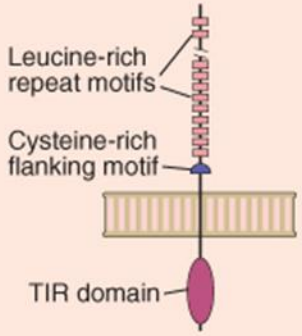
Concetti immunopatogenetici e possibili approcci immunoterapeutici nel trattamento del dolore neuropatico

Prof. Ferdinando Nicoletti

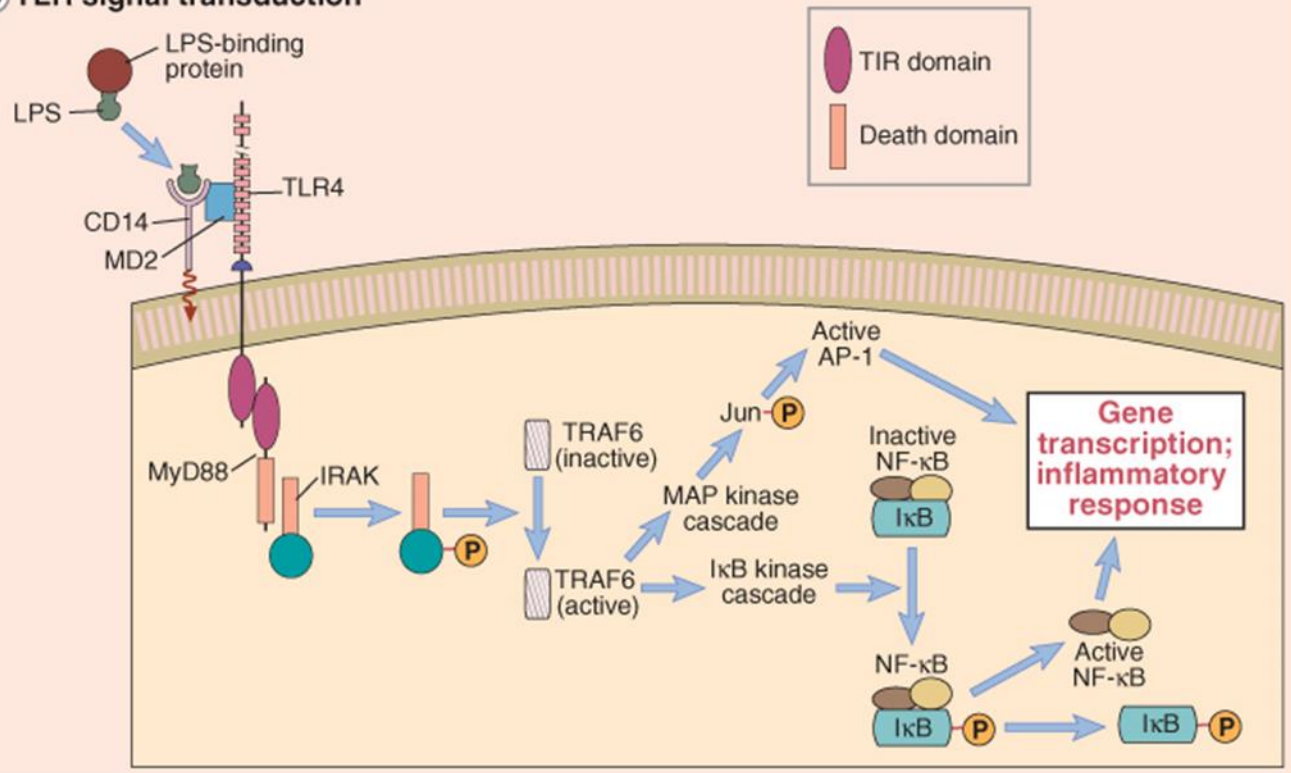
A TLR structure

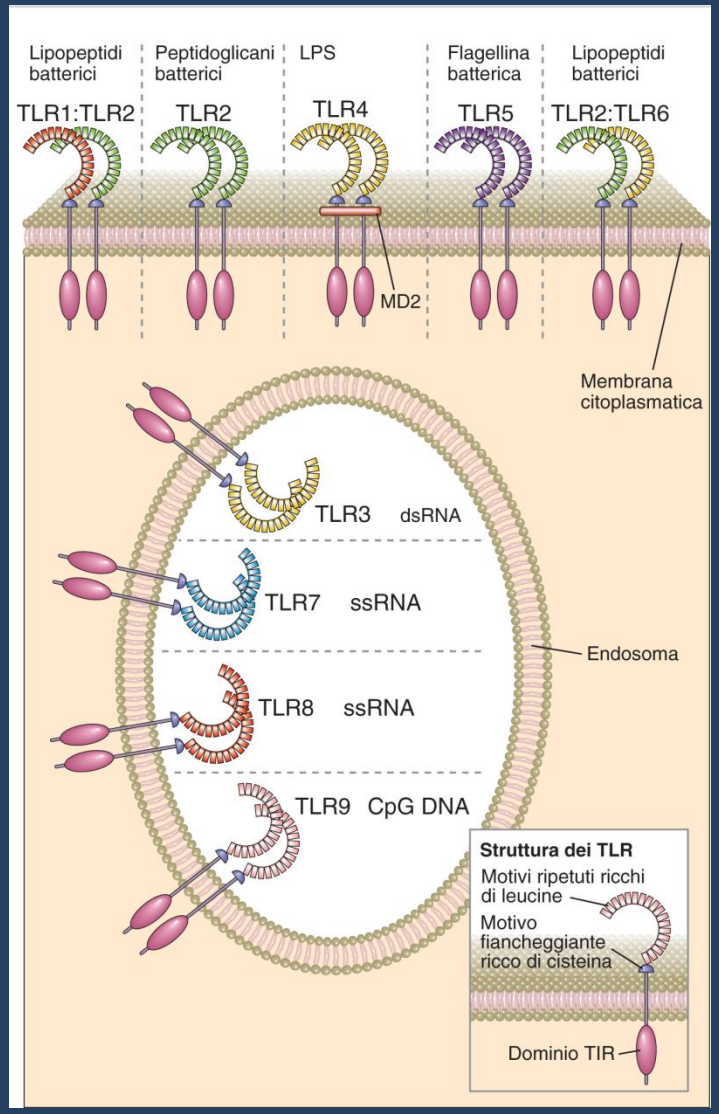


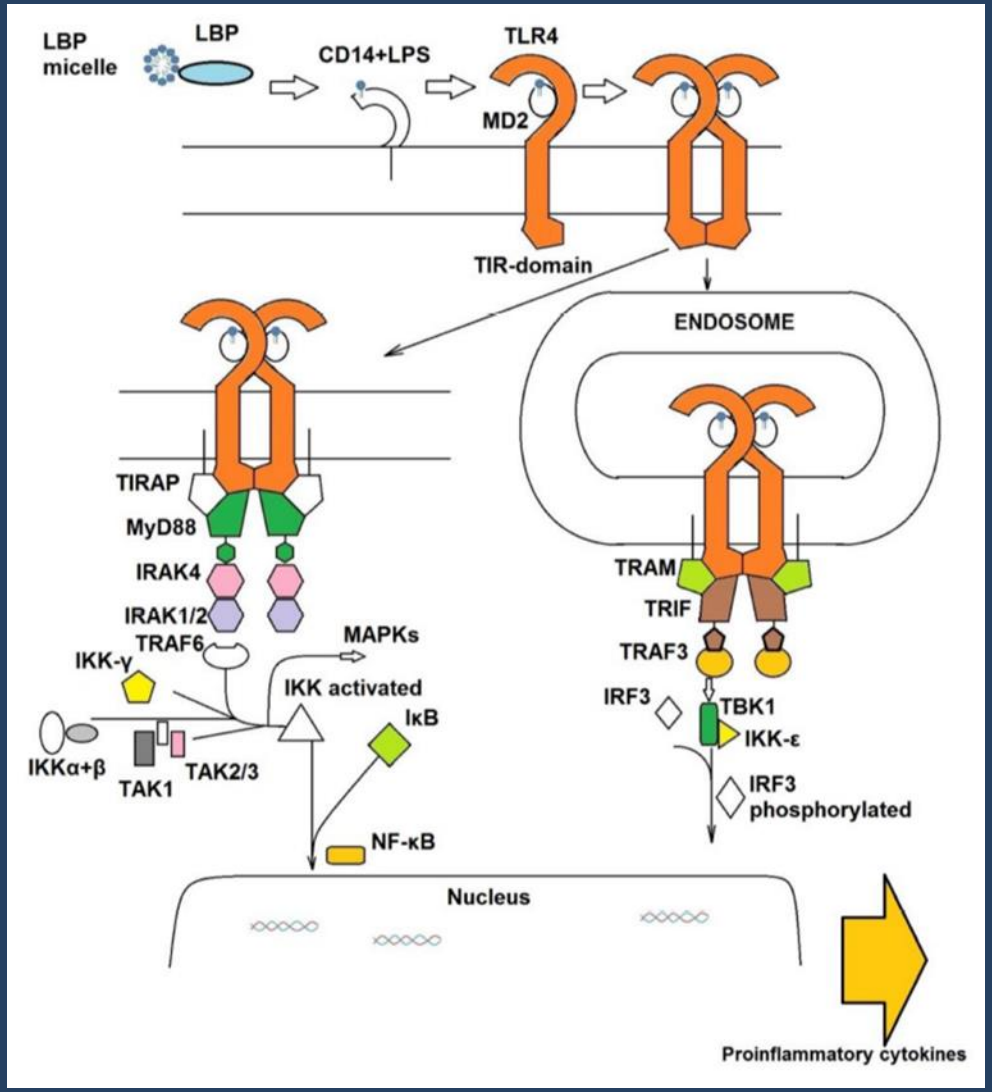
B Specificities of TLRs

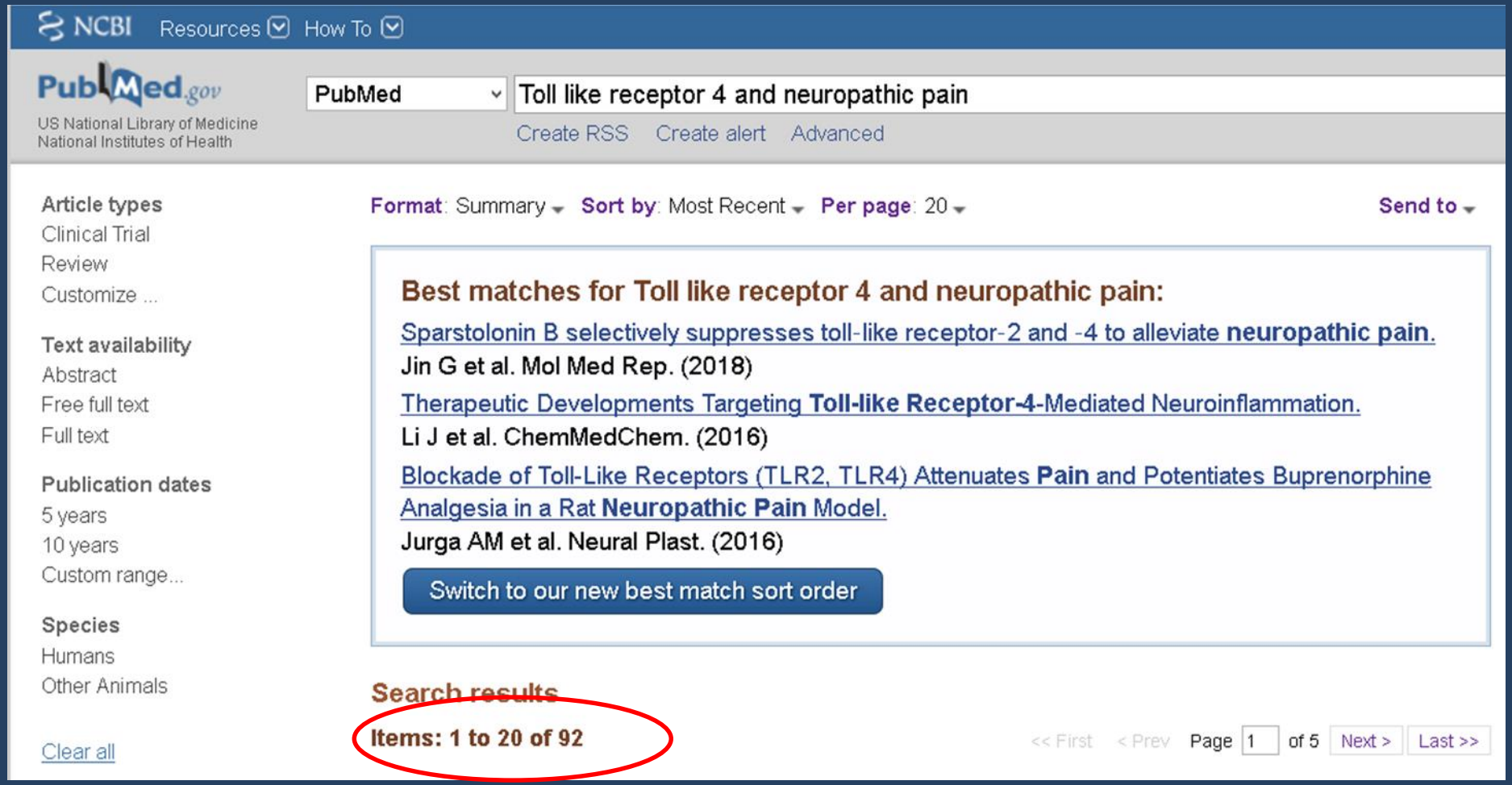
TLR	Ligand	Microbial source
TLR2	Lipoproteins Peptidoglycan Zymosan LPS GPI anchor Lipoarabinomannan Phosphatidylinositol dimannoside	Bacteria Gram-positive bacteria Fungi Leptospira Trypanosomes Mycobacteria Mycobacteria
TLR3	Double-stranded RNA	Viruses
TLR7/8	Single-stranded RNA	Viruses
TLR4	LPS HSP60	Gram-negative bacteria Chlamydia
TLR5	Flagellin	Various bacteria
TLR9	CpG DNA	Bacteria, protozoans

C TLR signal transduction




Lipopeptidi batterici
Peptidoglicani batterici
LPS
Flagellina batterica
Lipopeptidi batterici
TLR1:TLR2
TLR2
TLR4
TLR5
TLR2:TLR6
MD2
Membrana citoplasmatica
TLR3 dsRNA
TLR7 ssRNA
TLR8 ssRNA
TLR9 CpG DNA
Endosoma
Struttura dei TLR
Motivi ripetuti ricchi di leucine
Motivo fiancheggiante ricco di cisteina
Dominio TIR


LBP micelle
LBP
CD14+LPS
TLR4
MD2
TIR-domain
ENDOSOME
TIRAP
MyD88
IRAK4
IRAK1/2
TRAF6
MAPKs
IKK-γ
IKK activated
IκB
IKKα+β
TAK1
TAK2/3
NF-κB
TRAM
TRIF
TRAF3
IRF3
TBK1
IKK-ε
IRF3 phosphorylated
Nucleus
Proinflammatory cytokines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Therapeutic Developments Targeting Toll-like Receptor-4-Mediated Neuroinflammation.
Li J et al. ChemMedChem. (2016)
