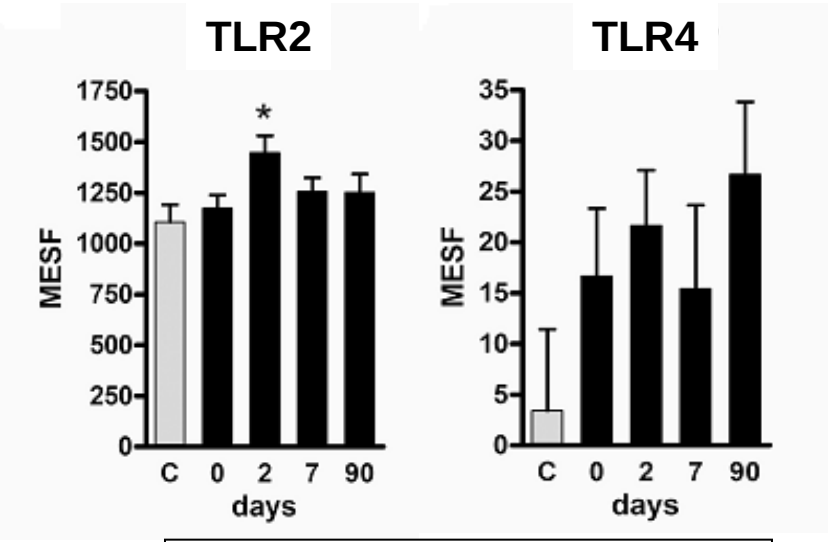
TLR-4 contributes to the brain lesion after ischemia in mice

