Christian Doppler Laboratory for Cardiac and Thoracic Diagnosis & Regeneration

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Hepatocyte growth factor mediates MSCs stimulated functional recovery in animal models of MS

Bai et al.

Nat Neurosci. (2012)

Thomas HAIDER

11.02.2013

Background

Multiple Sclerosis

- Incidence: 149/100,000
  - Worldwide: 2.5 million patients
  - AUT: 8.000 patients
- F:M = 2:1
- 50 % need walking assistance within 15 years

N Engl J Med **343**, 938-952 (2000)

http://www.msgoe.co.at

Background

Multiple Sclerosis

- Autoimmune disease
- Initiating factors largely unknown
  - Genetic polymorphisms
  - Infections
  - Smoking
- Progressive loss of myelin sheaths followed by astrocytic scars
- Relative preservation of Axons

N Engl J Med **343**, 938-952 (2000)

Background

Hepatocyte Growth Factor

- Glycoprotein, mesenchymal origin
- 1982 – first description, Hepatectomy
- Inactive Precursor
  - Cleaved after tissue damage
- HGF-receptor cMet
  - Associated Tyrosin-kinase
  - Expressed on every tissue
- Many functions, e.g. Mito-, Morphogenesis

J Cell Biol. 1995; **129**(5): 1177-80.

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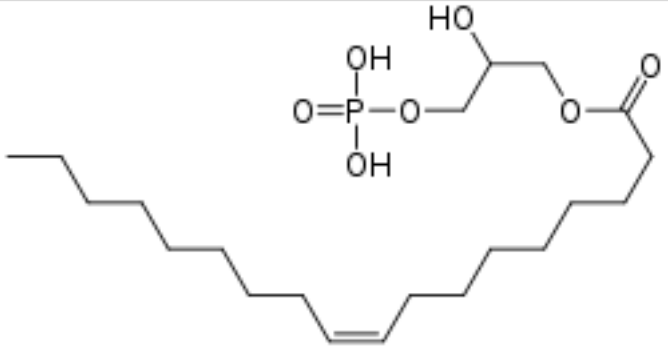
Methods

- Active EAE in C57/Bl6 mice with MOG_{35-55}
- Local demyelination in rats
  - LPC (Lysophosphatidyl acid)



