Regulation of astrocyte activity by glycolipid metabolism

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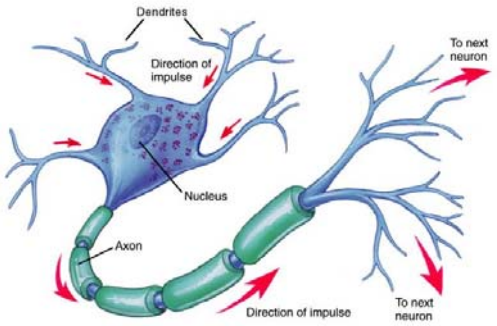
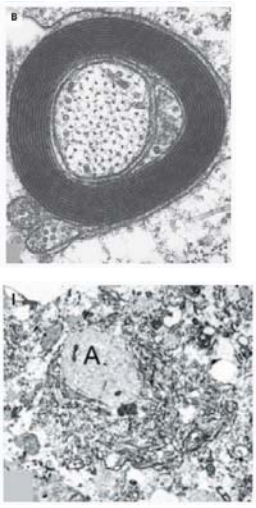
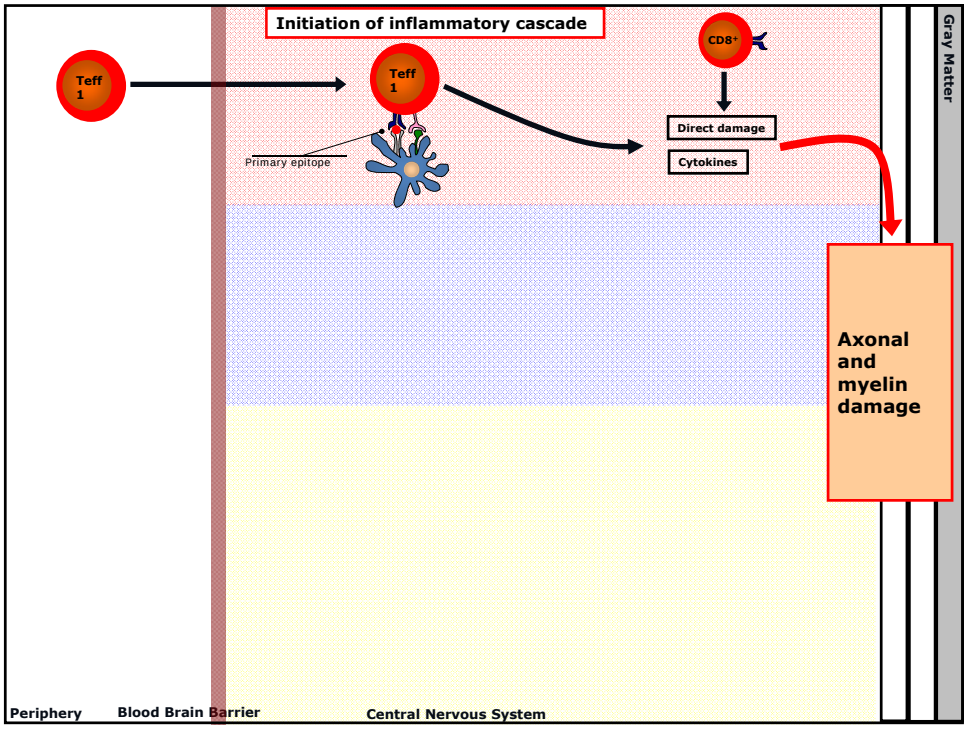
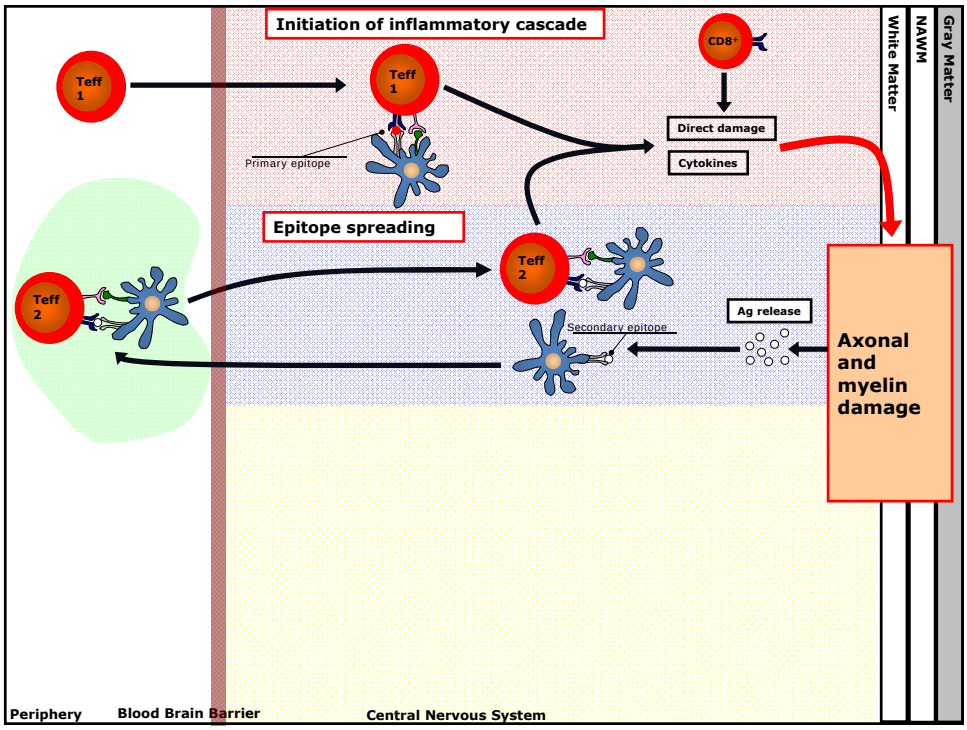
Myelin is the target of the autoimmune response in Multiple Sclerosis (MS) and Experimental Autoimmune Encephalomyelitis (EAE)