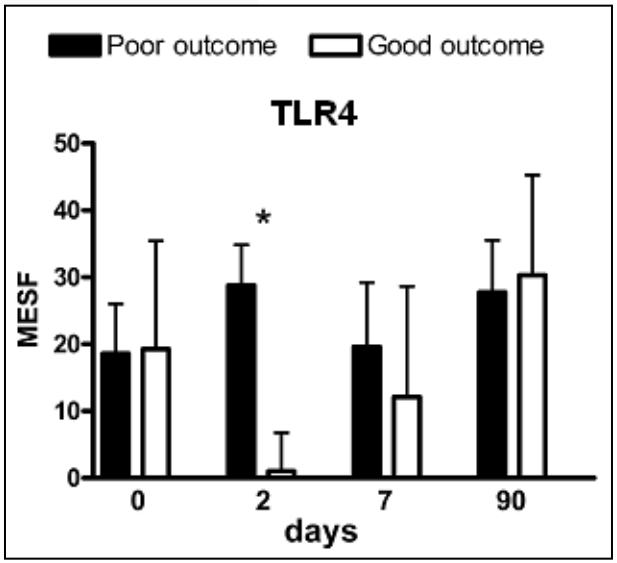
Caso et al., *Circulation*. 2007



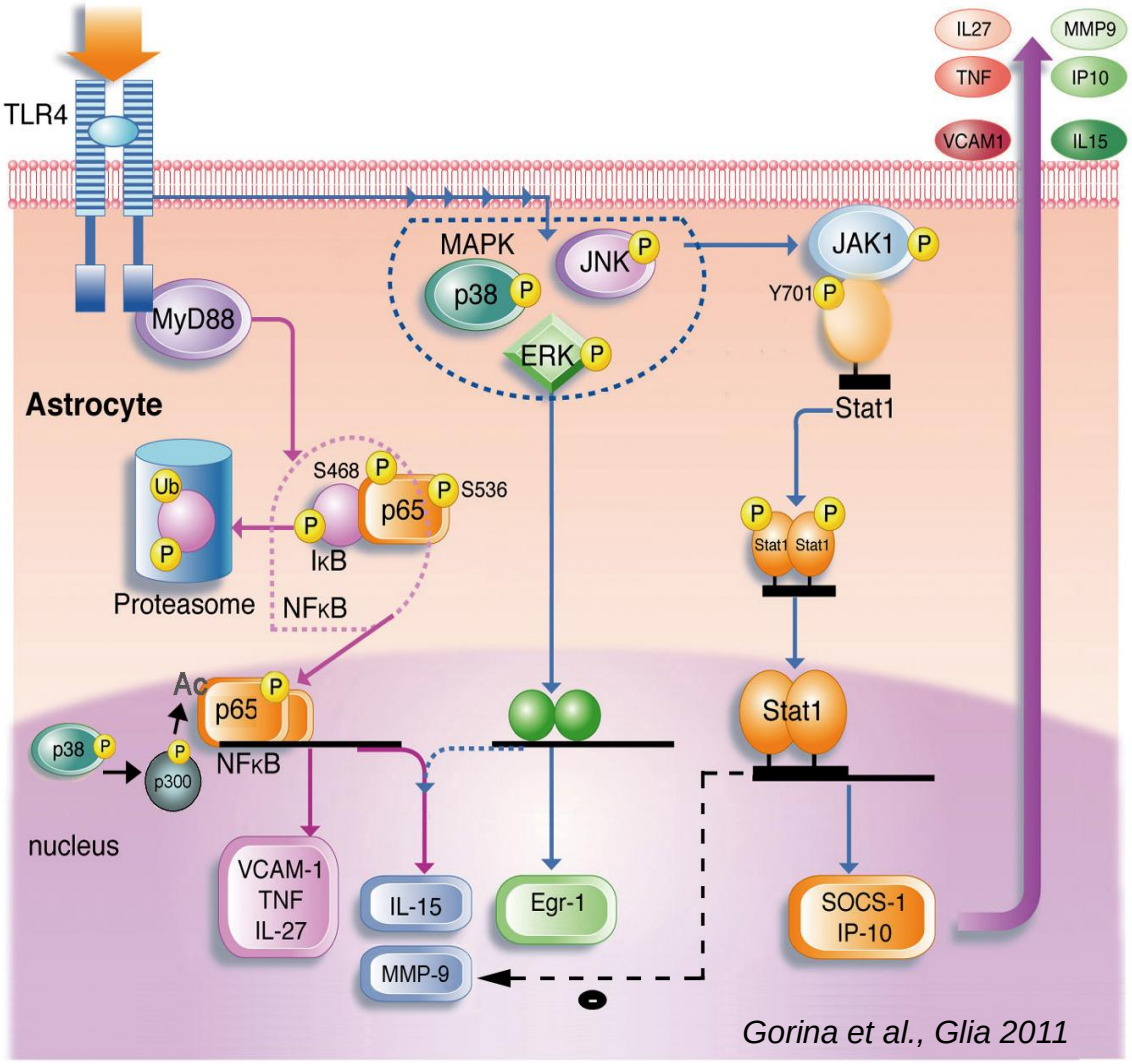
TLRs in monocytes of stroke patients

Urra et al., *Stroke* 2009

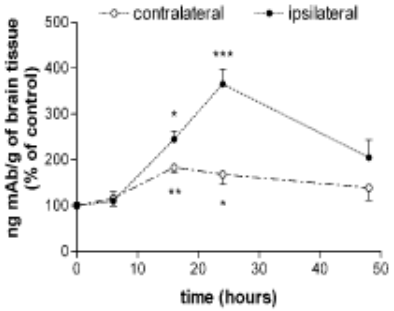


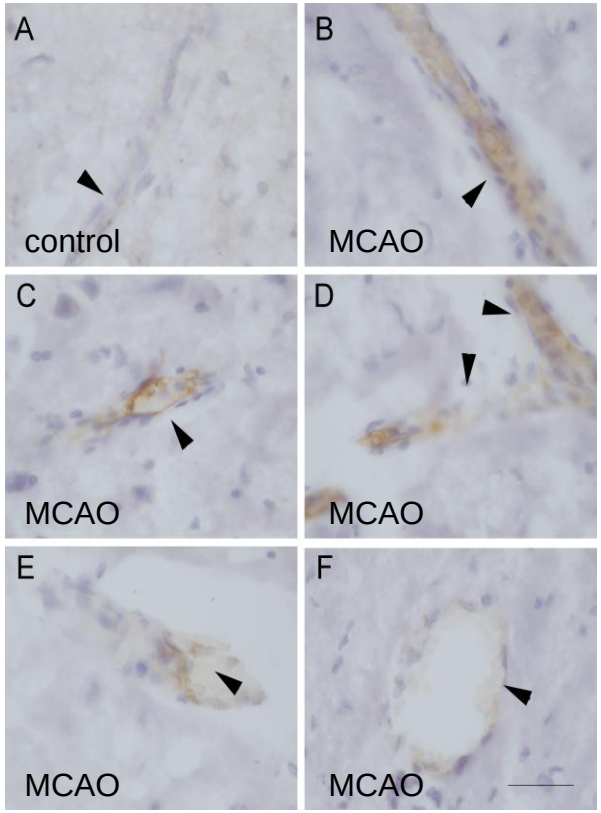


How does innate immune receptor activation contribute to inflammation?



VCAM-1



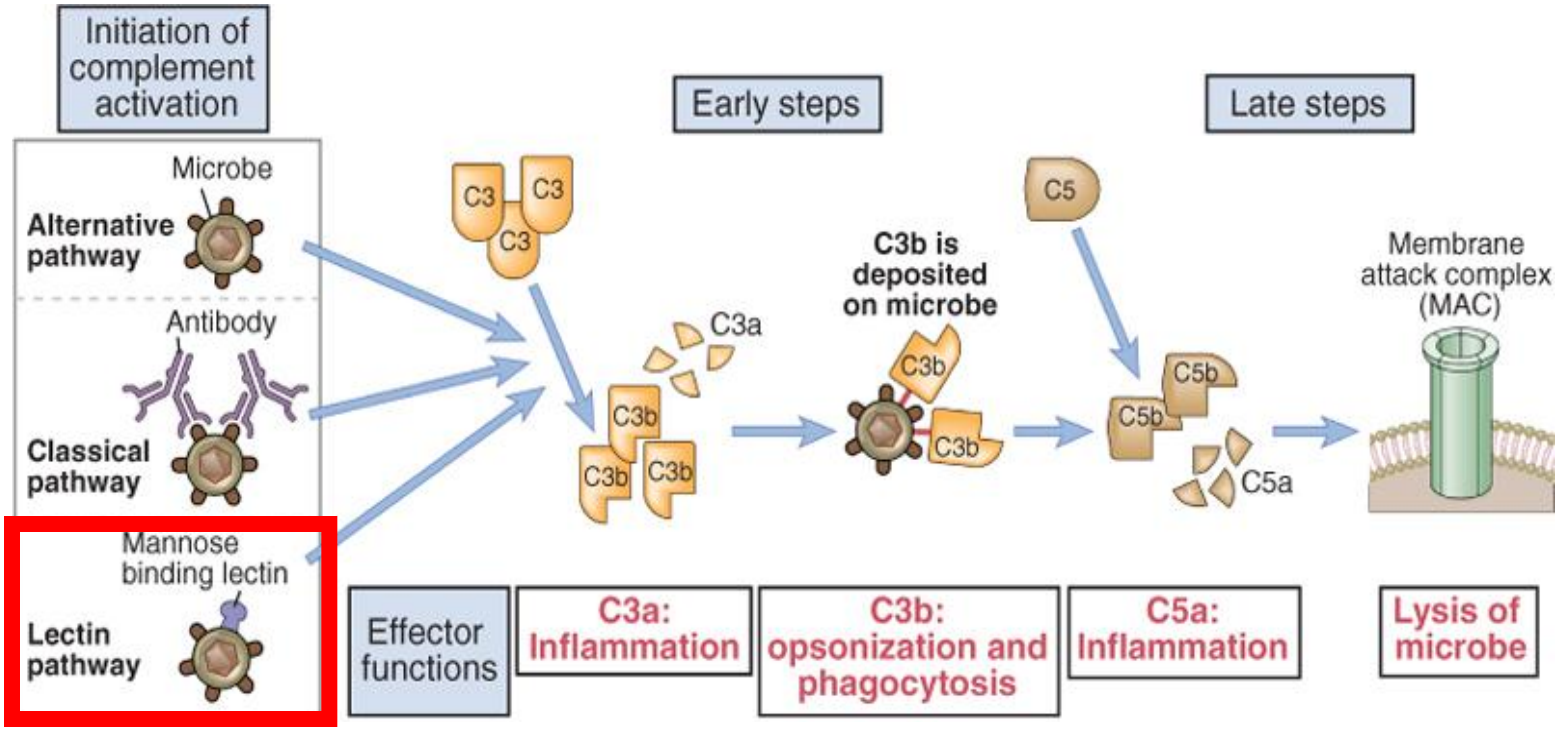


Justicia et al., 2006
J Cereb Blood Flow Metab. 26:421-32

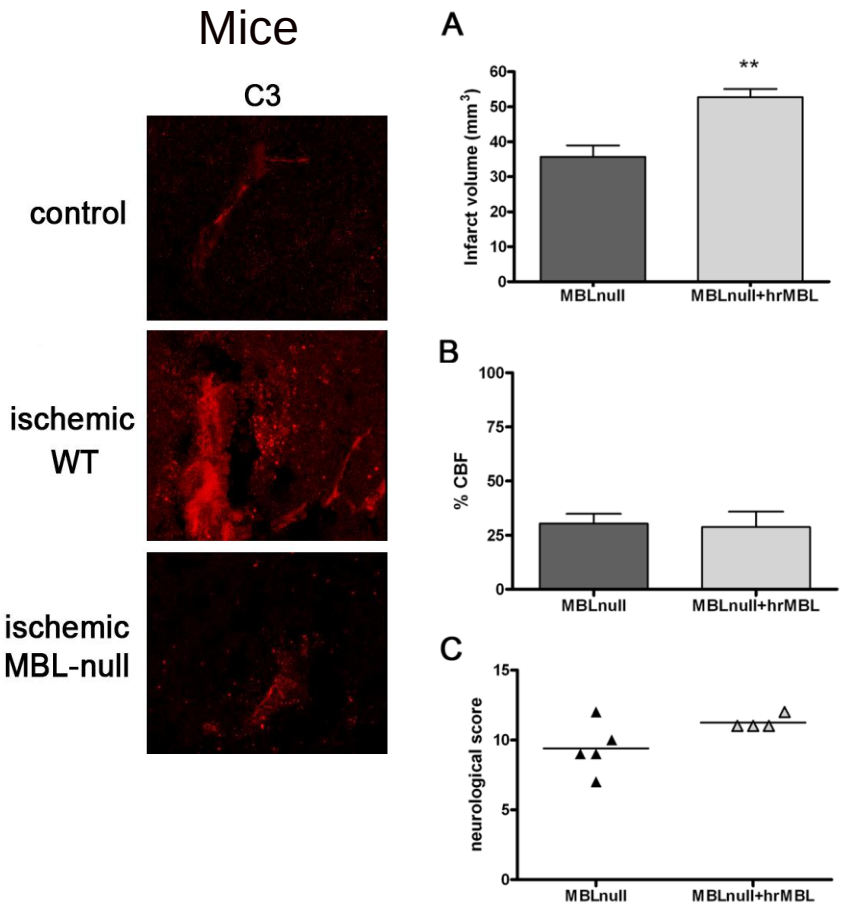
The Complement System responds to stroke