Blockade of Toll-Like Receptors (TLR2, TLR4) Attenuates Pain and Potentiates Buprenorphine Analgesia in a Rat Neuropathic Pain Model.
Jurga AM et al. Neural Plast. (2016)
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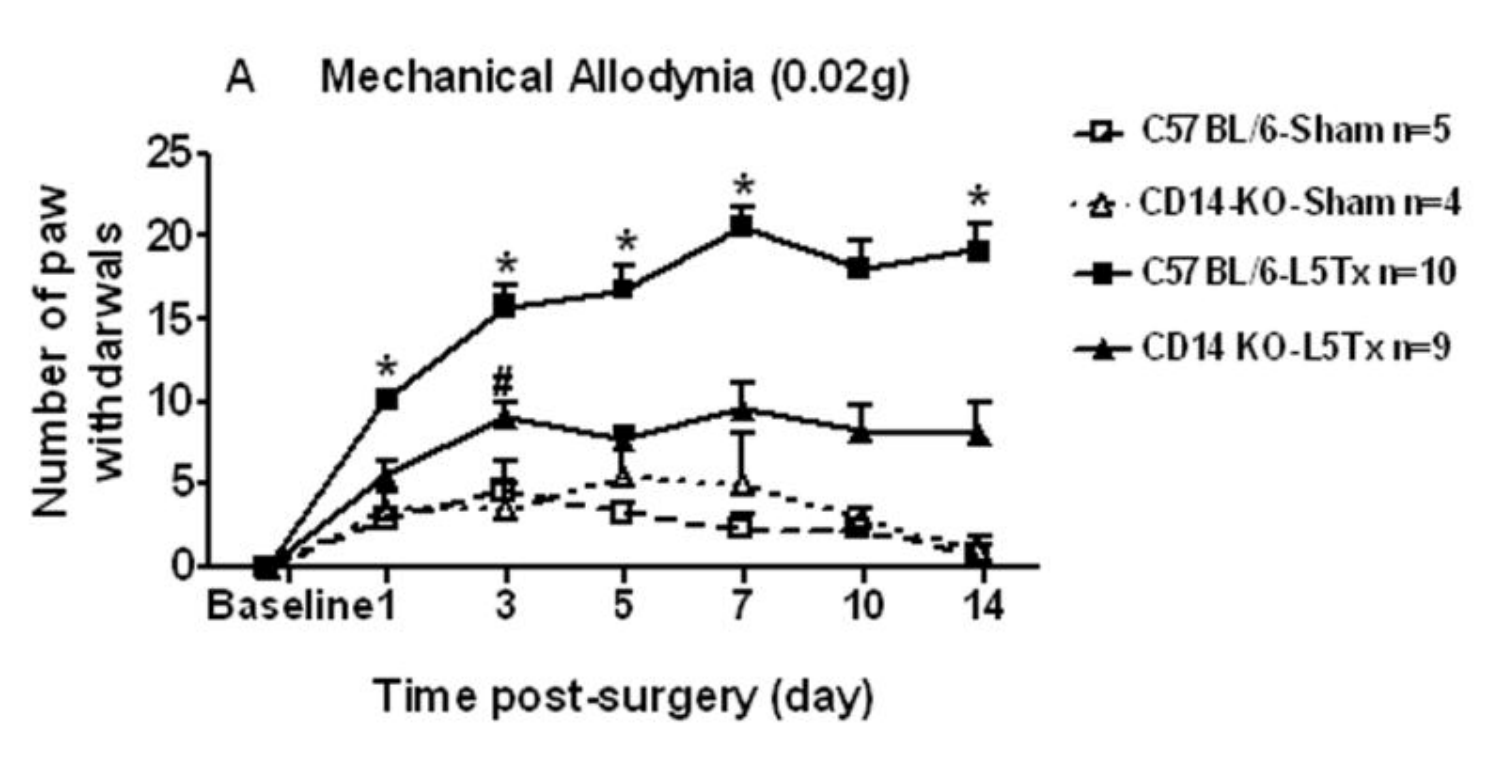

Cao et al., 2009

Glia. 2008 Sep;56(12):1312-9. doi: 10.1002/glia.20699.

Glial TLR4 receptor as new target to treat neuropathic pain: efficacy of a new receptor antagonist in a model of peripheral nerve injury in mice.

Bettoni I, Comelli F, Rossini C, Granucci F, Giagnoni G, Peri F, Costa B.

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J Cell Biochem. 2019 Mar;120(3):3009-3017. doi: 10.1002/jcb.27269. Epub 2018 Dec 11.
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PMID: 28685867
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Nat Rev Drug Discov. 2015 Dec;14(12):818. doi: 10.1038/nrd4785. No abstract available.
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5. Targeting Toll-like receptors to treat chronic **pain**.
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Nat Med. 2015 Nov;21(11):1251-2. doi: 10.1038/nm.3986. No abstract available.
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6. Inhibition of mechanical allodynia in **neuropathic pain** by TLR5-mediated A-fiber blockade.
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1: Jin G, Jin X, Zhou S. Sparstolonin B selectively suppresses toll-like receptor-2 and -4 to alleviate neuropathic pain. Mol Med Rep. 2018 Jan;17(1):1247-1252. doi: 10.3892/mmr.2017.7951. Epub 2017 Nov 3. PubMed PMID: 29115627.