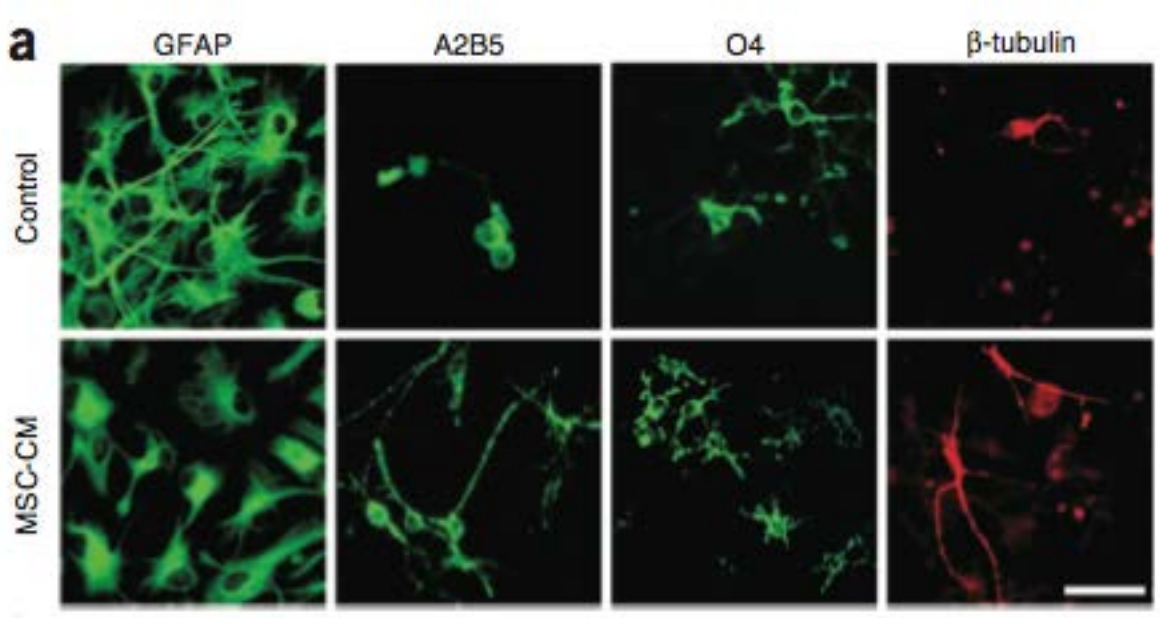
wikipedia.com

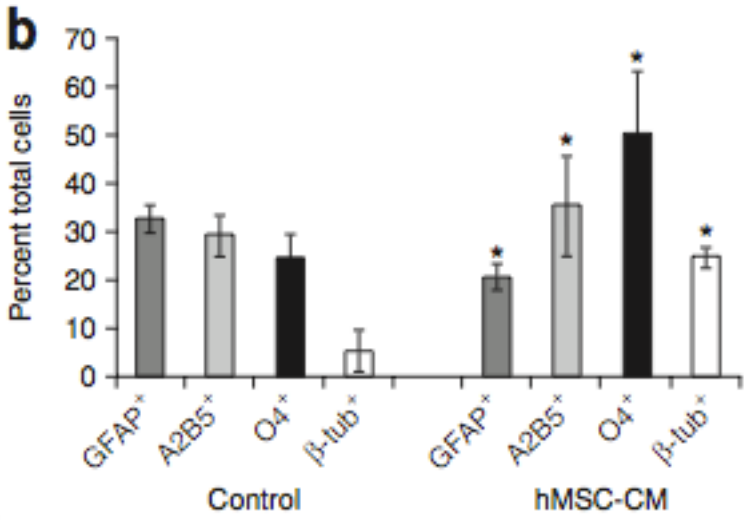
- Human MSCs
  - Bone marrow aspirates from 5 healthy probands
- Histology, Western Blot, ELISA

Nat Neurosci. 2012; **15**(6): 862-70.

Results

In-vitro results - neurospheres





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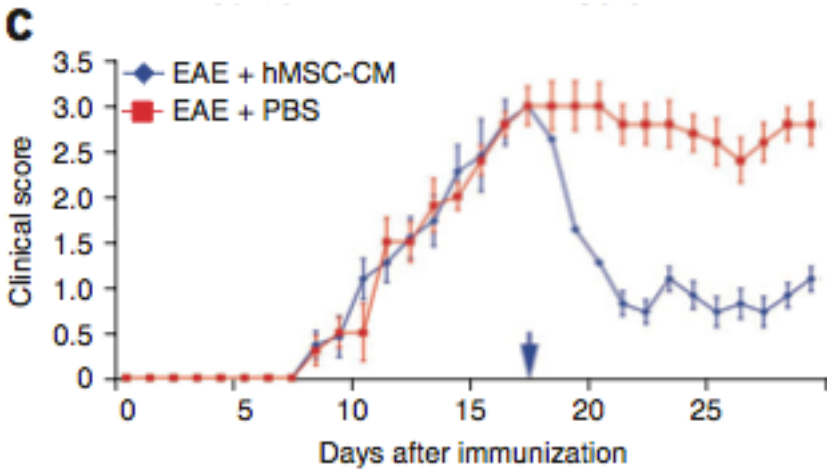
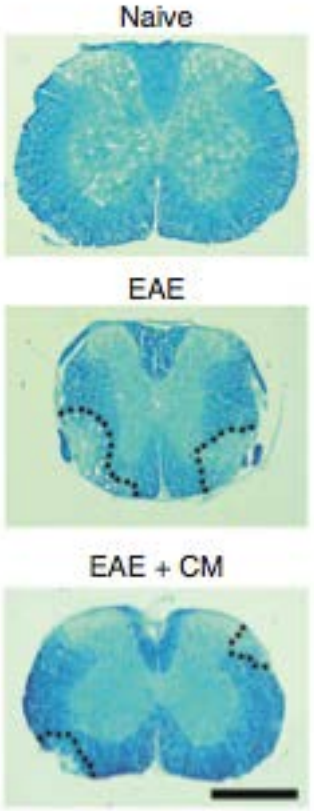
Results