The complement system is activated in rodents after brain ischemia
De Simoni et al., 2004, *Am J Pathol* 164:1857-63

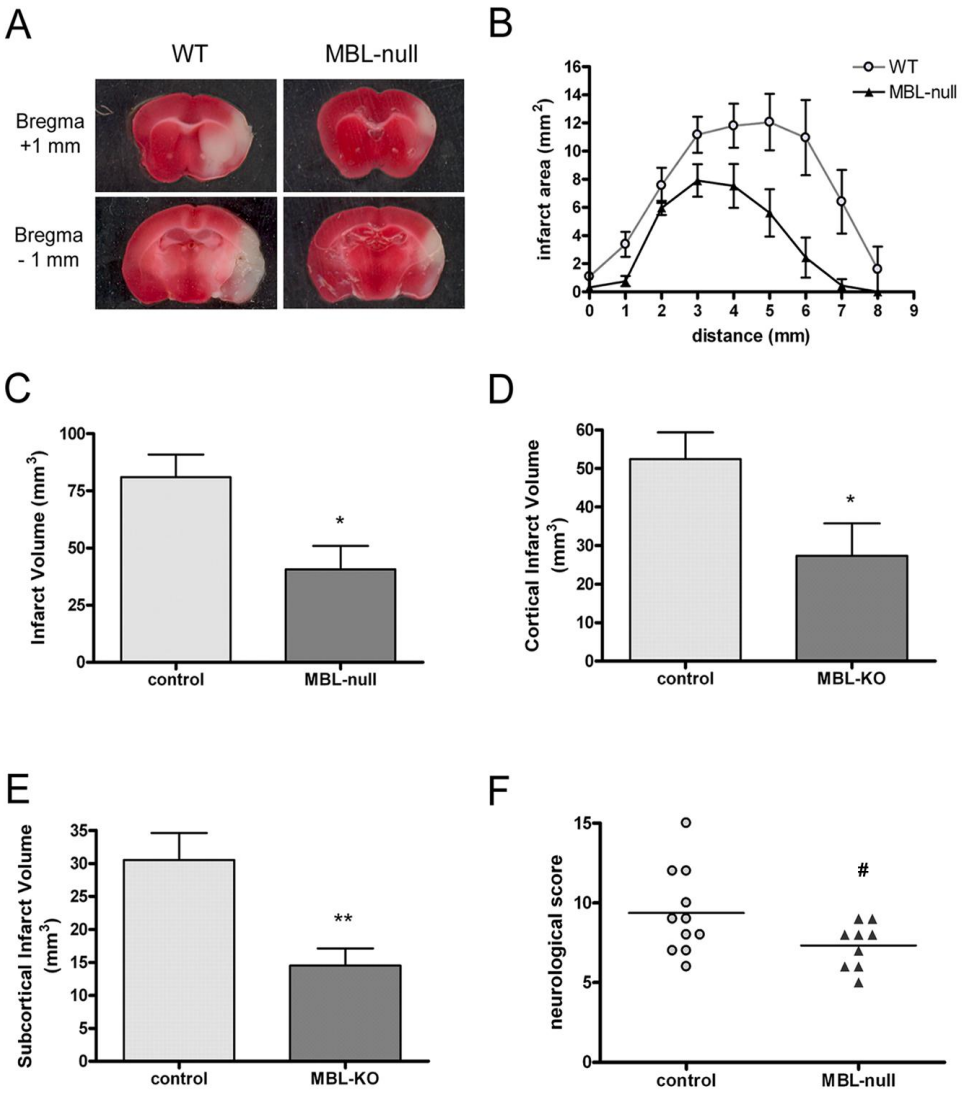
The complement system is activated in patients with acute stroke
Mocco et al., 2006, *Neurosurgery* 59:28-33 and *Circ Res* 99:209-17



The Lectin Pathway
Experimental ischemia/reperfusion in Manose-Binding Lectin (MBL) null and wt mice



2-h MCAO +48h reperfusion in mice WT / MBLnull



Cervera et al., PlosOne 2010

The Lectin Pathway in stroke patients

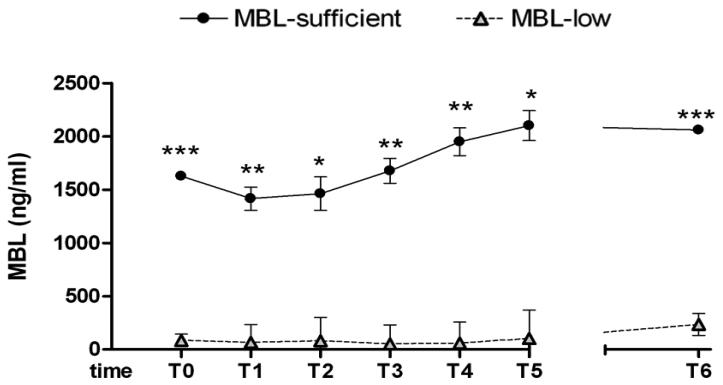
Manose-Binding Lectin (MBL) : MBL-sufficient and MBL-low genotypes

Baseline characteristics in the study population (n=135) according to MBL genotype

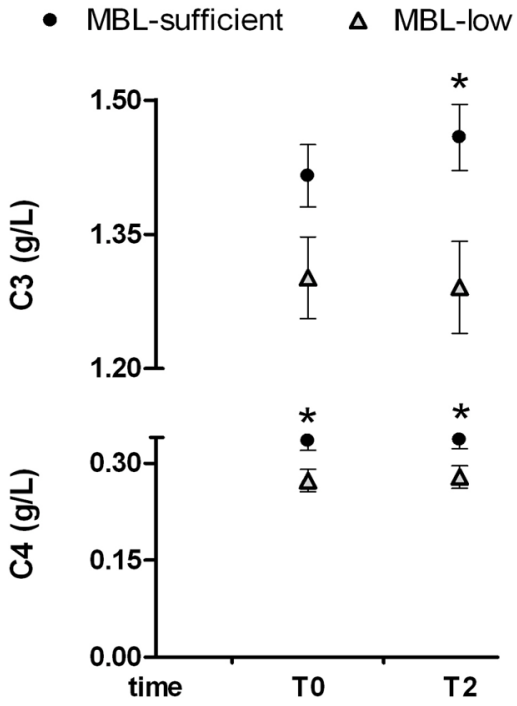
		MBL-low N=24 (18%)	MBL-sufficient N=111 (82%)	p value
Age (mean, SD), yrs		73.9 (12.8)	72.9 (11.5)	0.67
Male, no.(%)		9 (37.5)	59 (53.2)	0.16
Active smoking, no. (%)		3 (12.5)	20 (18.0)	0.77
Hypertension, no. (%)		12 (50.0)	73 (65.8)	0.15
Diabetes, no. (%)		6 (25.0)	24 (21.6)	0.72
Coronary heart disease, no. (%)		2 (8.3)	15 (13.5)	0.49
Previous stroke, no. (%)		4 (16.7)	19 (17.1)	1.00
Peripheral artery disease, no. (%)		2 (8.3)	9 (8.1)	1.00
Admission NIHSS score, no. (%)				0.10
	0 to 6	5 (21)	14 (13)	
	7 to 17	13 (54)	56 (51)	
	>17	6 (25)	41 (37)	