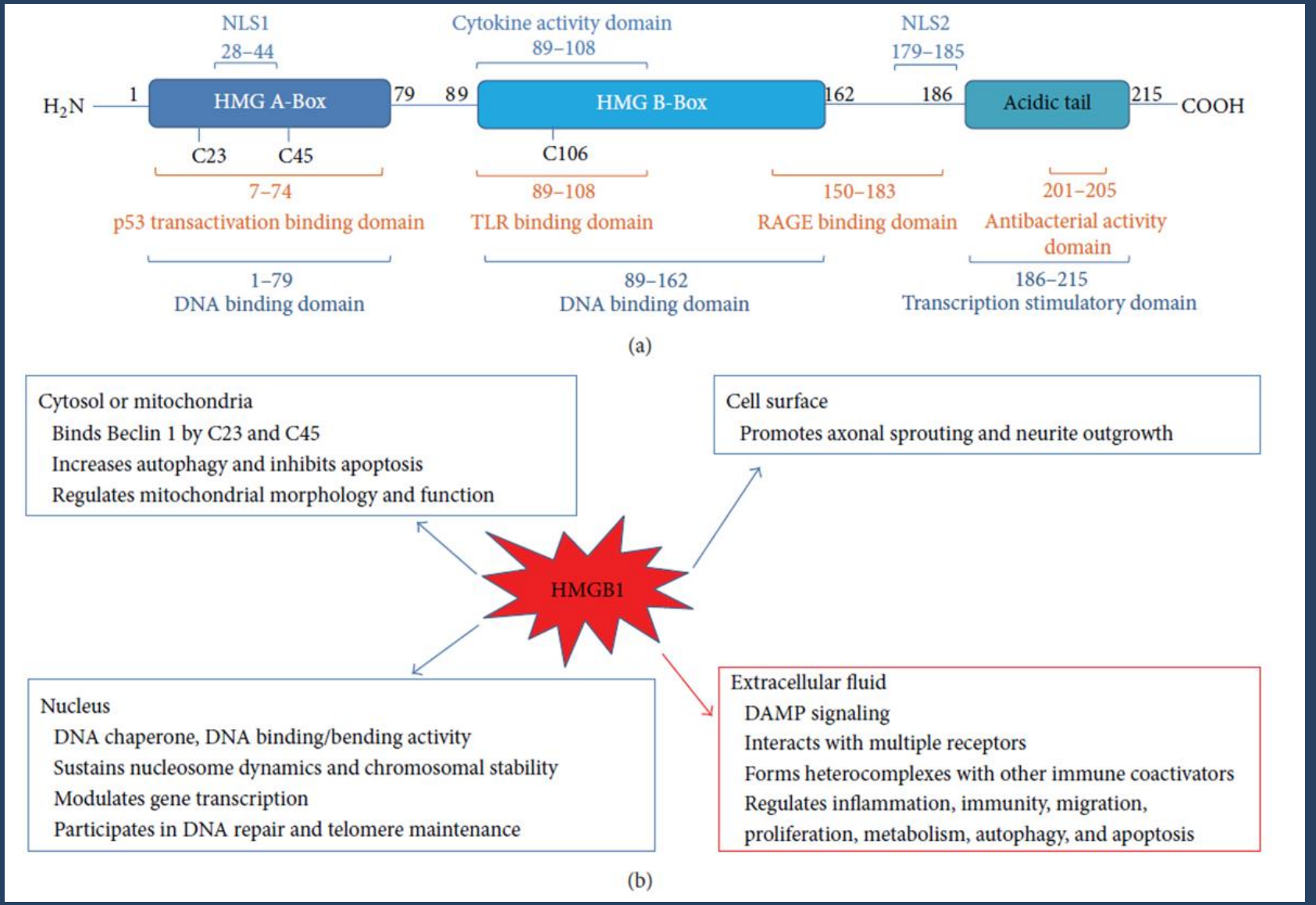
2: Jurga AM, Rojewska E, Piotrowska A, Makuch W, Pilat D, Przewlocka B, Mika J. Blockade of Toll-Like Receptors (TLR2, TLR4) Attenuates Pain and Potentiates Buprenorphine Analgesia in a Rat Neuropathic Pain Model. Neural Plast. 2016;2016:5238730. doi: 10.1155/2016/5238730. Epub 2015 Dec 29. PubMed PMID: 26962463; PubMed Central PMCID: PMC4709736.

3: Kim D, You B, Lim H, Lee SJ. Toll-like receptor 2 contributes to chemokine gene expression and macrophage infiltration in the dorsal root ganglia after peripheral nerve injury. Mol Pain. 2011 Sep 28;7:74. doi: 10.1186/1744-8069-7-74. PubMed PMID: 21951975; PubMed Central PMCID: PMC3192680.

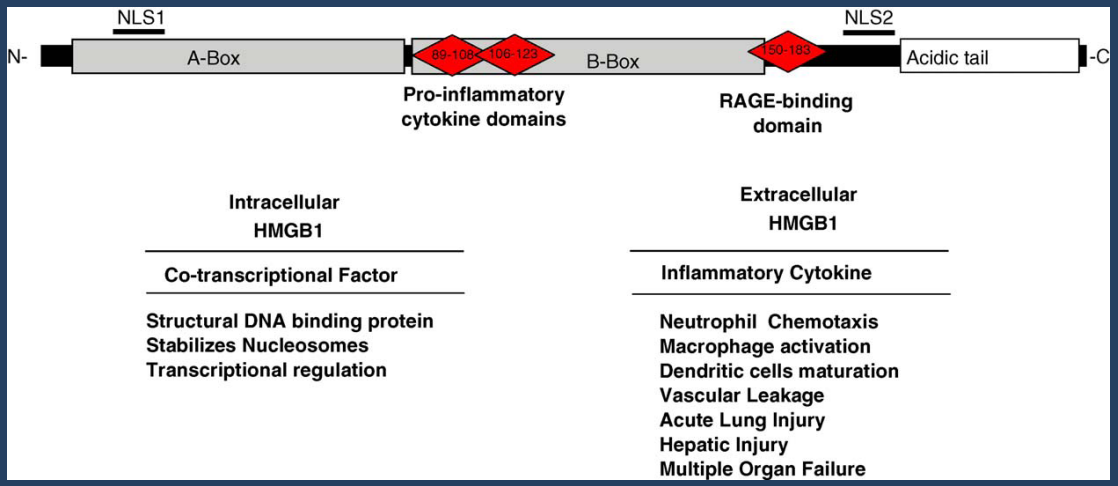
4: Shi XQ, Zekki H, Zhang J. The role of TLR2 in nerve injury-induced neuropathic pain is essentially mediated through macrophages in peripheral inflammatory response. Glia. 2011 Feb;59(2):231-41. doi: 10.1002/glia.21093. PubMed PMID: 21125644.

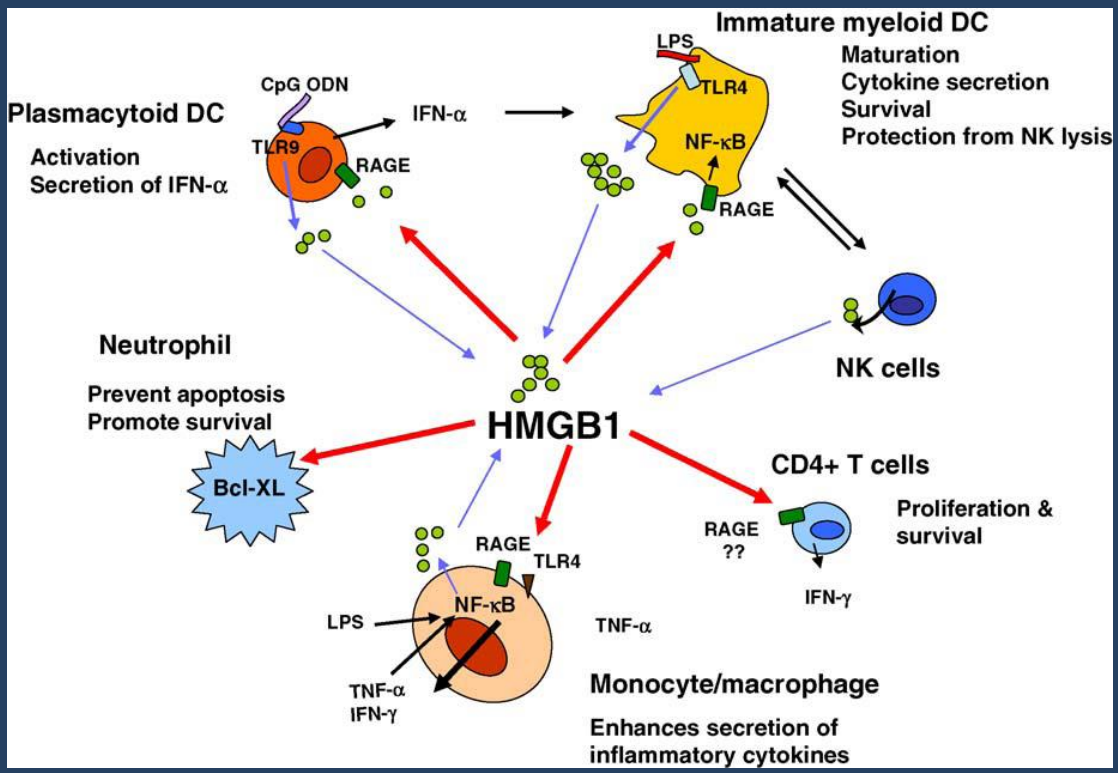
5: Kim D, Kim MA, Cho IH, Kim MS, Lee S, Jo EK, Choi SY, Park K, Kim JS, Akira S, Na HS, Oh SB, Lee SJ. A critical role of toll-like receptor 2 in nerve injury-induced spinal cord glial cell activation and pain hypersensitivity. J Biol Chem. 2007 May 18;282(20):14975-83. Epub 2007 Mar 13. PubMed PMID: 17355971.

High Motility Group box1



High Motility Group box1





Ulloa et al., 2006

Biomed Pharmacother. 2018 Nov;107:818-823. doi: 10.1016/j.biopha.2018.08.053. Epub 2018 Aug 22.