In-vivo results EAE

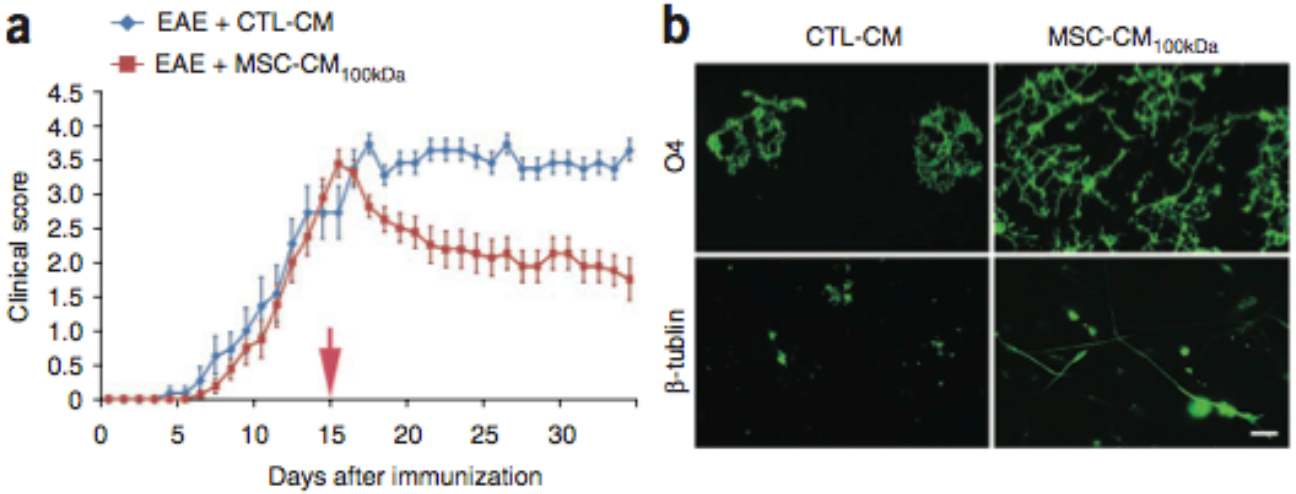




Nat Neurosci. 2012; **15**(6): 862-70.

Results

50-100 kDa fraction of MSC-CM is essential



Nat Neurosci. 2012; **15**(6): 862-70.

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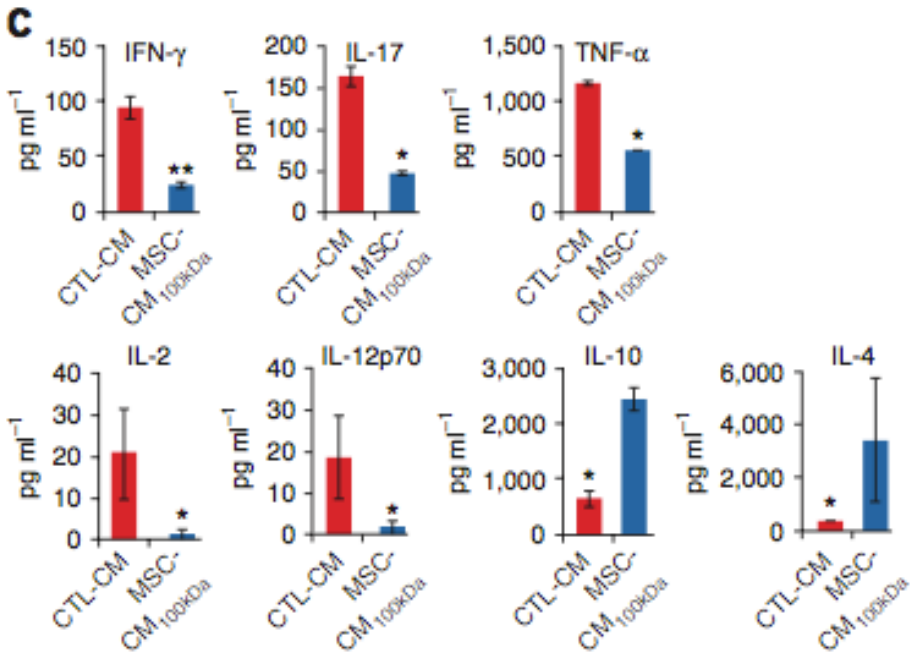
Results