Cervera et al., PlosOne 2010

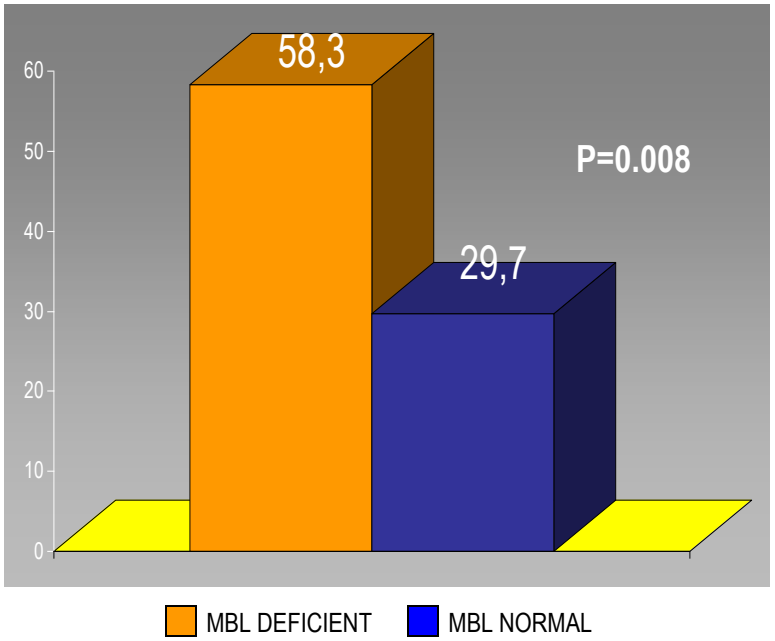
Stroke patients



60% MBL-low and
30% MBL-sufficient patients reached functional independence
(mRS score 0 to 2)
(χ2, p=0.008)



% GOOD OUTCOME AT 3 MONTHS

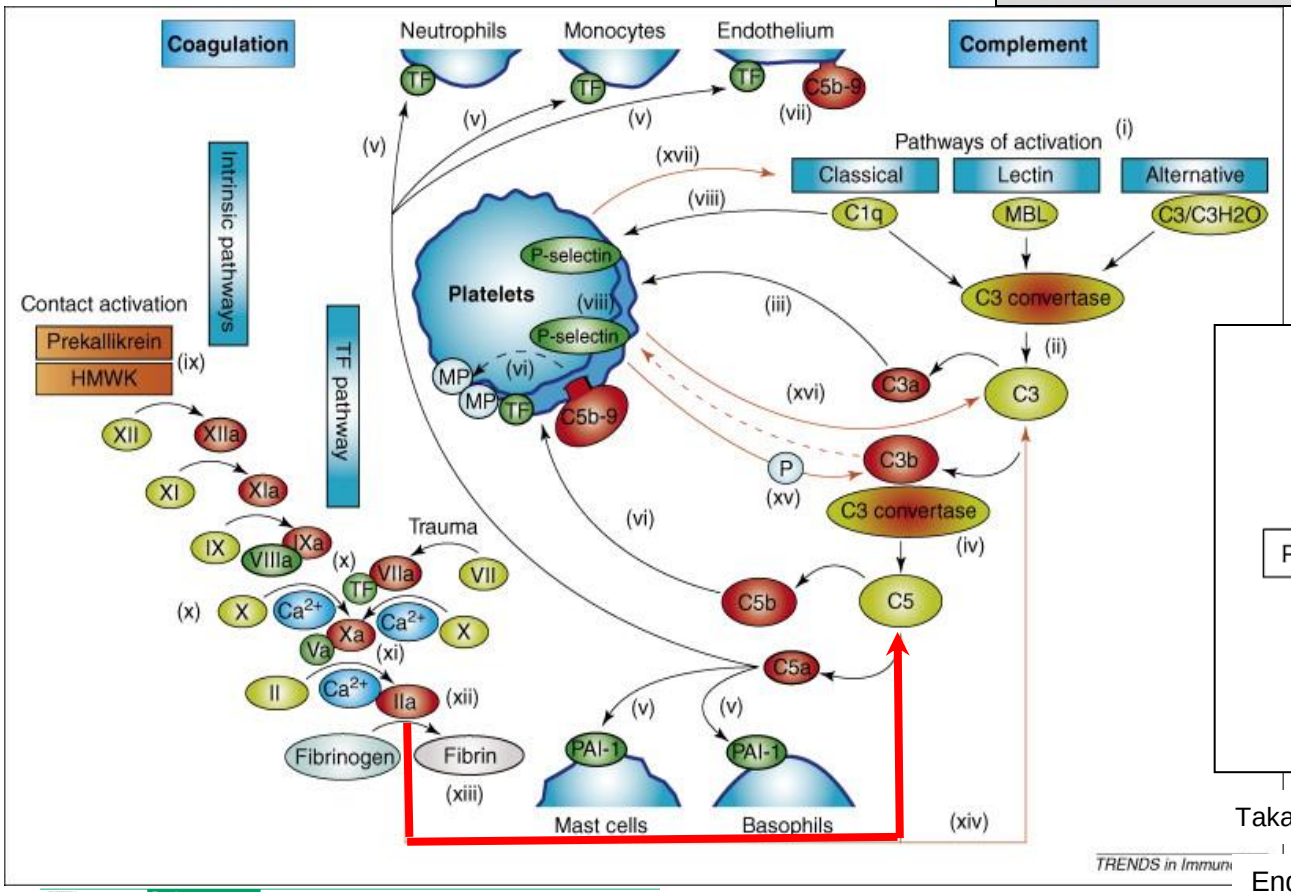


Cervera et al., PlosOne 2010

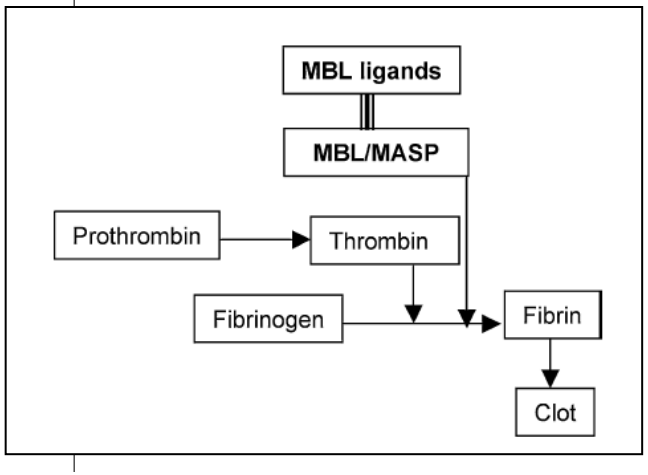
The complement can activate the coagulation cascade favoring secondary vessel occlusion