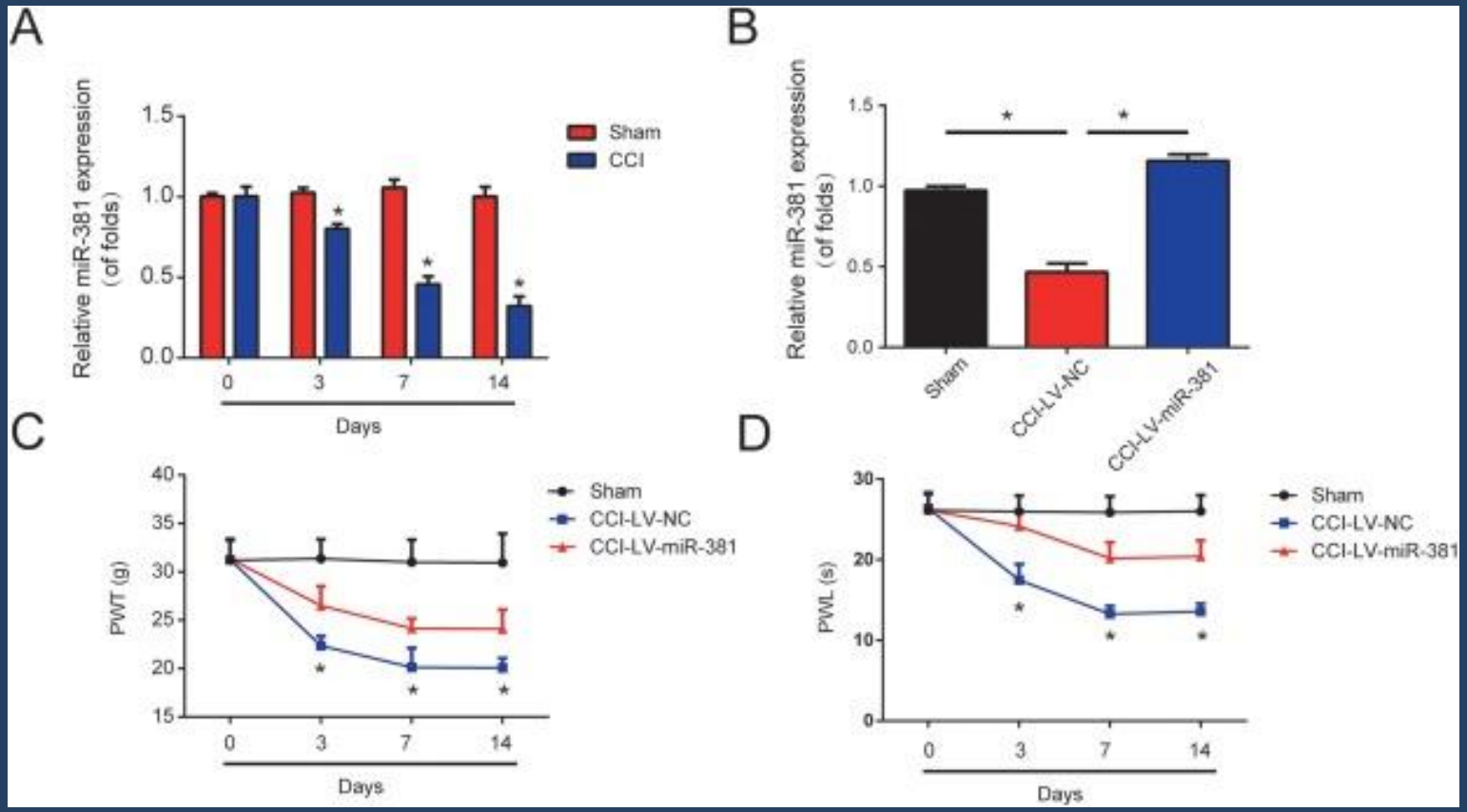
Overexpression of miR-381 relieves neuropathic pain development via targeting HMGB1 and CXCR4.

Zhan LY[1], Lei SQ[2], Zhang BH[3], Li WL[1], Wang HX[1], Zhao B[1], Cui SS[1], Ding H[1], Huang QM[1].

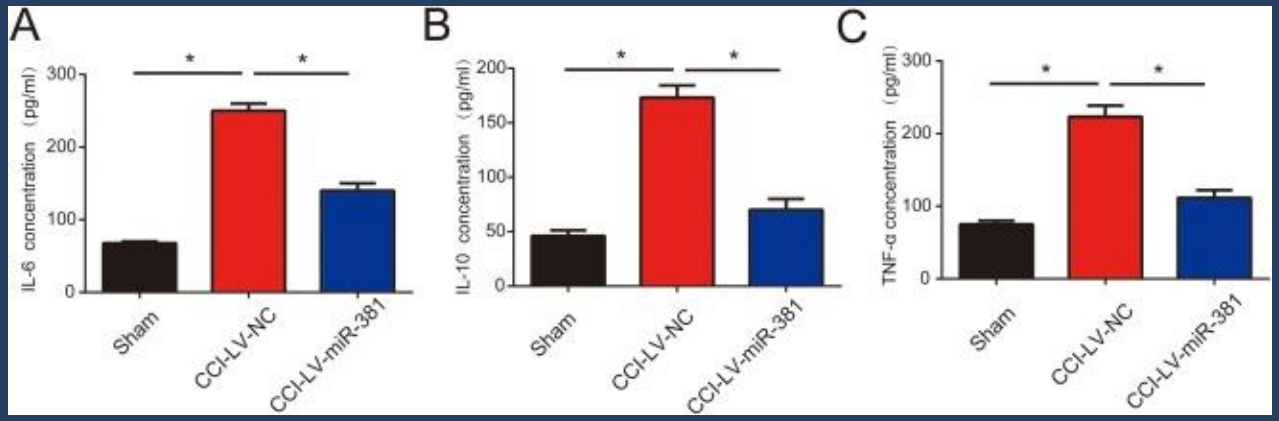
Author information

Abstract

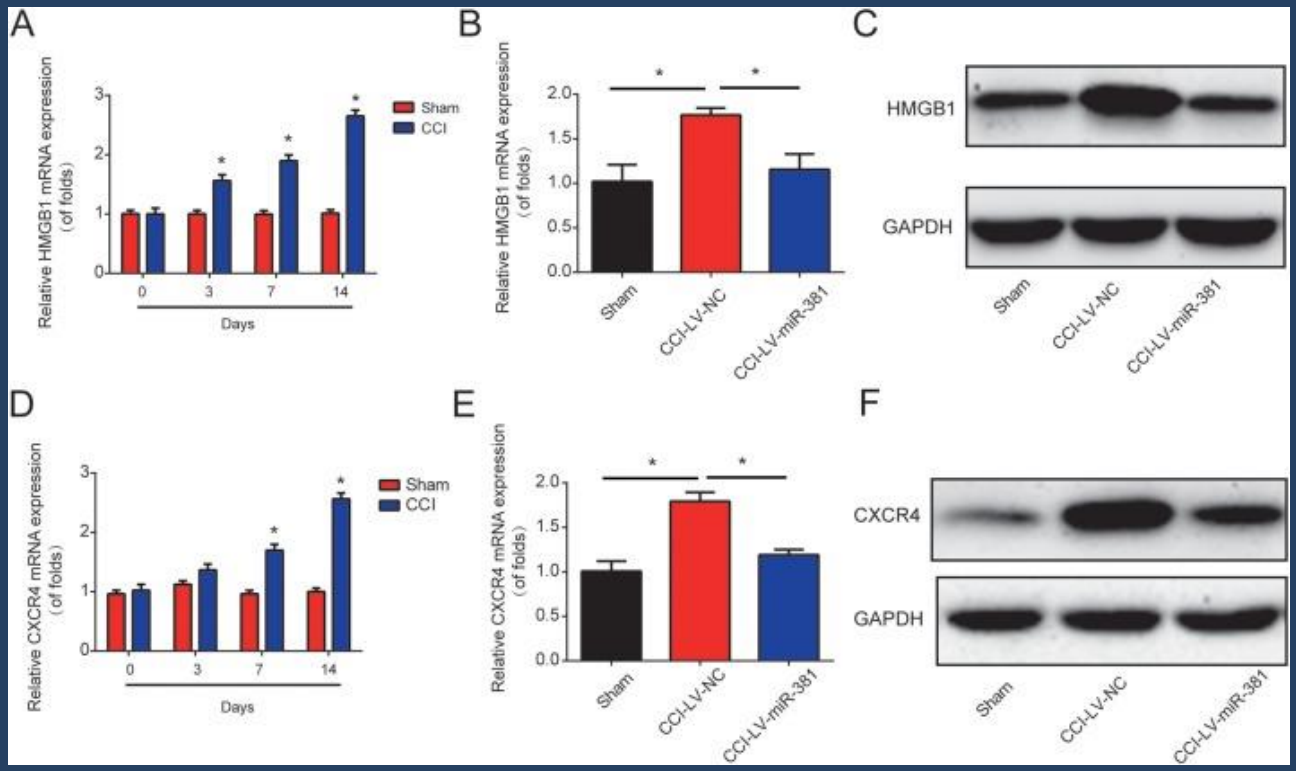
MicroRNA are significant regulators of neuropathic pain development. Neuroinflammation contributes a lot to the progression of neuropathic pain. miR-381 is involved in various pathological processes. However, the role of miR-381 in neuropathic pain development remains barely understood. Therefore, in our study, we aimed to investigate the effects of miR-381 on the process of neuropathic pain progression by establishing a rat model using chronic sciatic nerve injury (CCI). Here, we observed that miR-381 was dramatically decreased in CCI rats. Up-regulation of miR-381 strongly reduced neuropathic pain behaviors including mechanical and thermal hyperalgesia. In addition, inflammatory cytokine expression, including IL-6, IL-10 and TNF-α were significantly repressed by overexpression of miR-381. High mobility group box 1 protein (HMGB1) and Chemokine CXC receptor 4 (CXCR4) participate in neuropathic pain development. In our present study, HMGB1 and CXCR4 were predicted as direct targets of miR-381 by employing bioinformatics analysis. Overexpression of miR-381 was able to restrain the expression of HMGB1 and CXCR4 greatly. The direct correlation between HMGB1 and CXCR4 and miR-381 was confirmed in our research. Furthermore, we found that HMGB1 and CXCR4 were increased in CCI rats time-dependently. Moreover, it was demonstrated that silence of HMGB1 and CXCR4 in CCI rats depressed neuropathic pain progression greatly. In conclusion, it was indicated that miR-381could inhibit neuropathic pain development through targeting HMGB1 and CXCR4.