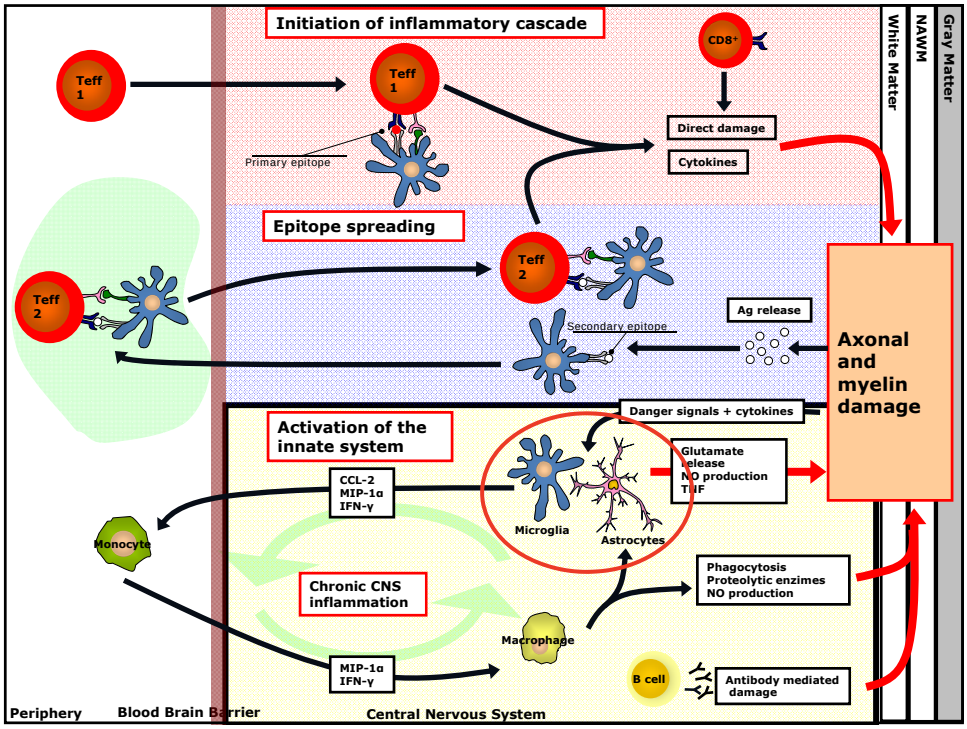




Frohman et al , N Engl J Med 354:94202

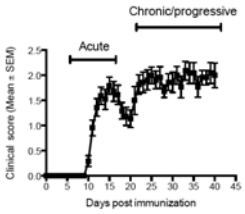

Initiation of inflammatory cascade
Teff 1
Teff 1
Primary epitope
CD8+
Direct damage
Cytokines
Axonal and myelin damage
Gray Matter
Periphery
Blood Brain Barrier
Central Nervous System