Coagulation activates complement:
- Platelets phosphorylate C3b and cleave C3
- Trombin and factor XIIa: cleave C3, C5

Complement has Procoagulant activity:
- Induces platelet activation
-↑ Cellular TF expression (C5)
- Modifies phospholipid membranes and facilitates the extrinsic coagulation pathway (TF)



In infections, complement induces local thrombus formation as a barrier to prevent bacterial dissemination in the circulation



Takahashi et al., 2011, *Immunobiology* 216:96–102

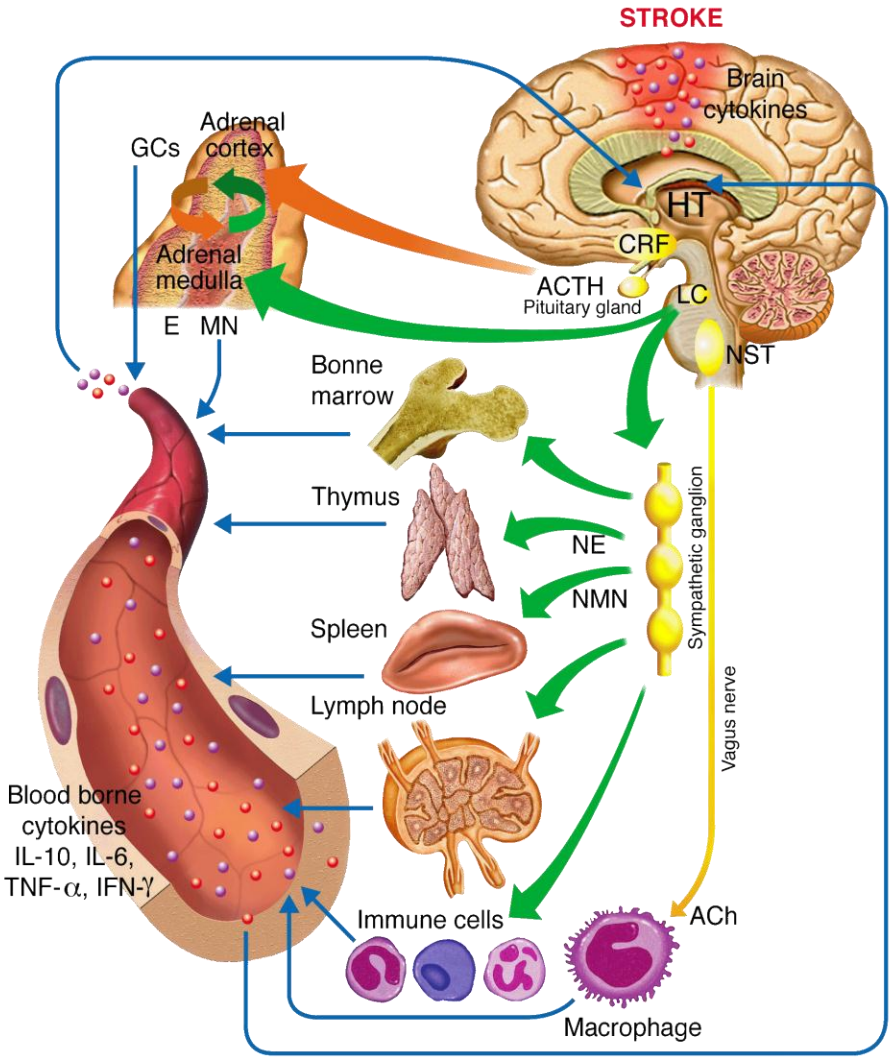
Endo et al., 2009 *J Innate Immun* 2:33-42

Review TRENDS in Immunology Vol.28 No.4

Complement and coagulation: strangers or partners in crime?

Markiewski et al., *TRENDS Immunol* 2007

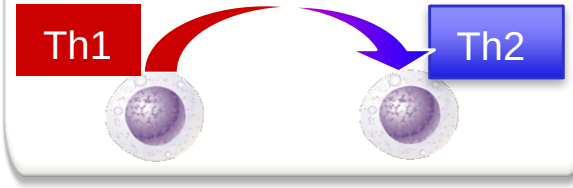
The cross-talk between the CNS and the immune system: *stroke-induced immunodepression facilitates infection*

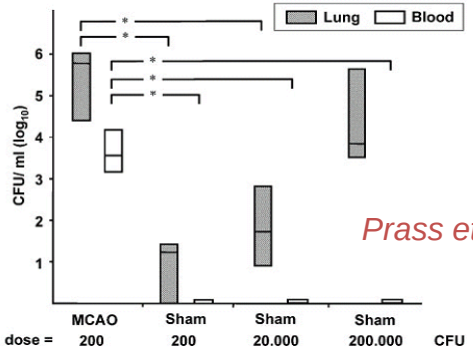


Chamorro et al, Stroke, 2007

Prass et al, J Exp Med, 2003

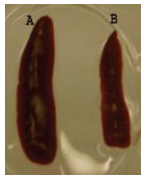
Lymphocytopenia
Apoptosis of thymocytes
Change in cytokine production