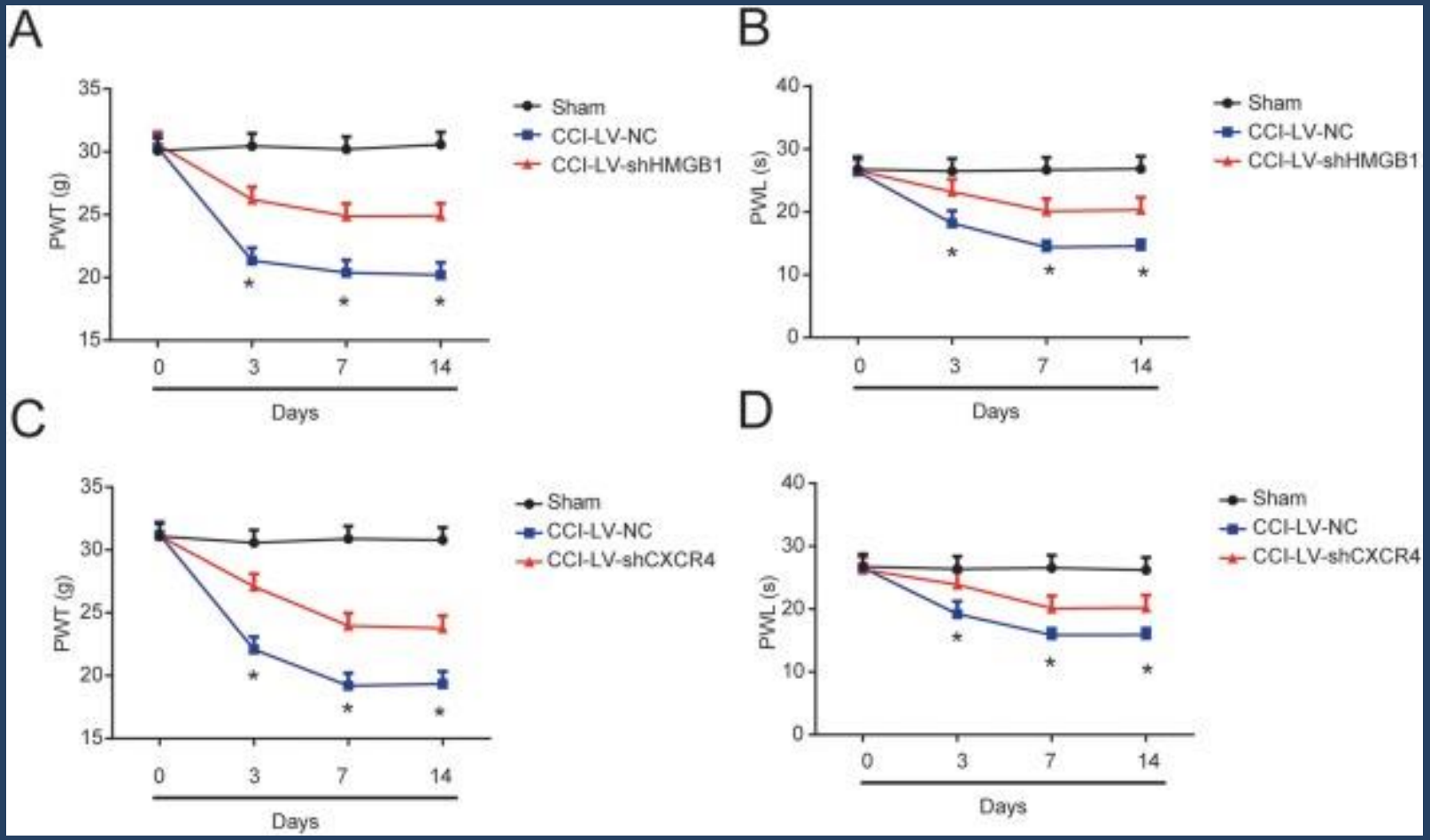
Expression of miR-381 in CCI rats. (A) MiR-381 expression in the L4-L6 dorsal spinal cord of rats. qRT-PCR was employed at postoperative days 0, 3, 7 and 14. U6 was used as an internal control. (B) Expression of miR-381 in CCI rat models infected with LV-miR-381 or LV-NC at postoperative day 7 with U6 as an internal control. (C) The effect of miR-381 on mechanical allodynia was assessed by PWT at postoperative days 0, 3, 7 and 14. (D) The effect of miR-381 on thermal hyperalgesia was evaluated by PWL at postoperative days 0, 3, 7 and 14. N = 6 for each group. Three independent experiments were performed. Error bars stand for the mean ± SD of at least triplicate experiments. *$P < 0.05$.



MiR-381 suppressed neuroinflammation in CCI rats. The protein levels of IL-6 (A), IL-10 (B) and TNF-α(C) in the L4-L6 dorsal spinal cord of rats were measured by ELISA at postoperative day 7.



Overexpression of miR-381 suppressed HMGB1 and CXCR4 expression in vivo. (A) mRNA expression of HMGB1 in rat CCI models. (B) mRNA levels of HMGB1 in rat CCI models. CCI rats were infected with LV-miR-381 or LV-NC. qRT-PCR was performed at postoperative day 7. (C) Protein levels of HMGB1 in rat CCI models. Western blot was carried out at postoperative day 7. (D) mRNA expression of CXCR4 in rat CCI models. (E) mRNA levels of CXCR4 in rat CCI models. (F) Protein levels of CXCR4 in rat CCI models. N = 6 for each group.



Silence of HMGB1 and CXCR4 repressed neuropathic pain development in vivo. (A) The effect of HMGB1 on mechanical allodynia was assessed by PWT at postoperative days 0, 3, 7 and 14. (B) The effect of HMGB1 on thermal hyperalgesia was evaluated by PWL at postoperative days 0, 3, 7 and 14. (C) The effect of CXCR4 on mechanical allodynia was assessed by PWT at postoperative days 0, 3, 7 and 14. (D) The effect of CXCR4 on thermal hyperalgesia was evaluated by PWL. N = 6 for each group at postoperative days 0, 3, 7 and 14.

J Neurosurg Spine. 2011 May;14(5):583-97. doi: 10.3171/2010.12.SPINE10480. Epub 2011 Feb 18.

Spatiotemporal CCR1, CCL3(MIP-1α), CXCR4, CXCL12(SDF-1α) expression patterns in a rat spinal cord injury model of posttraumatic neuropathic pain.

Knerlich-Lukoschus F[1], von der Ropp-Brenner B, Lucius R, Mehdorn HM, Held-Feindt J.

Mol Pain. 2016 Mar 8;12. pii: 1744806916636385. doi: 10.1177/1744806916636385. Print 2016.

Crosstalk between astrocytic CXCL12 and microglial CXCR4 contributes to the development of neuropathic pain.

Luo X[1], Tai WL[1], Sun L[1], Pan Z[2], Xia Z[3], Chung SK[4], Cheung CW[5].

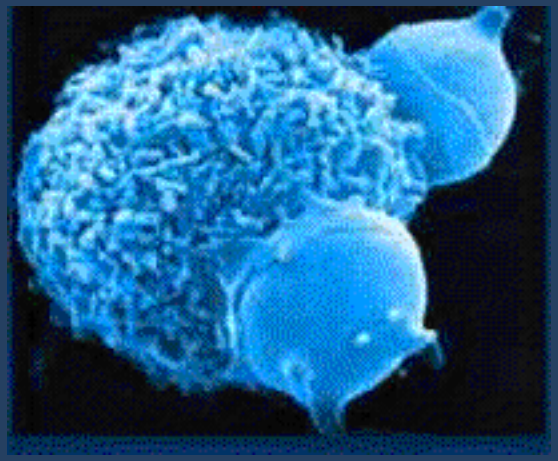
J Pain Res. 2017 Sep 7;10:2205-2212. doi: 10.2147/JPR.S139619. eCollection 2017.

CXCR4 antagonist AMD3100 elicits analgesic effect and restores the GlyRα3 expression against neuropathic pain.

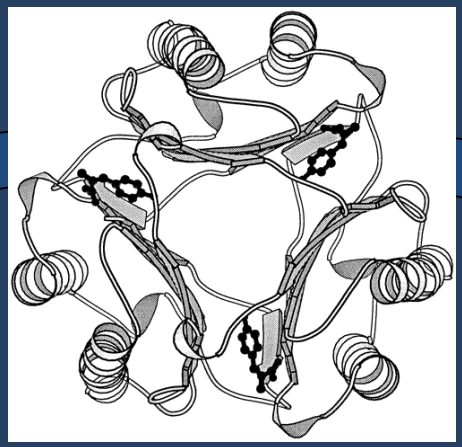
Liu X[1], Liu H[1], Dai L[1], Ma B[1], Ma K[1].

MIF

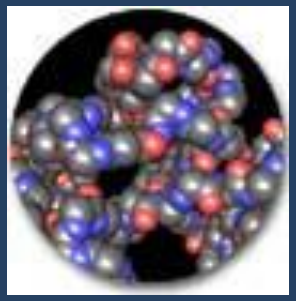
(Macrophage Migration Inhibitory Factor)