Initiation of inflammatory cascade
Teff 1
Teff 1
Primary epitope
CD8+
Direct damage
Cytokines
Epitope spreading
Teff 2
Teff 2
Secondary epitope
Ag release
Axonal and myelin damage
White Matter
NAWM
Gray Matter
Periphery
Blood Brain Barrier
Central Nervous System



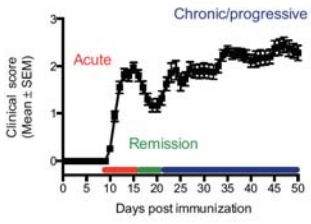
Astrocytes play a pathogenic role in chronic CNS inflammation

NOD model of progressive EAE



Farez *et al*, Nat. Immunology 10, 958-64 (2009)

NOD/B6 model of progressive EAE



Mayo *et al,* Nat. Medicine (2014) 20:1147-1156

Astrocytes play a pathogenic role in chronic CNS inflammation

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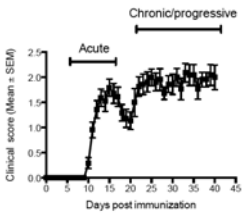


Farez *et al*, Nat. Immunology 10, 958-64 (2009)

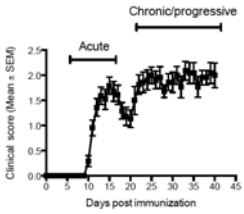
GFAP $^{HSV\text{-}TK}$

Deletion of reactive astrocytes in response to ganciclovir administration

Astrocytes play a pathogenic role in chronic CNS inflammation

Depletion of activated astrocytes

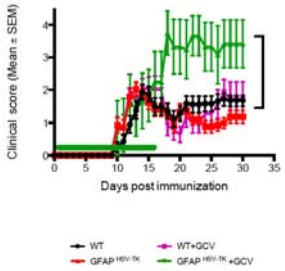
NOD model of progressive EAE



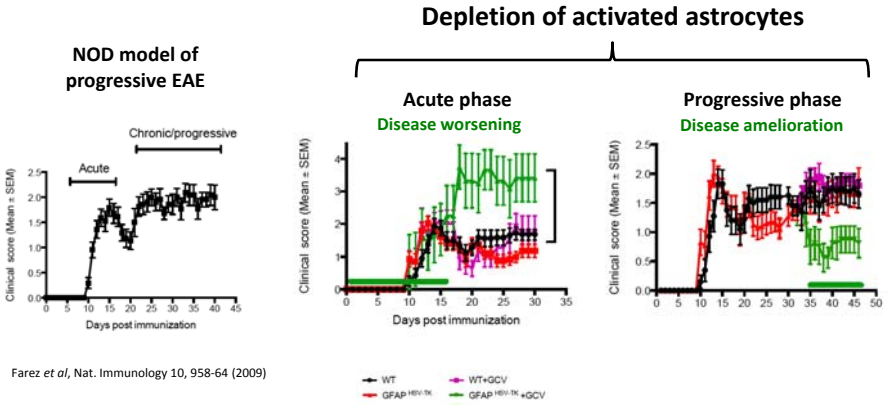
Farez *et al*, Nat. Immunology 10, 958-64 (2009)

Acute phase

Disease worsening



Astrocytes play a pathogenic role in chronic CNS inflammation



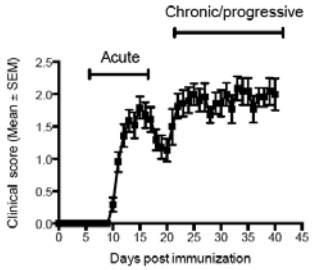
Farez *et al*, Nat. Immunology 10, 958-64 (2009)

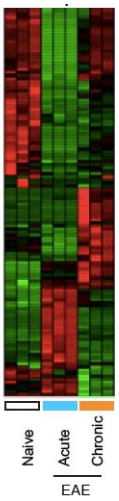
Summary

- Astrocytes contribute to disease pathology during chronic CNS inflammation.