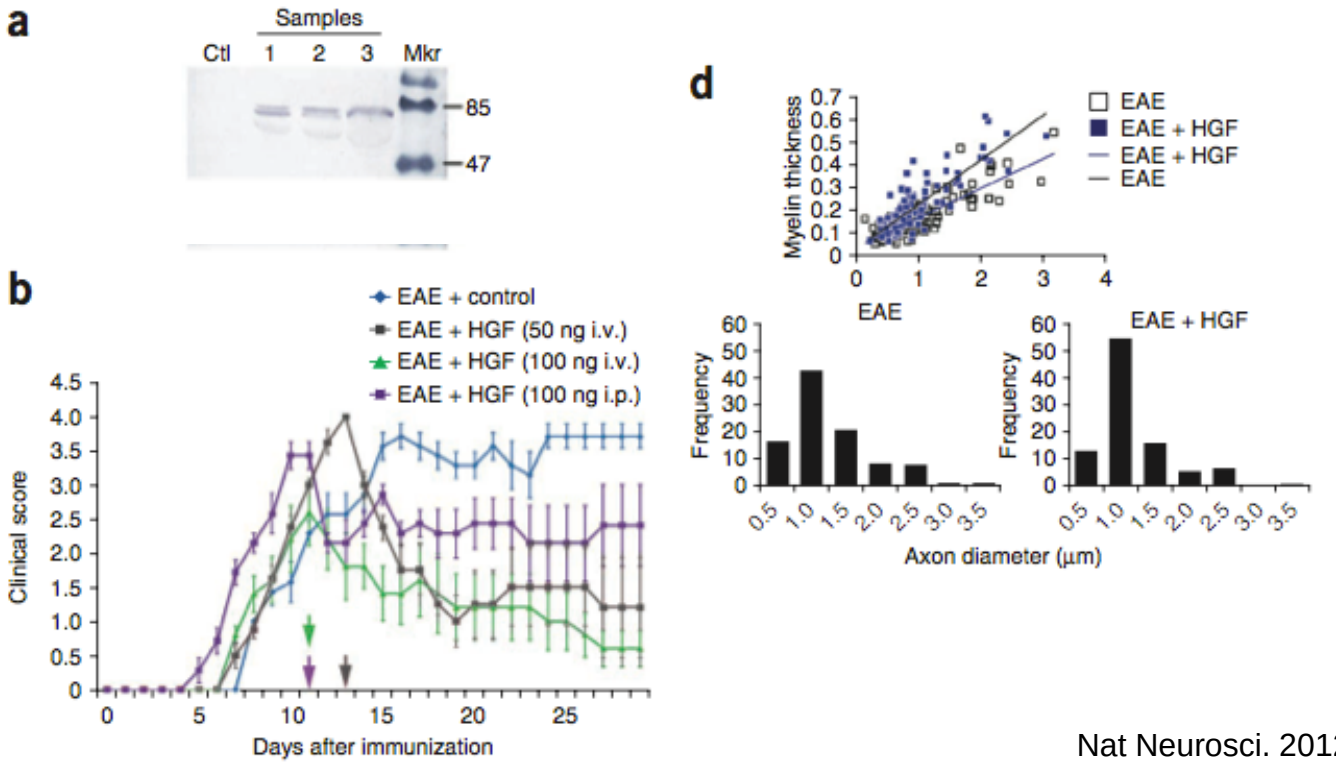
Reduction of pro-inflammatory cytokines in SC-derived MNCs



Nat Neurosci. 2012; **15**(6): 862-70.

Results

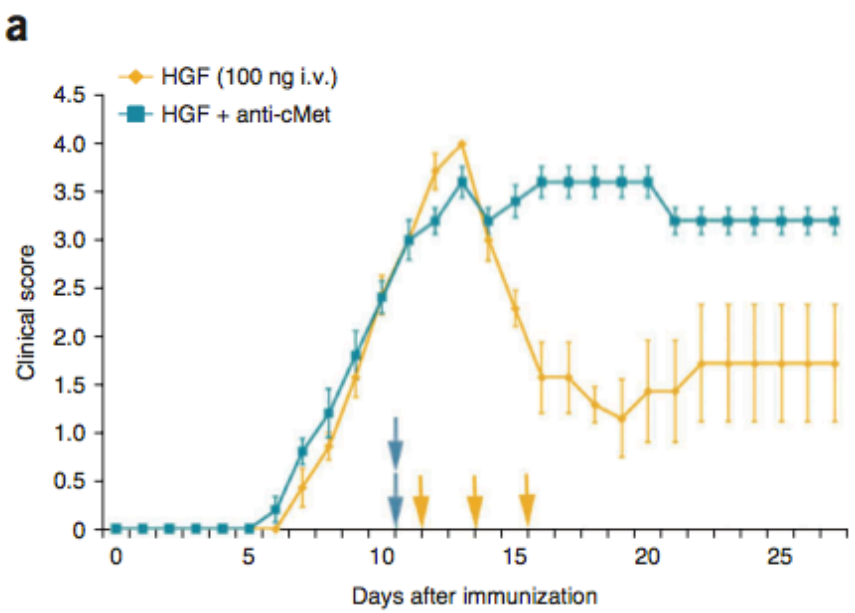
HGF is responsible for functional improvement of EAE