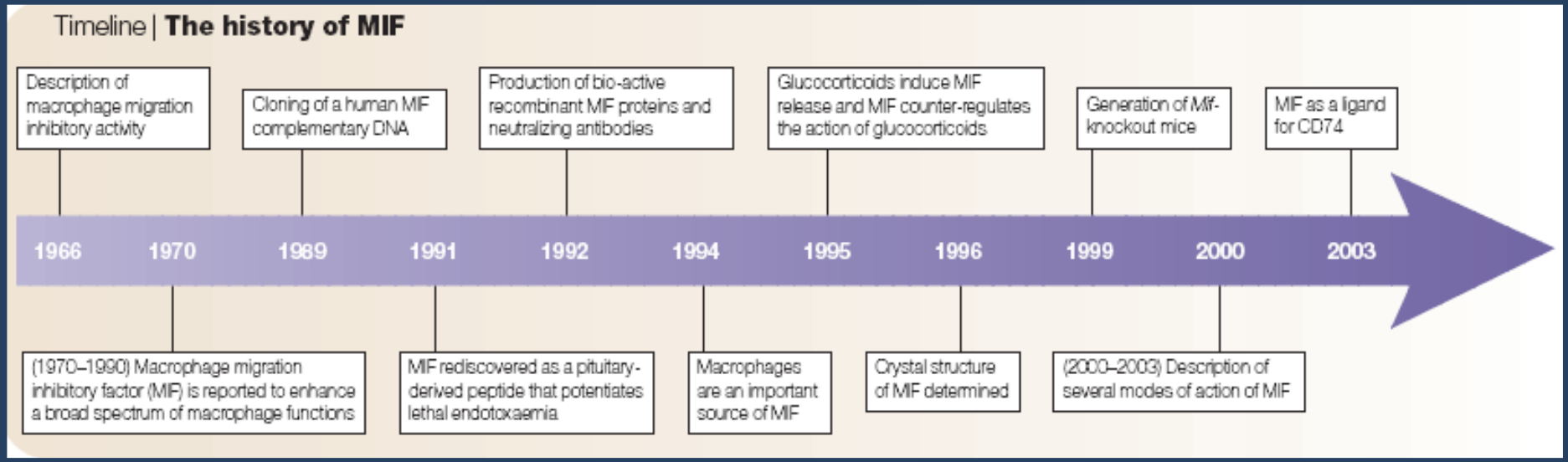
Macrophage

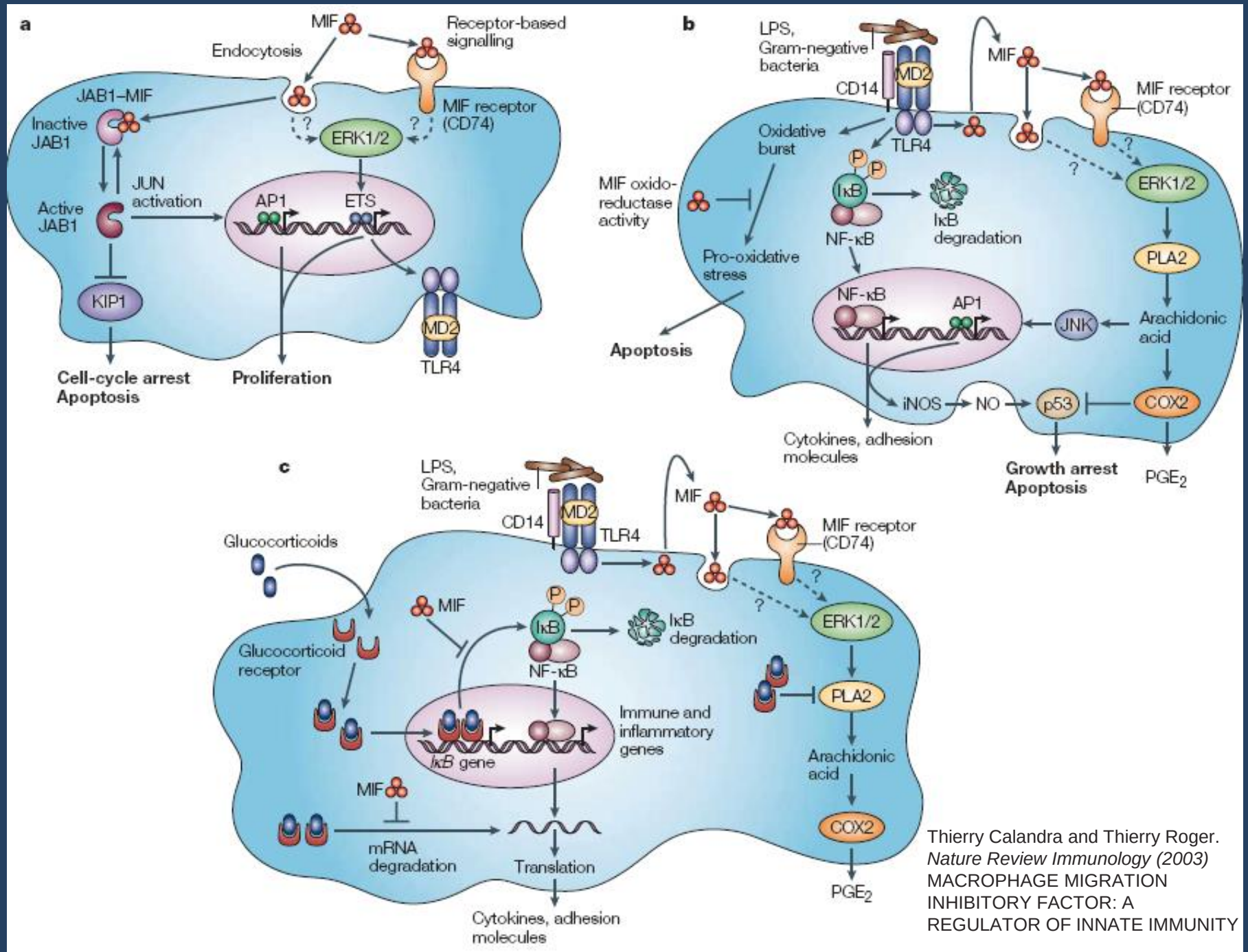


MIF



Macrophage Migration Inhibitory Factor (MIF) is a potent, proinflammatory cytokine that has been shown to stimulate an immune response in the presence of steroids and other immune suppressants. MIF has also been shown to play a role in the cytokine cascades involved in certain inflammatory diseases and to inhibit the activity of p53, an important tumor suppressor. Numerous animal studies have demonstrated that MIF-neutralizing antibodies can provide beneficial effects in arthritis, septic shock, cancer, glomerulonephritis and colitis. Blocking the production or bioactivity of MIF, therefore, may be useful in the treatment of a wide spectrum of diseases.


Timeline | The history of MIF
Description of macrophage migration inhibitory activity
Cloning of a human MIF complementary DNA
Production of bio-active recombinant MIF proteins and neutralizing antibodies
Glucocorticoids induce MIF release and MIF counter-regulates the action of glucocorticoids
Generation of Mif-knockout mice
MIF as a ligand for CD74
1966
1970
1989
1991
1992
1994
1995
1996
1999
2000
2003
(1970–1990) Macrophage migration inhibitory factor (MIF) is reported to enhance a broad spectrum of macrophage functions
MIF rediscovered as a pituitary-derived peptide that potentiates lethal endotoxaemia
Macrophages are an important source of MIF
Crystal structure of MIF determined
(2000–2003) Description of several modes of action of MIF



Thierry Calandra and Thierry Roger.
Nature Review Immunology (2003)
MACROPHAGE MIGRATION INHIBITORY FACTOR: A REGULATOR OF INNATE IMMUNITY

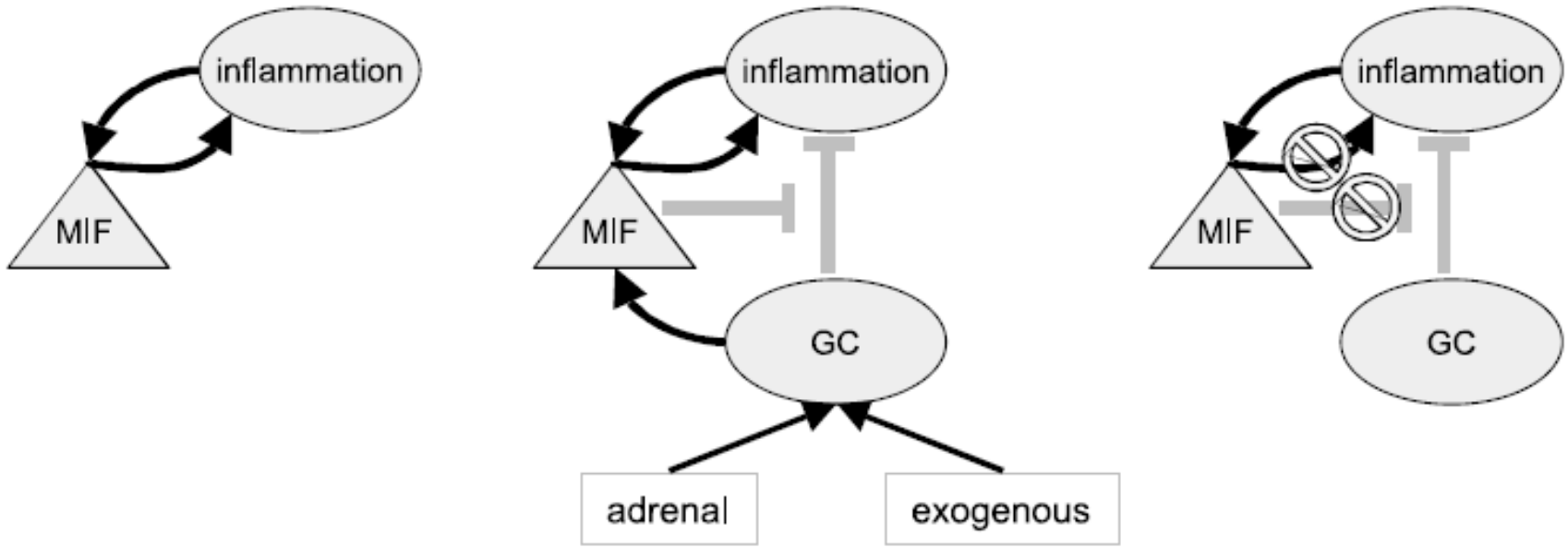


Figure 1 The relationship between migration inhibitory factor (MIF), glucocorticoids (GC), and inflammation: 1. MIF is produced during inflammation and acts to support and amplify the inflammatory response via the induction of its own expression as well as that of other cytokines and mediators; 2. Endogenous or exogenous GC inhibit inflammation, but induce the expression of MIF, which in turn antagonizes the effects of GC. The net anti-inflammatory effect of GC is impaired; 3. MIF antagonism inhibits the direct effects of MIF on inflammation. In addition, by neutralizing an endogenous antagonist of GC, MIF antagonism enhances the effects of GC on inflammation.

E. F. MORAND. *Internal Medicine Journal* 2005. New therapeutic target in inflammatory disease: macrophage migration inhibitory factor

Action of MIF in inflammation

Cell	Observation
Monocyte/macrophage	Expression of MIF
	Induction by endotoxin
	Induction of TNF
	Increase phagocytosis
	Increase intracellular killing
	Induce IL-8
	Inhibit apoptosis
T lymphocyte	Expression of MIF
	Inhibition of activation by MIF antagonism
	Inhibition of DTH by MIF antagonism
Endothelial cell	Expression of MIF
	Proliferation, activation
	Angiogenesis
Eosinophil	Expression of MIF
B lymphocyte	Expression of MIF
	Growth factor

DTH, delayed-type hypersensitivity; IL-8, interleukin-8; MIF, migration inhibitory factor; TNF, tumour necrosis factor.

E. F. MORAND. *Internal Medicine Journal* 2005. New therapeutic target in inflammatory disease: macrophage migration inhibitory factor

Drug Discov Today. 2018 Nov 13. pii: S1359-6446(18)30329-5. doi: 10.1016/j.drudis.2018.11.003. [Epub ahead of print]

Role of MIF and D-DT in immune-inflammatory, autoimmune, and chronic respiratory diseases: from pathogenic factors to therapeutic targets.

Günther S[1], Fagone P[2], Jalce G[3], Atanasov AG[4], Guignabert C[5], Nicoletti F[6].

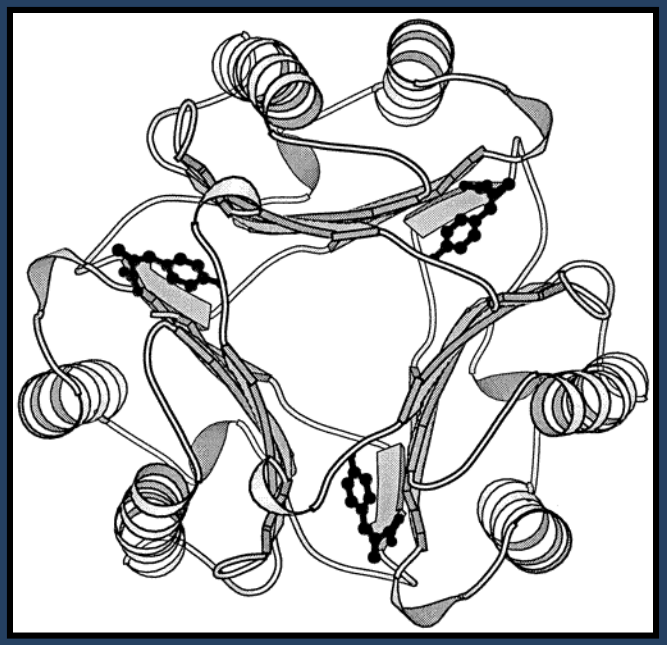
Author information

Abstract

Macrophage migration inhibitory factor (MIF) is a protein that acts as a cytokine-, enzyme-, endocrine- and chaperon-like molecule. It binds to the cell-surface receptor CD74 in association with CD44, which activates the downstream signal transduction pathway. In addition, MIF acts also as a noncognate ligand for C-X-C chemokine receptor type 2 (CXCR2), type 4 (CXCR4), and type 7 (CXCR7). Recently, D-dopachrome tautomerase (D-DT), a second member of the MIF superfamily, was identified. From a pharmacological and clinical point of view, the nonredundant biological properties of MIF and D-DT anticipate potential synergisms from their simultaneous inhibition. Here, we focus on the role of MIF and D-DT in human immune-inflammatory, autoimmune, and chronic respiratory diseases, providing an update on the progress made in the identification of specific small-molecule inhibitors of these proteins.