What are the differences between astrocytes in the different phases of EAE?

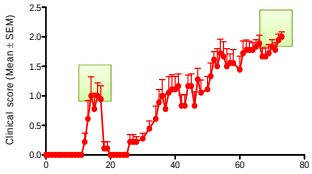
Gene expression profiling of astrocytes during the acute and progressive phases of NOD EAE

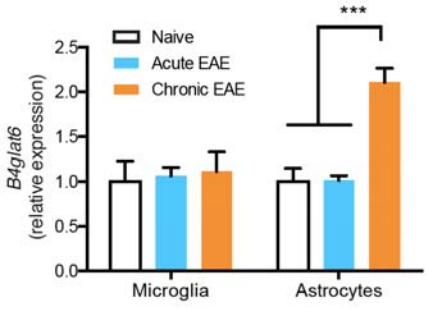




Mayo *et al,* Nat. Medicine (2014) 20:1147-1156

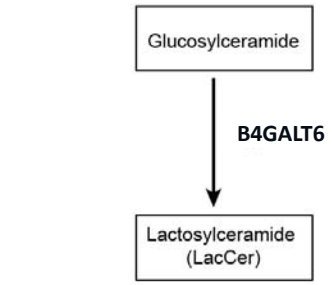
B4GALT6 is up-regulated during chronic CNS-inflammation





Mayo *et al,* Nat. Medicine (2014) 20:1147-1156

B4GALT6 controls lactosylceramide (LacCer) synthesis

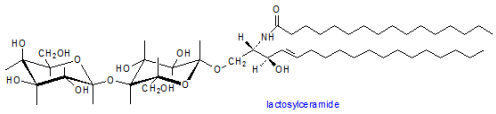


Role of B4GALT6 in astrocyte activation

J. Neurosci **24**, 5942-5954 (2004)

Association of LacCer to MS

Nat Med **12,** 138–43 (2006).
PNAS **105,** 18889–94 (2008).
Nat Immunol **10,** 958–64 (2009).
Brain 137:2271-86 (2014).
Multiple Sclerosis Journal (n press)



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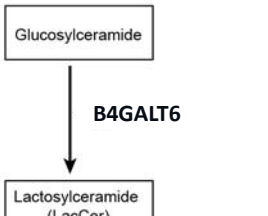
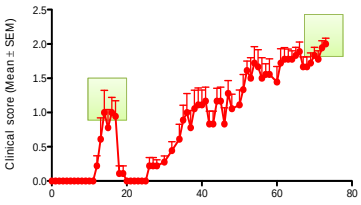
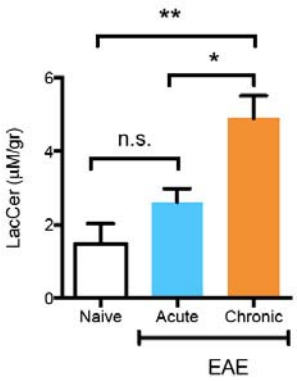
Lactosylceramide (LacCer) synthesis is up-regulated during chronic CNS-inflammation