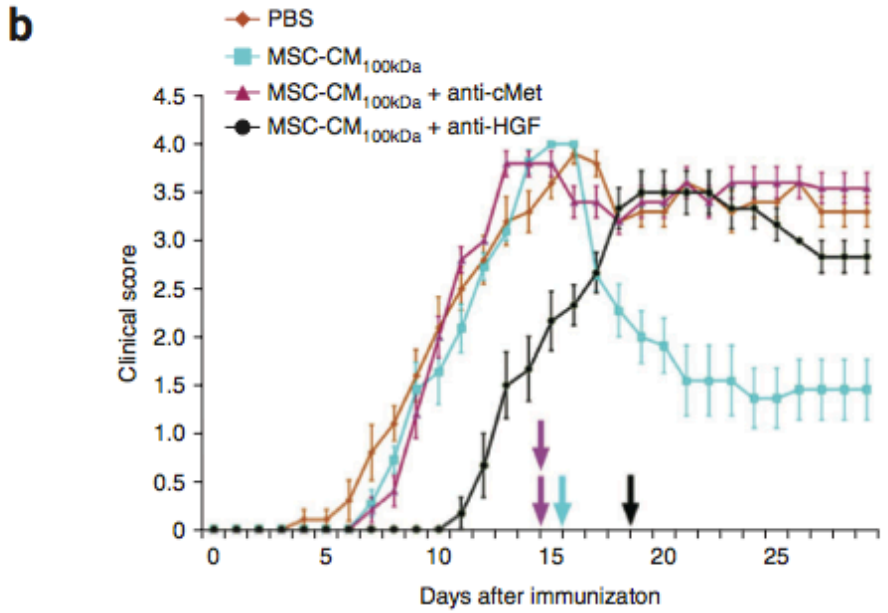


Nat Neurosci. 2012; **15**(6): 862-70.