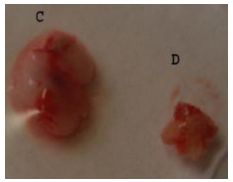


Prass et al, Stroke, 2006

Martin et al ., Mol Imaging, 2008

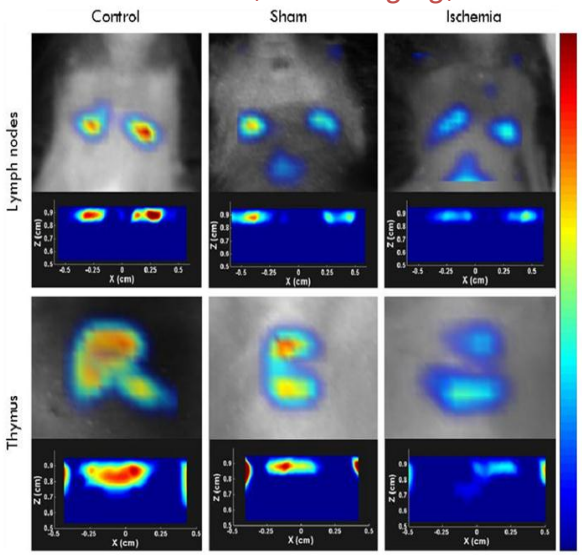


Spleen

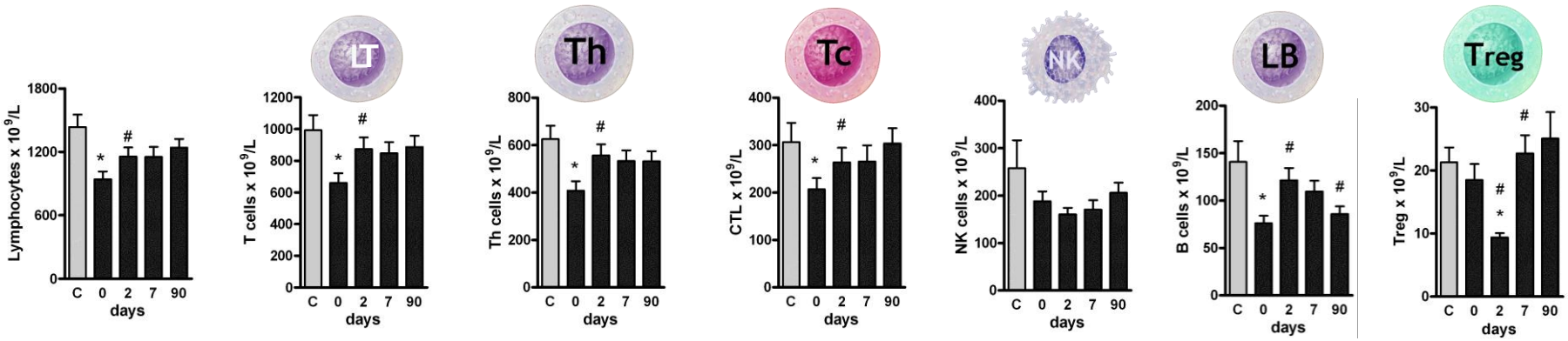


Thymus

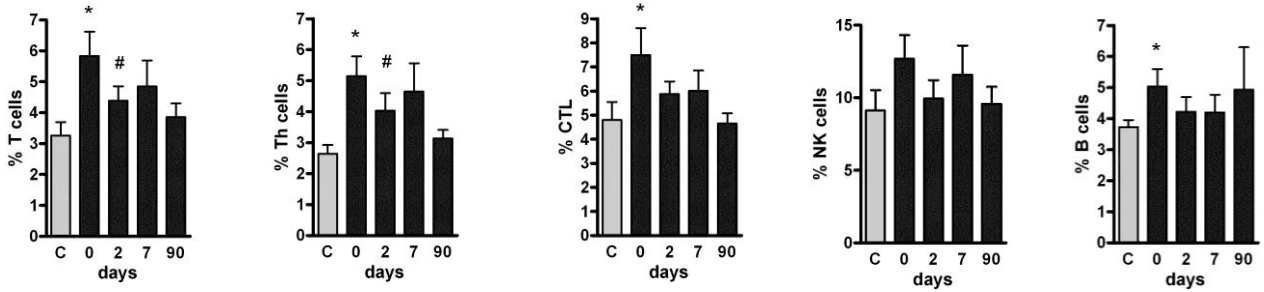
Offner et al, J Immunol, 2006



Lymphocytes



Apoptosis



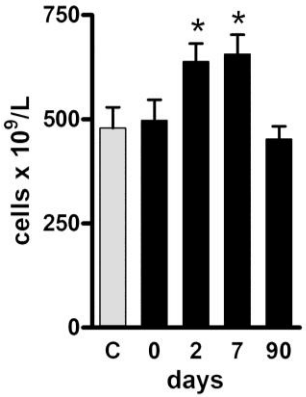
Infection **Prognosis**

Lymphocytes ↓ Activated B cells ↑

T cells ↓ B cell count ↓

Urra et al, Neuroscience, 2009; Vogelgesang et al, Stroke, 2008, Haeusler et al, Cerebrov Dis, 2009

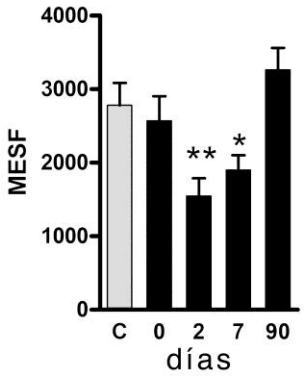
Monocytes



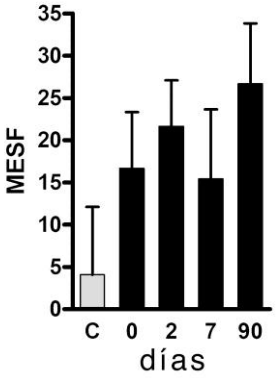
Phenotype

Function

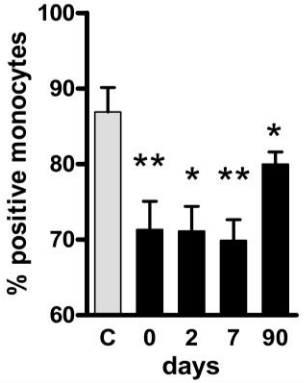
HLA-DR



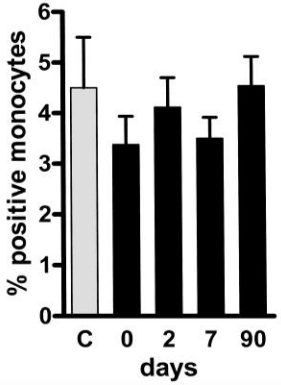
TLR4



TNF-α



IL-10



Infection

HLA-DR CD49d

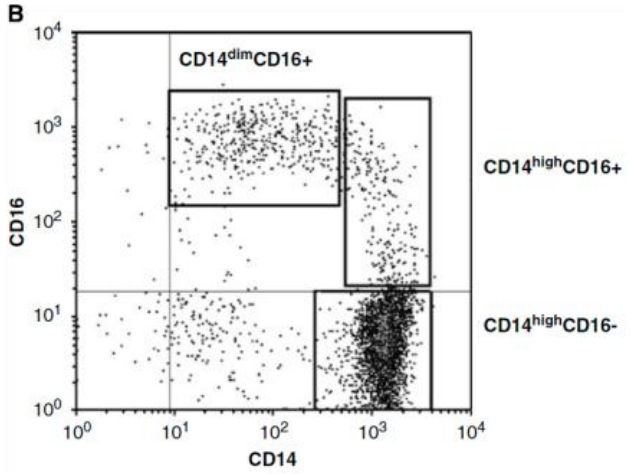
CD86 TNF-α

Prognosis

TLR4

Urra et al, Stroke, 2009; Yang et al, JCBFM, 2008, Haeusler et al, Cerebrov Dis, 2009