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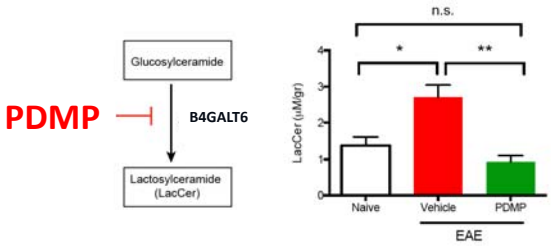
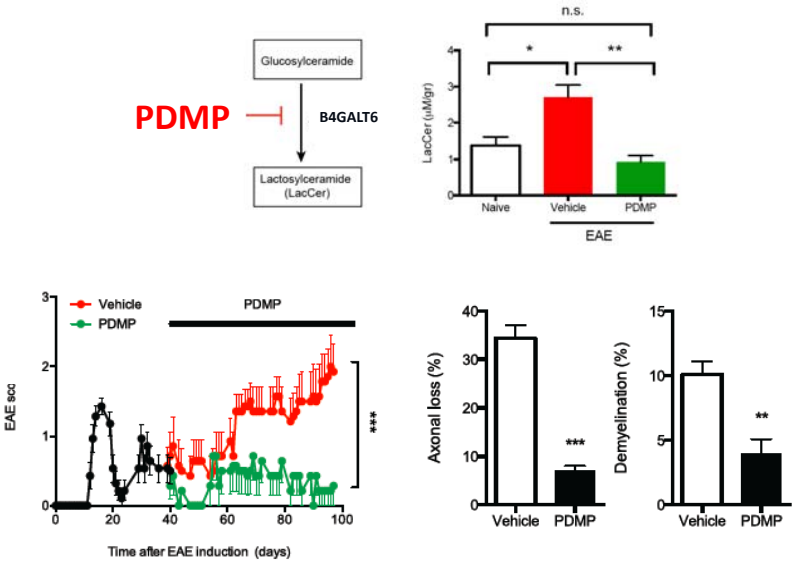
B4GALT6 inhibition ameliorates progressive EAE



B4GALT6 inhibition ameliorates progressive EAE



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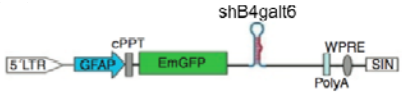
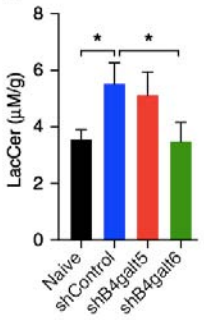
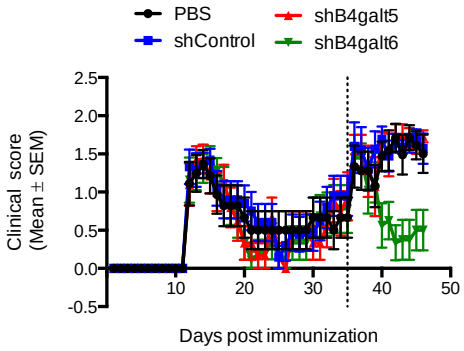
B4GALT6 knock-down in astrocytes ameliorates progressive EAE



*Molecular therapy **20,** 1338-1348 (2012)*





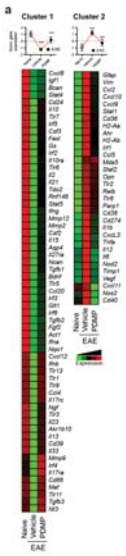
Mayo *et al,* Nat. Medicine (2014) 20:1147-1156

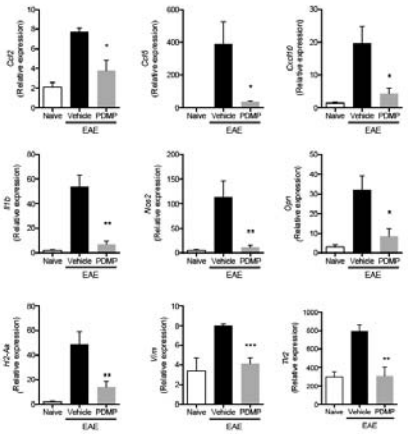
Summary

- Astrocytes contribute to disease pathology during chronic CNS inflammation.
- B4GALT6/LacCer in astrocytes promotes disease pathology.

How does B4GALT6/LacCer contribute to disease pathology?