Results

HGF-associated improvement is cMet-dependent



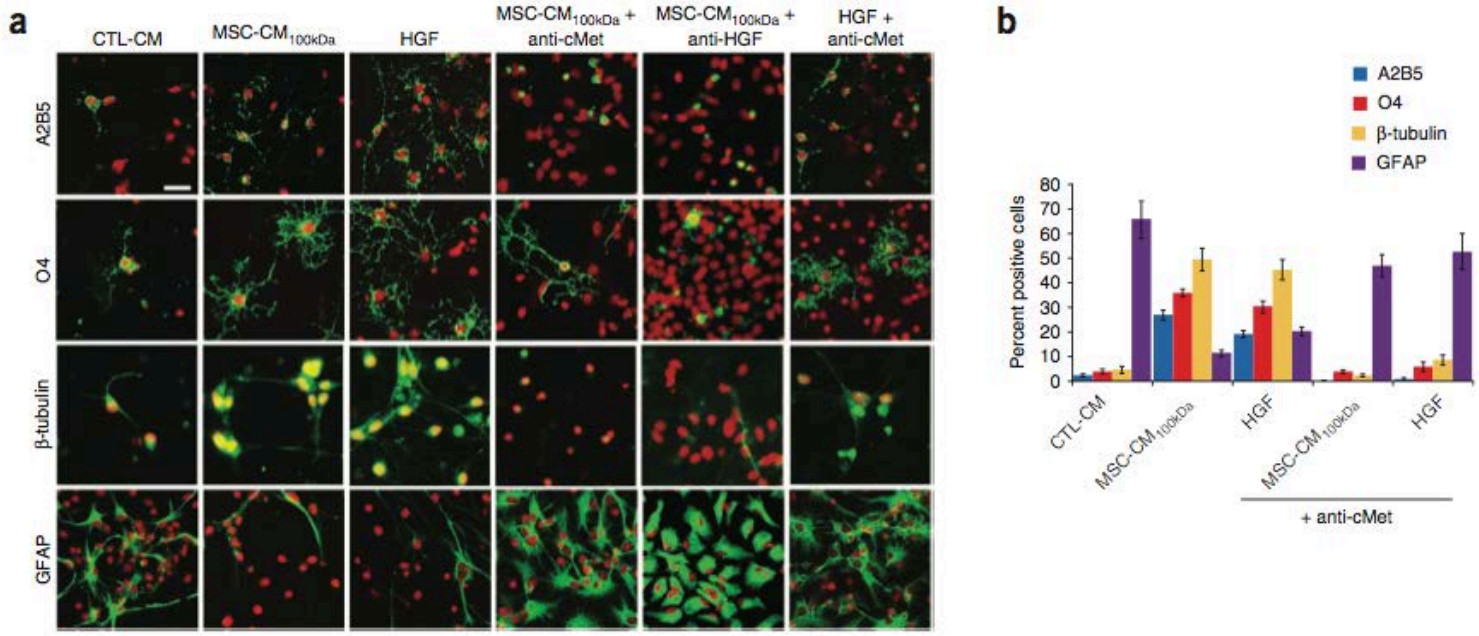


Anti-inflammatory effects vanished

Nat Neurosci. 2012; **15**(6): 862-70.

Results

HGF stimulates neural development in-vitro



Nat Neurosci. 2012; **15**(6): 862-70.

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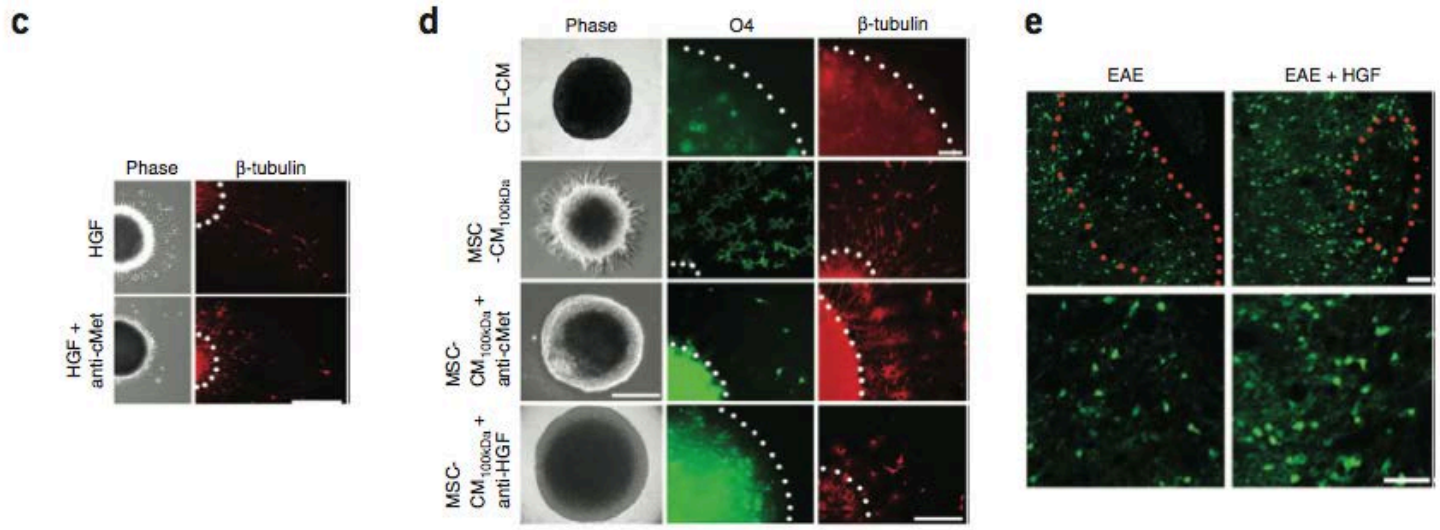
Results