PMID: 30439447 DOI: 10.1016/j.drudis.2018.11.003

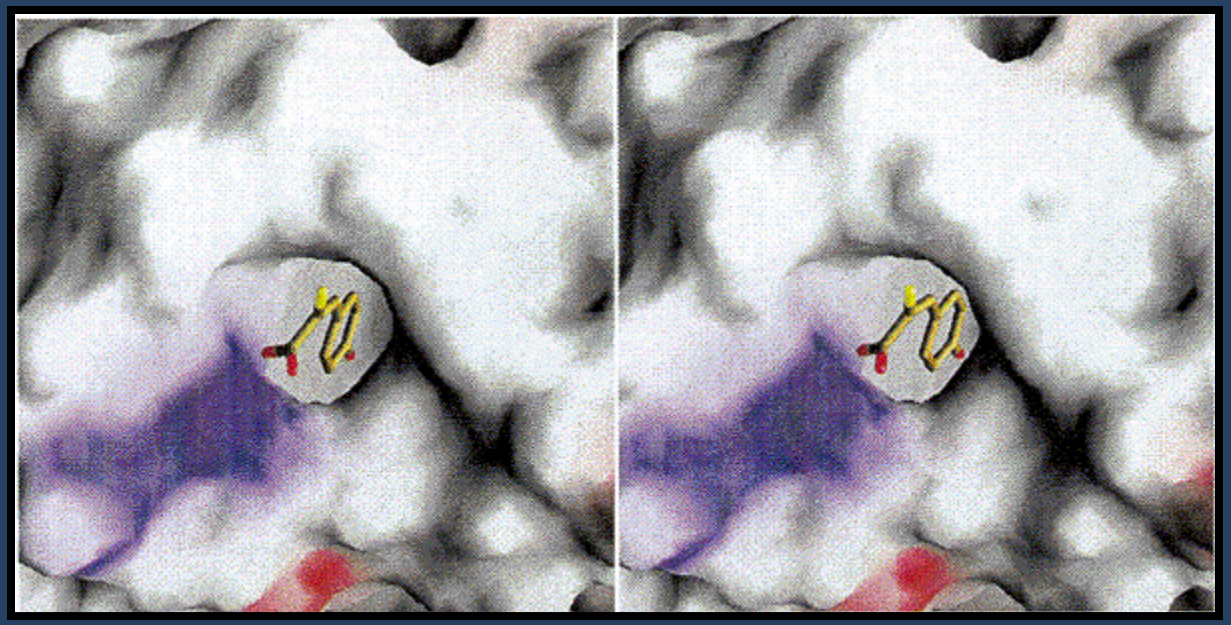
Model	Effect	Reference
Peripheral nerve injury-induced hypersensitivity	MIF suppressed the descending dopaminergic system	Wang et al., 2018
T13/L1 dorsal root avulsion	The MIFinhibitor ibudilast reversed below-level allodynia bilaterally	Ellis et al., 2014
Spared nerve injury	Mif−/− mice do not develop mechanical hypersensitivity after nerve injury	Alexander et al., 2012
	Systemic injection of a MIF inhibitor after nerve injury reduces hypersensitivity	
Sciatic chronic constriction nerve injury	Intrathecal MIF tautomerase inhibitor reversed pain behaviors	Wang et al., 2011
Bladder pain	Spinal treatment with MIF monoclonal antibody temporarily reversed bladder pain	Ma et al., 2019



Ray X Cristallography:

Omotrymer

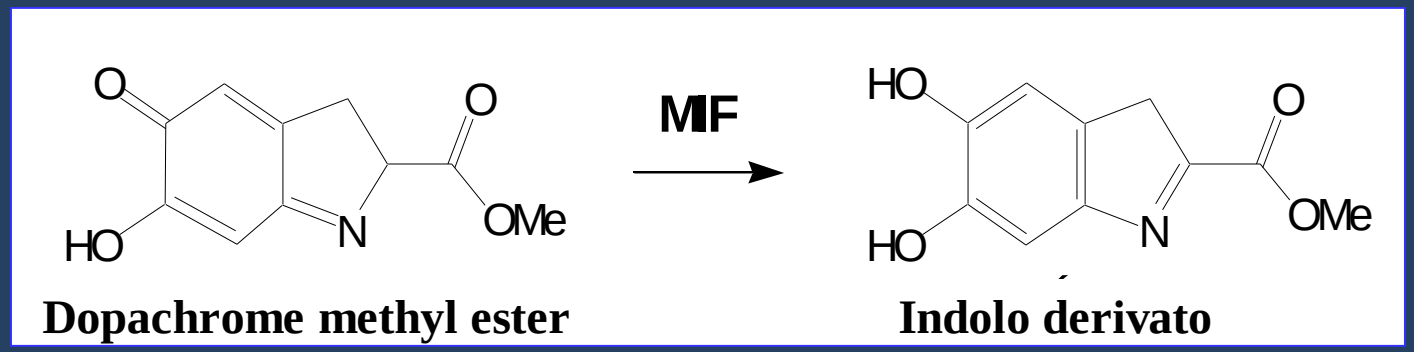
MIF active site:
hydrophobic cavity with an amino terminal proline



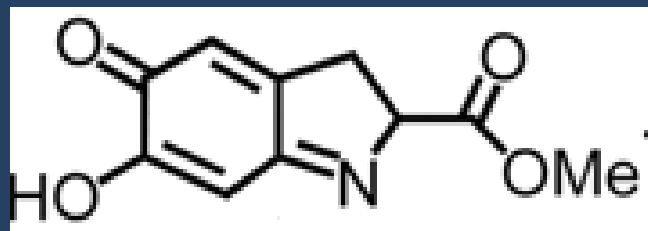
Macrophage migration Inhibitory Factor (MIF)

MIF has at least two distinct catalytic activities:

- tautomerase
- oxidoreductase

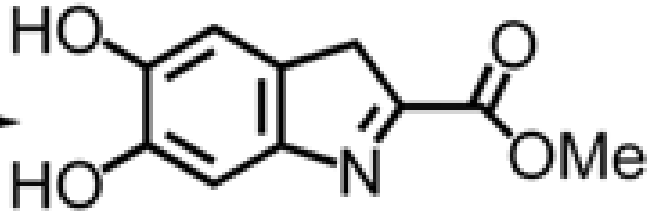


H. Lue et al ; Microbes and Infection 2002

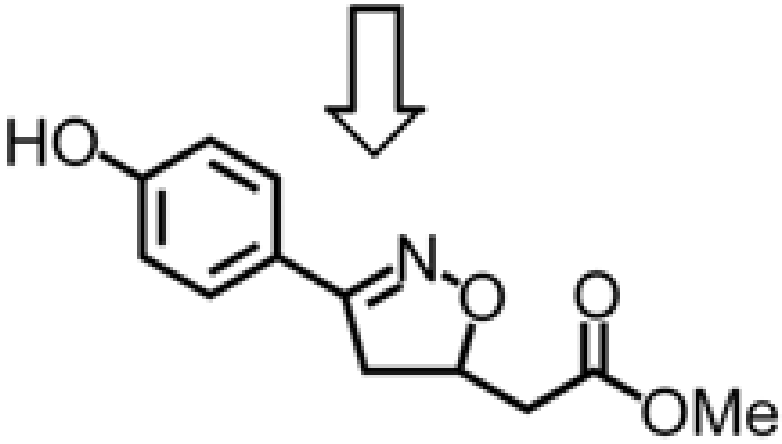


Dopachrome methyl ester

MIF



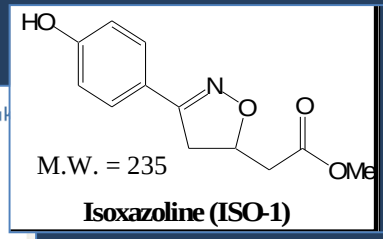
Indolo derivato



ISO-1

Peter D. Senter et al ; PNAS 2002

Synthesis of ISO-1 and derivatives



Isoxazoline (ISO-1)

5: Lubetsky JB, Dios A, Han J, Aljabari B, Ruzsicska B, Mitchell R, Lolis E, Al-Abed Y. Related Articles, Link

The tautomerase active site of macrophage migration inhibitory factor is a potential target for discovery of novel anti-inflammatory agents.

J Biol Chem. 2002 Jul 12;277(28):24976-82. Epub 2002 May 7.
PMID: 11997397 [PubMed - indexed for MEDLINE]

4: Al-Abed Y, Dabideen D, Aljabari B, Valster A, Messmer D, Ochani M, Tanovic M, Ochani K, Bacher M, Nicoletti F, Metz C, Pavlov VA, Miller EJ, Tracey KJ. Related Articles, Links

ISO-1 binding to the tautomerase active site of MIF inhibits its pro-inflammatory activity and increases survival in severe sepsis.

J Biol Chem. 2005 Nov 4;280(44):36541-4. Epub 2005 Aug 22.
PMID: 16115897 [PubMed - indexed for MEDLINE]

3: Cheng KF, Al-Abed Y. Related Articles, Links

Critical modifications of the ISO-1 scaffold improve its potent inhibition of macrophage migration inhibitory factor (MIF) tautomerase activity.

Bioorg Med Chem Lett. 2006 Jul 1;16(13):3376-9. Epub 2006 May 6.
PMID: 16682188 [PubMed - indexed for MEDLINE]

Effects of ISO-1 in preclinical models of immunoinflammation

5: Cvetkovic I, Al-Abed Y, Miljkovic D, Maksimovic-Ivanic D, Roth J, Bacher M, Lan HY, Nicoletti F, Stosic-Grujicic S. Related Articles, Links

Critical role of macrophage migration inhibitory factor activity in experimental autoimmune diabetes.

Endocrinology. 2005 Jul;146(7):2942-51. Epub 2005 Mar 24.
PMID: 15790730 [PubMed - indexed for MEDLINE]

4: Al-Abed Y, Dabideen D, Aljabari B, Valster A, Messmer D, Ochani M, Tanovic M, Ochani K, Bacher M, Nicoletti F, Metz C, Pavlov VA, Miller EJ, Tracey KJ. Related Articles, Links

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J Biol Chem. 2005 Nov 4;280(44):36541-4. Epub 2005 Aug 22.
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3: Nicoletti F, Créange A, Orlikowski D, Bolgert F, Mangano K, Metz C, Di Marco R, Al Abed Y. Related Articles, Links

Macrophage migration inhibitory factor (MIF) seems crucially involved in Guillain-Barré syndrome and experimental allergic neuritis.