B4GALT6 inhibition suppresses astrocyte activation during EAE





Activation

Neurotoxicity

Chemokines

Genes regulated by B4GALT6 are controlled by NF-κb and IRF1

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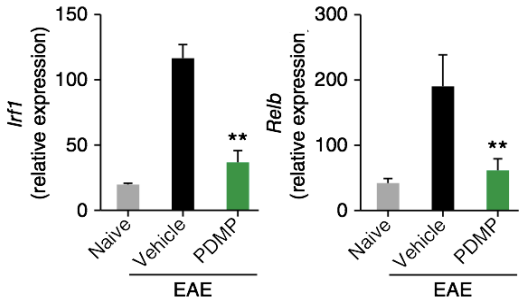
B4GALT6 inhibition reduces *irf1* and *relb* expression in astrocytes



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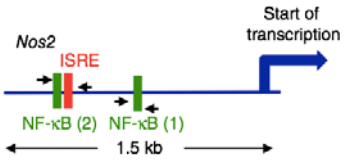
B4GALT6/LacCer controls the expression of *Nos2* By regulating NF-κb and IRF1 activation



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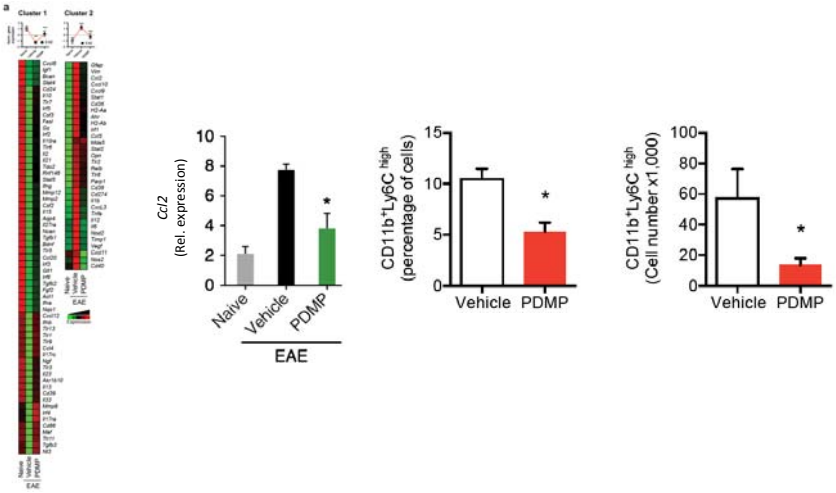
B4GALT6 inhibition arrests the recruitment of peripheral monocytes to the CNS during progressive EAE



B4GALT6/LacCer controls *ccl2* expression by regulating NF-kB and IRF1 activation

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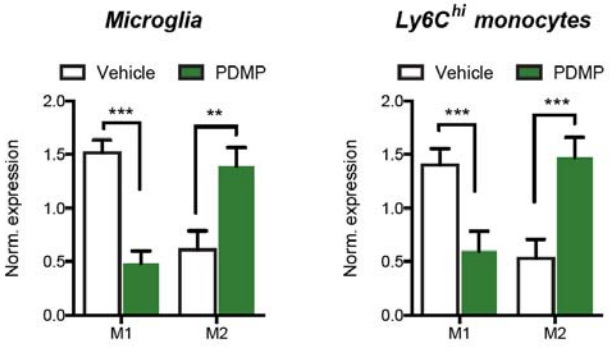
B4GALT6 inhibition interferes with the acquisition of a pro-inflammatory phenotype by macrophages and microglia



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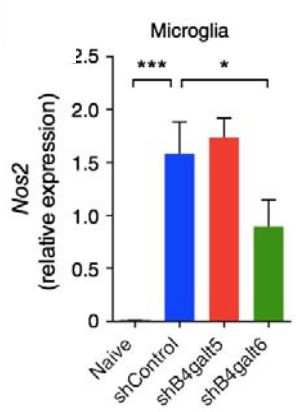
B4GALT6 knockdown in astrocytes modulates microglia activation *in vivo*



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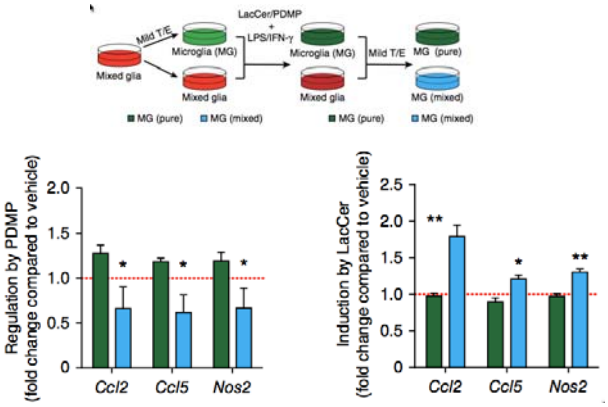
B4GALT6 in astrocytes modulates the phenotype of microglia *in vitro*