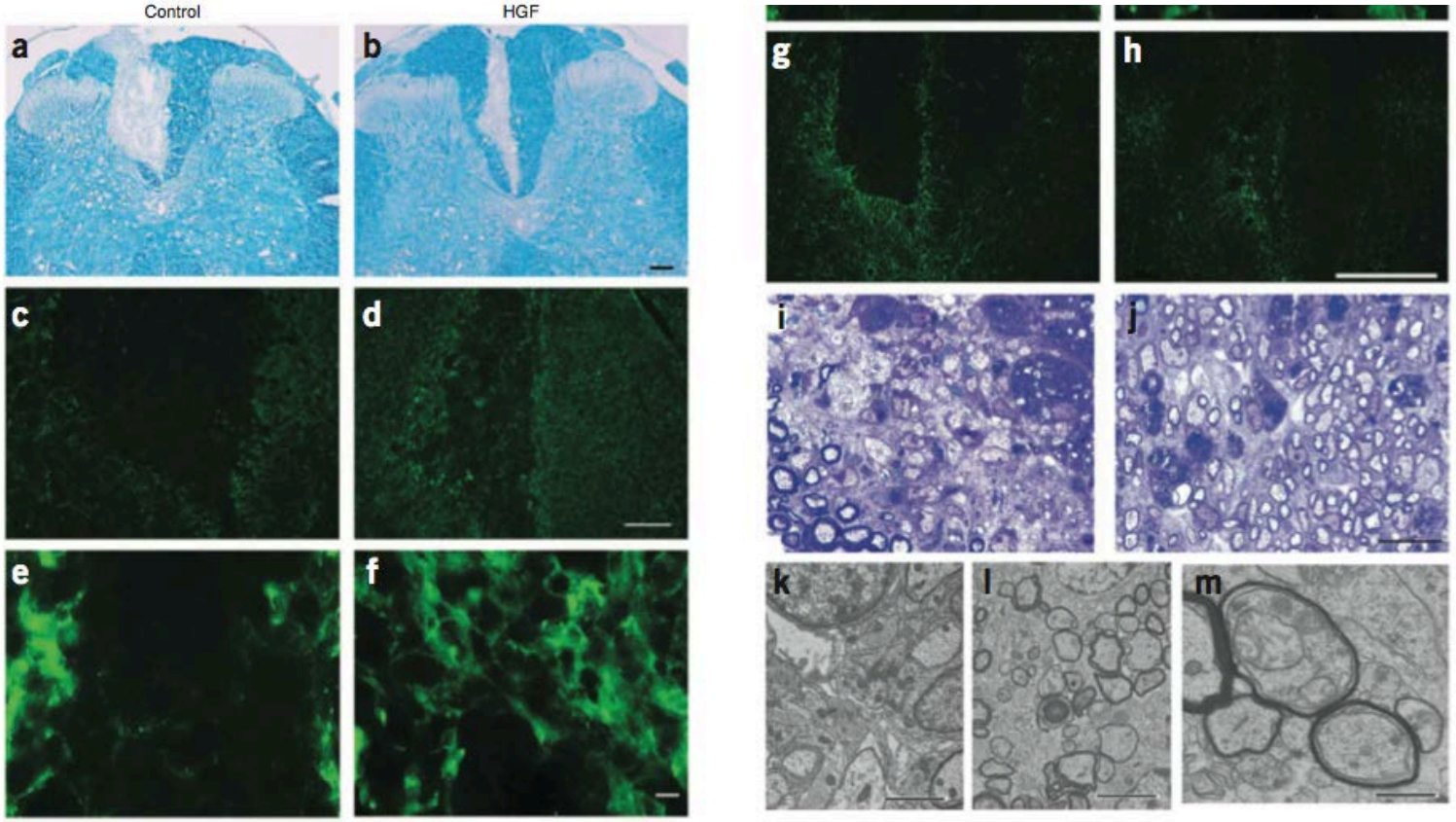
HGF stimulates neural development in-vitro



Nat Neurosci. 2012; **15**(6): 862-70.

Results

HGF also improves non-immune-mediated demyelination



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Summary

- Fraction studies indicates active fraction between 50 and 100 kDa (HGF≈85kDa)
- Recombinant HGF showed similar results to MSC-CM
- Anti-HGF, Anti-cMet neutralized effect
- Mechanism of action not only anti-inflammatory

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Discussion

- HGF – half-life short -> long-lasting effects unclear
- In MS -> HGF is increased in CSF, repair mechanism?
- Prerequisite HGF as susceptibility factor?
- Therapeutic options?