Monocyte subtypes



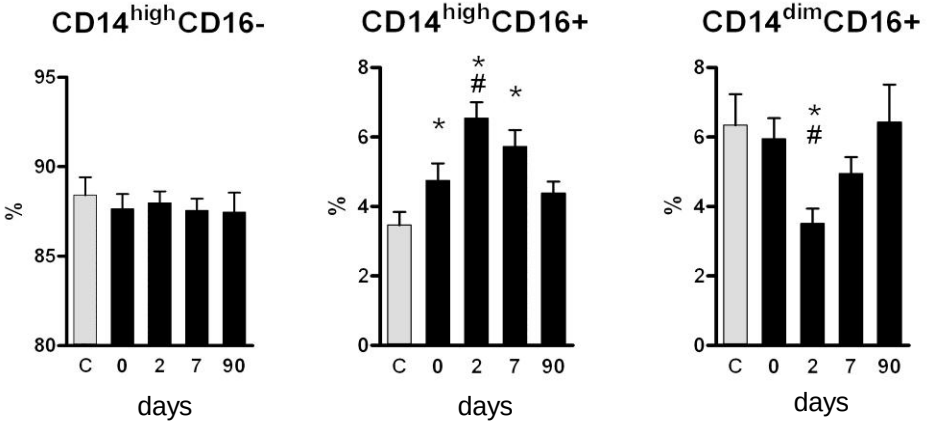
CD16: *"bad guys"* inflammation
cancer

CD14: main subtype

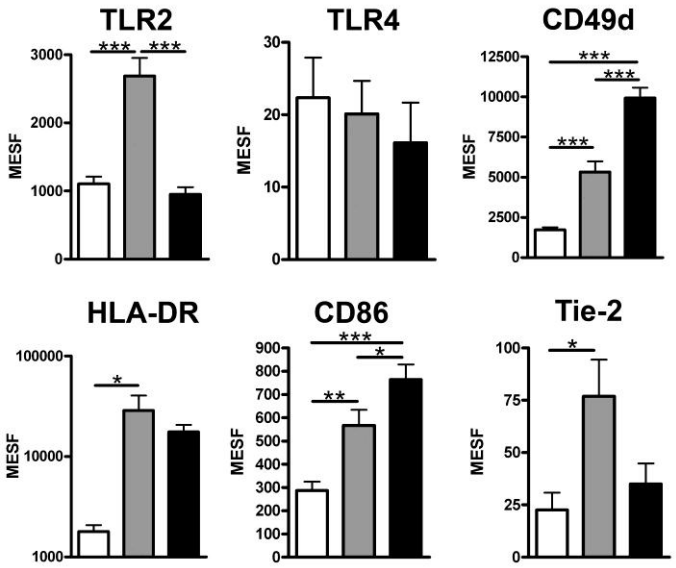
Phenotype	$CD14^{high}CD16-$	$CD14^{dim}CD16+$	$CD14^{high}CD16+$
Frequency	85%	10%	5%
Function	Inflammation	TNF-α Non-inflammed tissues	IL-10

Urra et al, JCBFM, 2009

Monocyte subtypes after stroke

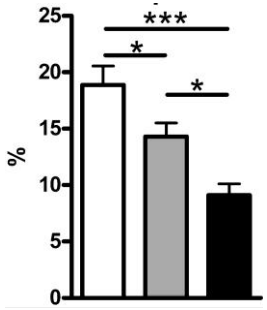


Phenotype

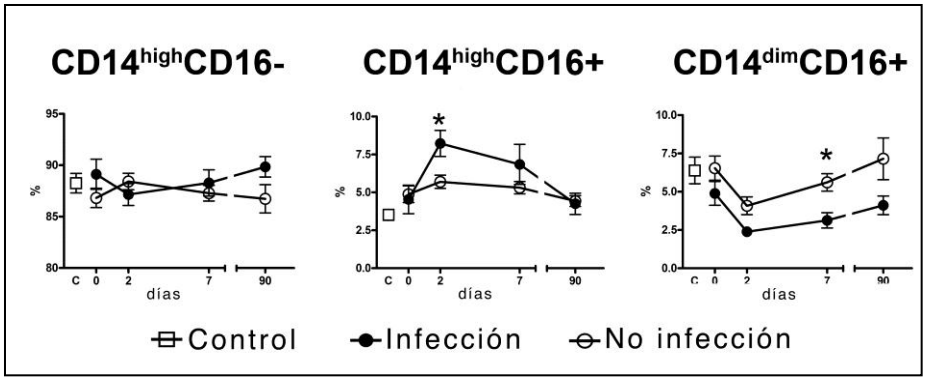


CD14highCD16-
CD14highCD16+
CD14dimCD16+

Platelet-monocyte complexes

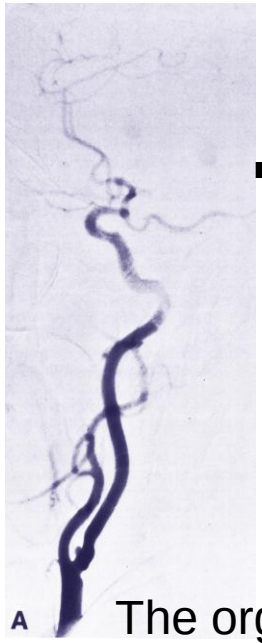


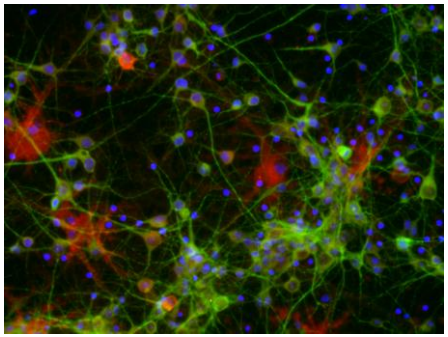
Infection



Urra et al (2009) J Cereb Blood Flow Metab;
Urra et al (2009) Stroke

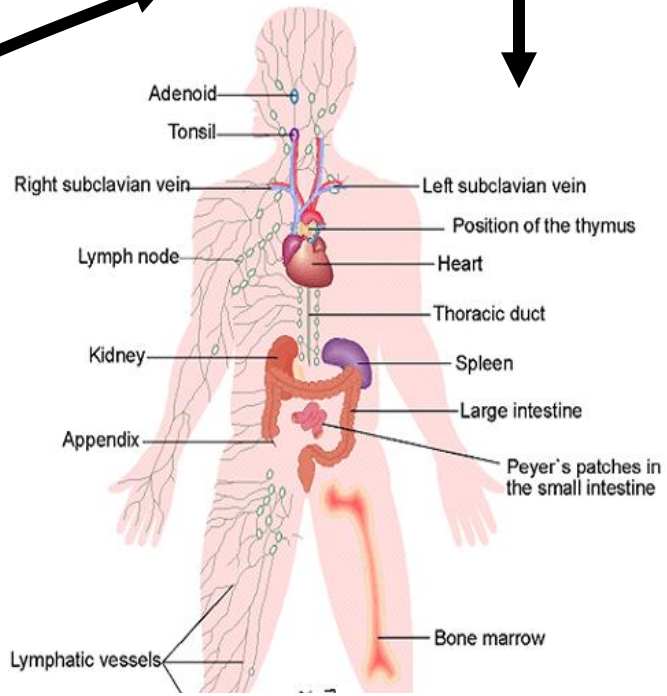
	Early worsening	Poor prognosis	Mortality
CD14^{h}CD16-, OR	**1,29**	**1,38**	**1,40**





The organism becomes aware of brain damage and reacts to it through the immune system. The innate immune system is quickly activated and mediates secondary reactions.

But how and why???



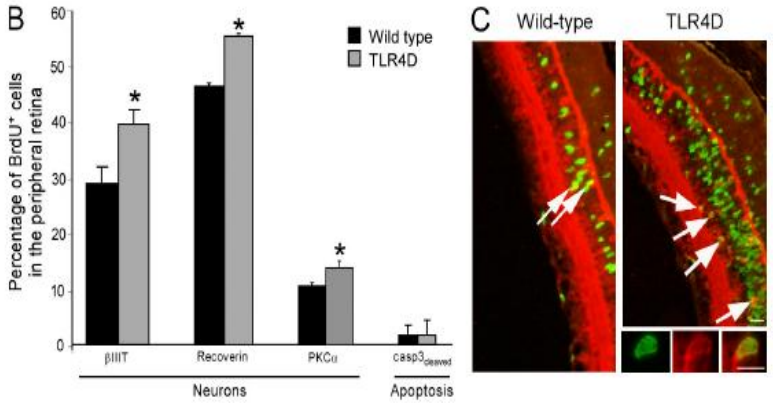
Initiation of damage resolution and repair???