B4GALT6/LacCer controls microglia and monocyte activation via GM-CSF

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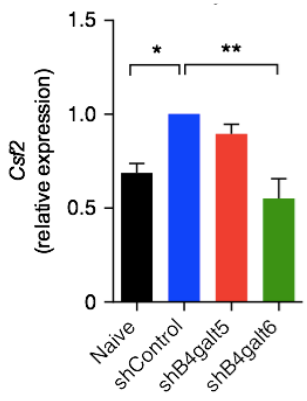
B4GALT6 controls *Csf2* (GM-CSF) expression in astrocytes *in vivo*



B4GALT6/LacCer controls GM-CSF expression by regulating NF-kB and IRF1 activation

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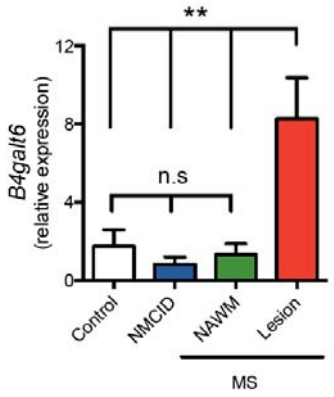
Summary

- Astrocytes contribute to disease pathology during chronic CNS inflammation.
- B4GALT6/LacCer in astrocytes promotes disease pathology.
- B4GALT6/LacCer controls NF-kB and IRF1 activation in astrocytes, regulating the expression of iNOS (NO production), CCL-2 (recruitment of inflammatory monocytes) and GM-CSF (microglia and monocyte activation)

B4GALT6 expression and LacCer levels are up-regulated in Multiple Sclerosis CNS lesions



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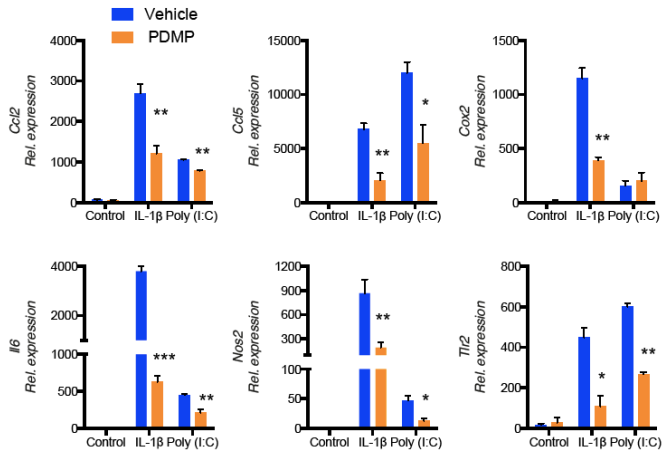
B4GALT6 interferes with the transcriptional response of human astrocytes to activation



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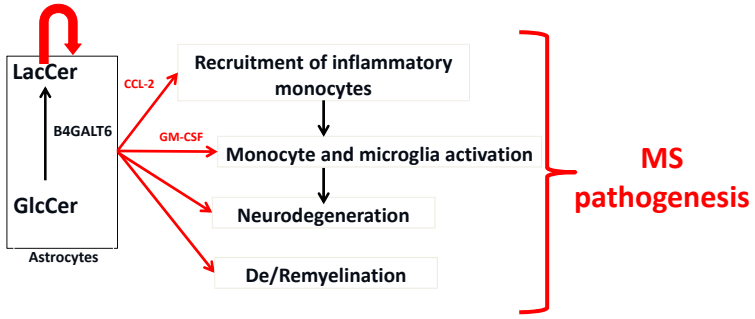
SUMMARY

LacCer produced by B4GALT6 in astrocytes promotes MS pathogenesis



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