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Limitations

- MSC cultivation – insufficient description
- Control medium – „similar medium“
- PBS control instead of medium control in in-vivo experiments
- Onset of disease varied – Different MOG preparation

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Thank you for your attention!

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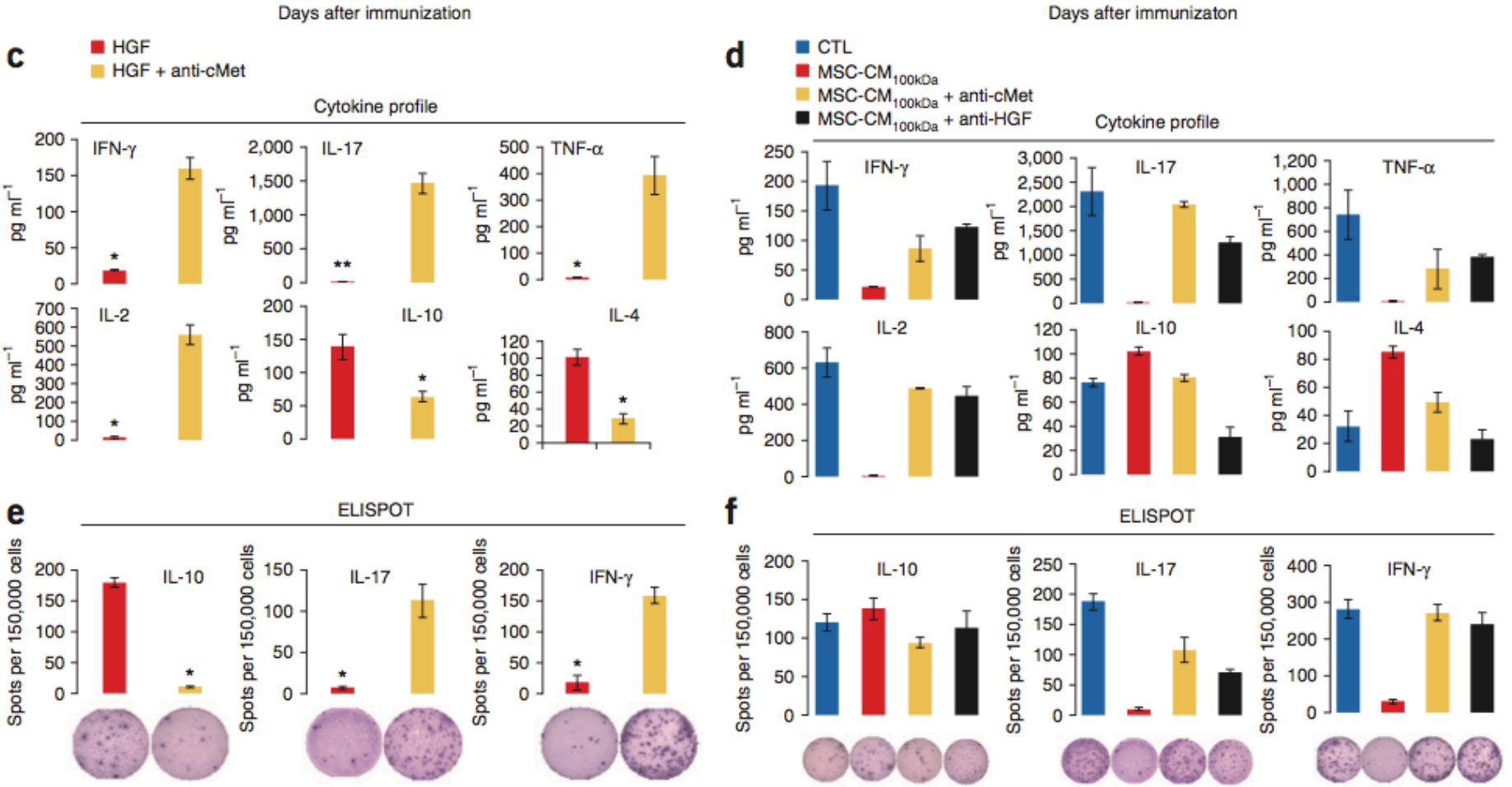
Appendix



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