Certain immune responses can alter mechanisms of protection and repair

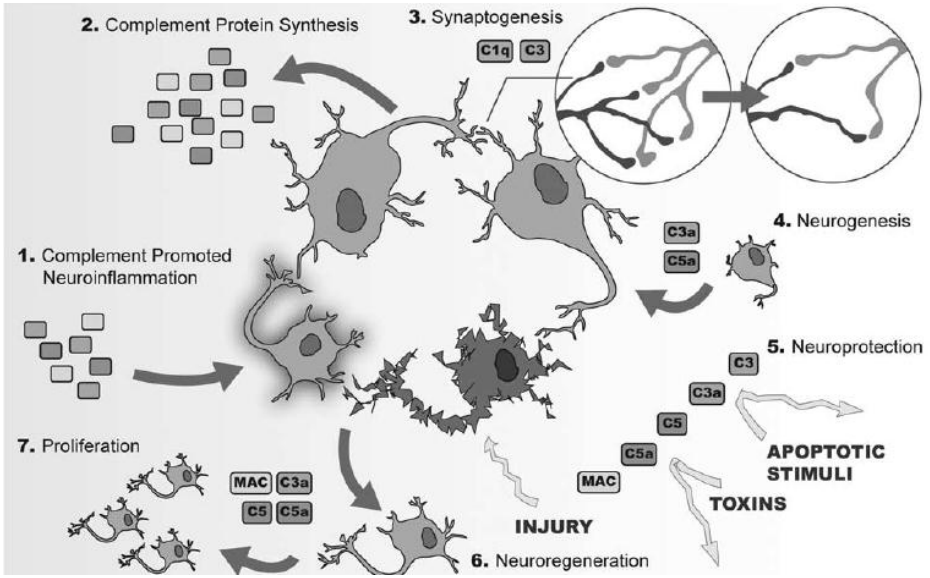
Inflammation and innate immunity in neurogenesis

Deficiency in TLR4 in the early postnatal retina results in increased neuronal differentiation

Shechter et al 08 J Cell Biol 183:393

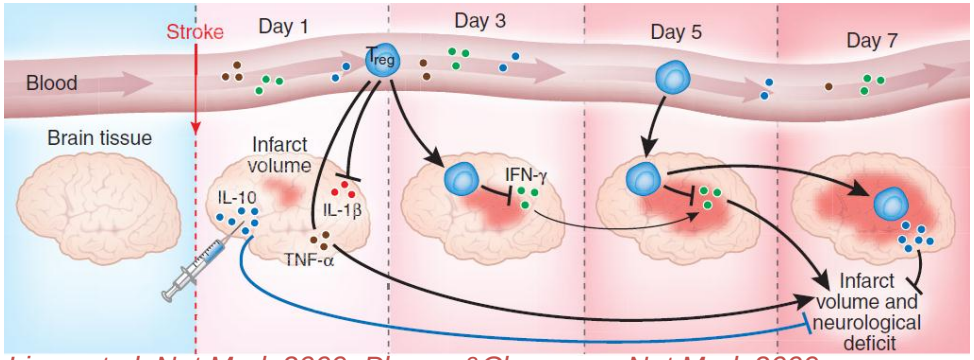


Complement affects neurogenesis and regeneration



Rutkowski et al., Immunol Cell Biol. 2010

Regulatory T cells protect the brain after stroke



Liesz et al, Nat Med, 2009; Planas &Chamorro, Nat Med, 2009

CD14++CD16+Tie2+ monocytes

Phagocytosis / Angiogenesis

Protective effects in myocardial ischemia

Nahrendorf et al, J Exp Med, 2007
Tsujioka et al, JACC, 2009

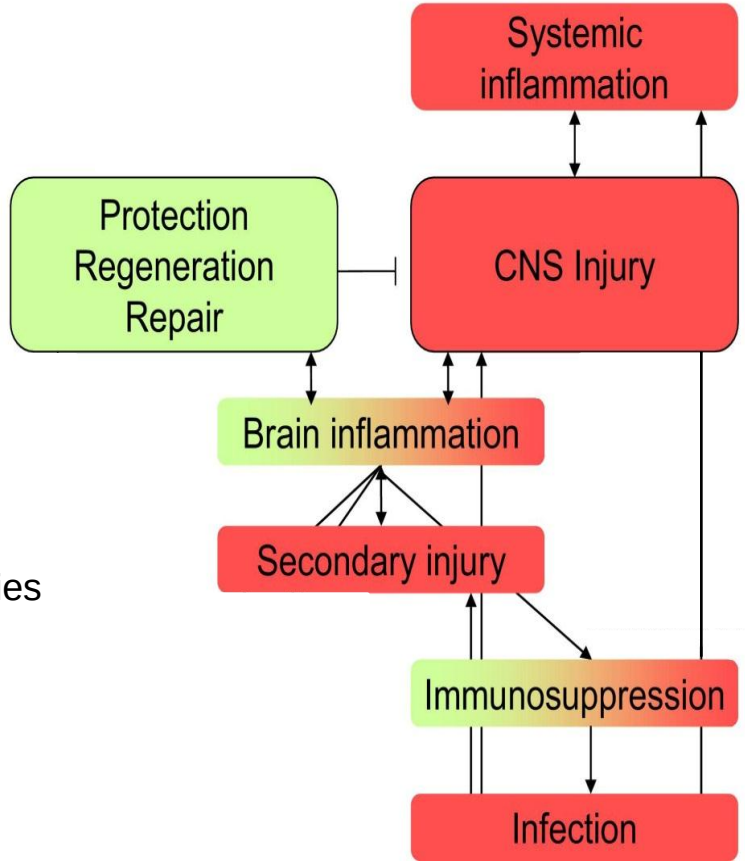
Therapeutic strategies

Modulate post-stroke immune responses

Downregulate deleterious responses and enhance protective mechanisms

- Attenuate lymphocyte activity
- Promote the action of regulatory lymphocytes
- Prevent complement activation
- Limit proinflammatory cytokines
- Favour antiinflammatory cytokines
- Promote recovery
- Antibiotics
- Combine immunomodulatory and thrombolytic therapies

Will effective treatments in experimental ischemia translate into the clinic?



Urra et al., *Stroke* 2010

Conclusions

- Innate immunity plays an active role in inflammation and brain damage after stroke
- Genetics may affect the features and magnitude of inflammatory and/or immune responses: towards a more personalised treatment?
- Stroke induces a transient immunodepression that favours systemic infections
- The study of blood cells can improve our understanding of the interactions between brain and immune system in stroke
- The modulation of specific immunological targets offers new therapeutic avenues that are being explored
- Inflammation and innate immunity affect neurogenesis and repair. Understanding the intensity of the signals and their time course is essential for the design of novel therapeutic strategies.

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EUROPEAN STROKE NETWORK

GOBIERNO DE ESPAÑA MINISTERIO DE CIENCIA E INNOVACIÓN

Agència de Gestió d'Ajuts Universitaris i de Recerca