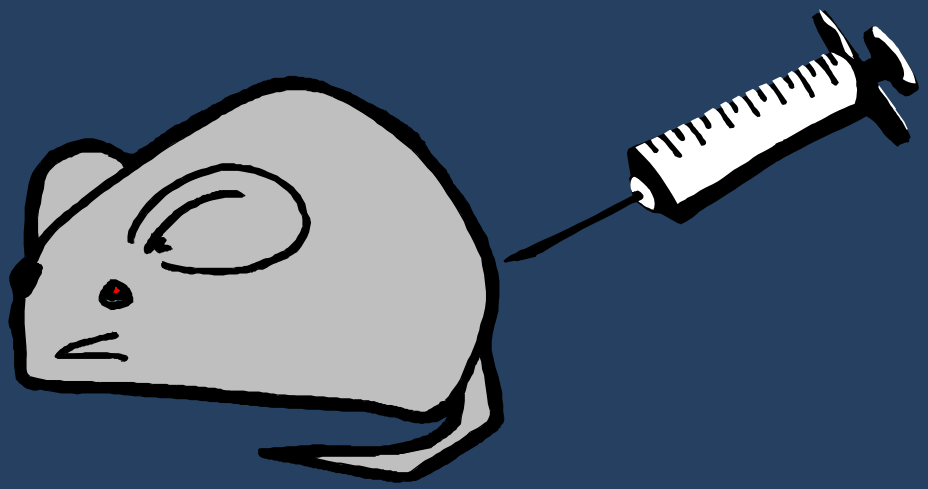
J Neuroimmunol. 2005 Nov;168(1-2):168-74.
PMID: 16171874 [PubMed - indexed for MEDLINE]

1: Stosic-Grujicic S, Stojanovic I, Maksimovic-Ivanic D, Momcilovic M, Popadic D, Harhaji L, Miljkovic D, Metz C, Mangano K, Papaccio G, Al-Abed Y, Nicoletti F. Related Articles, Links

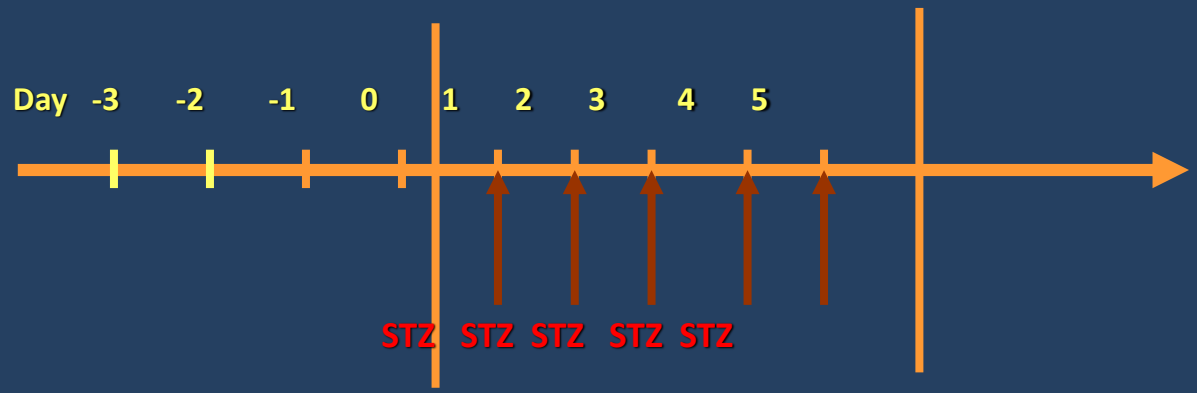
Macrophage migration inhibitory factor (MIF) is necessary for progression of autoimmune diabetes mellitus.

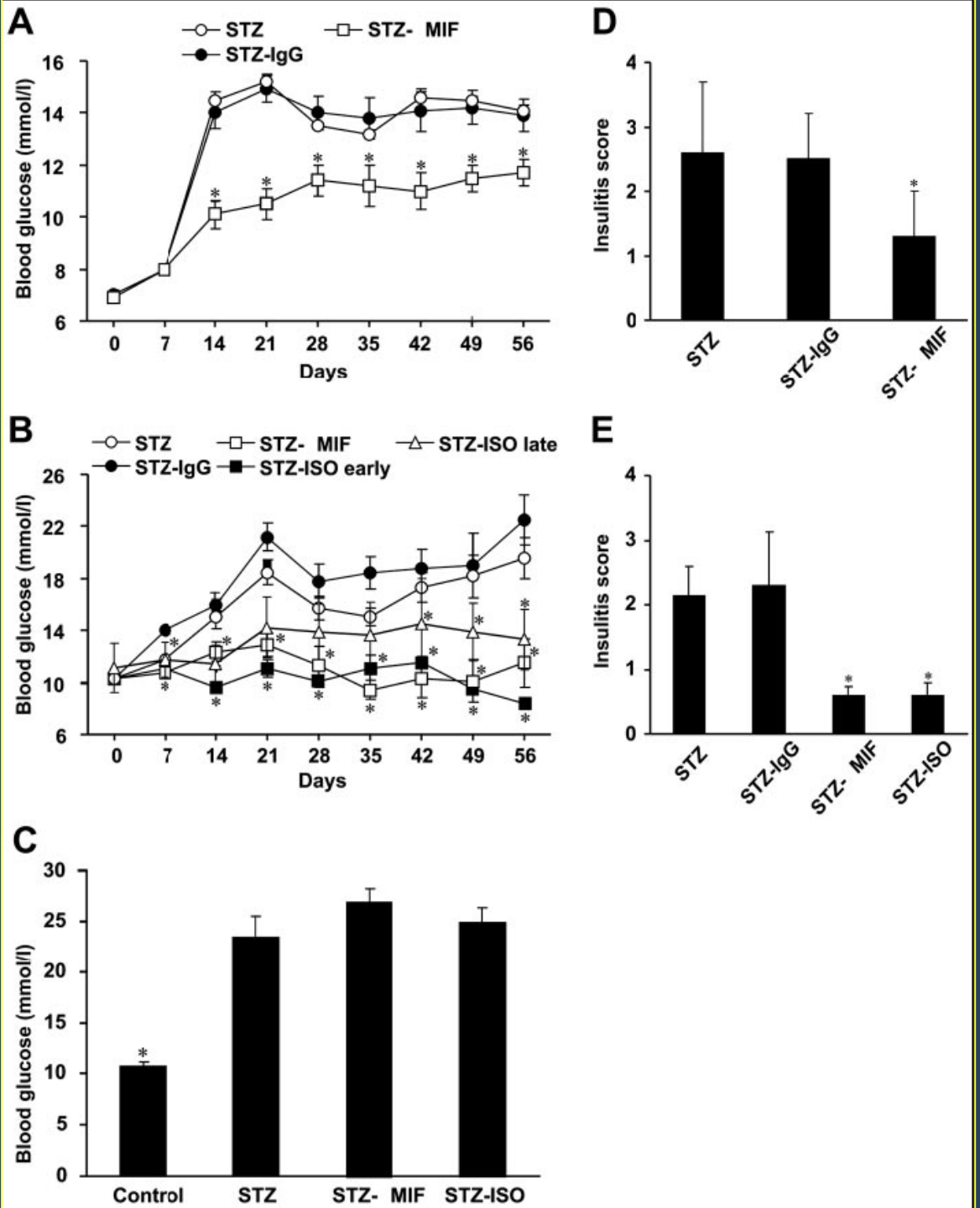
J Cell Physiol. 2007 Dec 6; [Epub ahead of print]
PMID: 18064633 [PubMed - as supplied by publisher]

Diabetes induced in mice by multiple low doses of streptozotocin

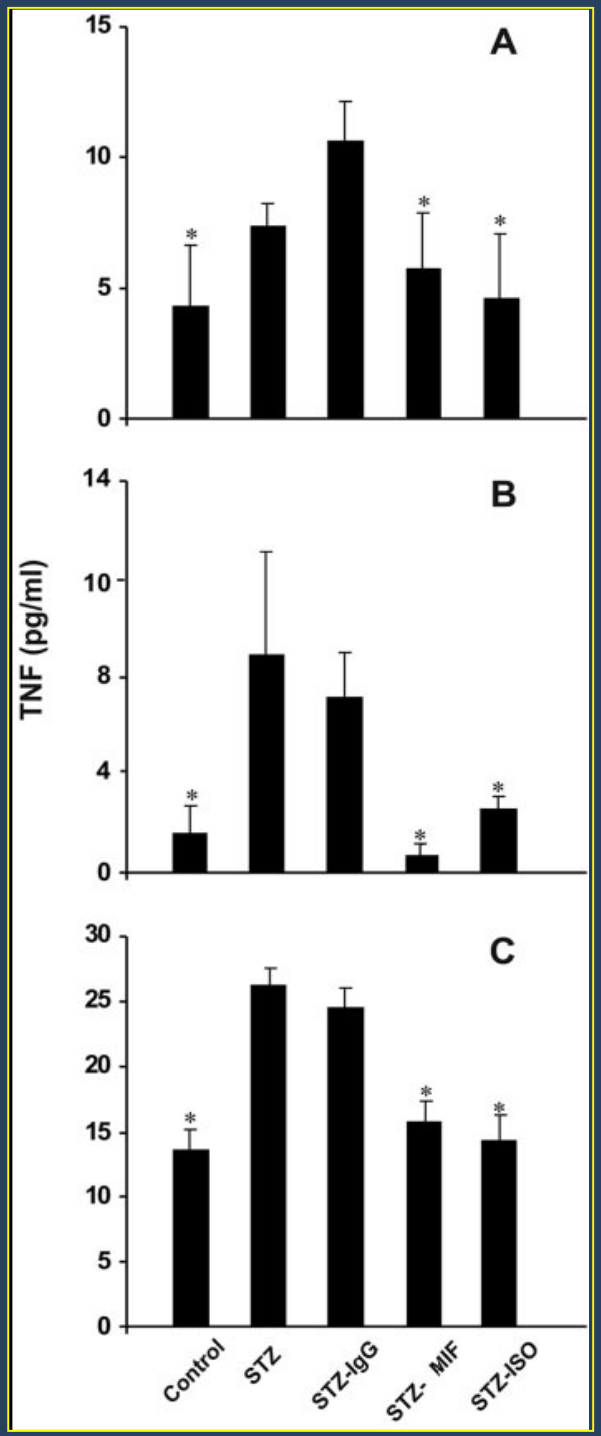


To induce diabetes, mice are injected i.p. for 5 consecutive days with 40 mg STZ/Kg body weight. STZ is dissolved in 0.1 mol/l sodium citrate buffer (pH 4.0) at a concentration of 0.4% and injected within 5 min. after preparation.





Effects of MIF targeting on the development of hyperglycemia and insulitis induced by STZ. Blood glucose levels were determined in C57BL/6 mice (A; n 24/group) or in CBA/H mice (B; n 5–10/group). Animals received MLD-STZ injections (five injections, 40 mg/kgd; A) or a single high dose of STZ (200 mg/kg; C) and were treated with vehicle (STZ), nonimmune rabbit IgG (STZIgG), anti-MIF IgG (STZ-MIF on days –3, -1, 2 and +5), or ISO-1 (1 mg mouse) given as an early (3 d before the first injection with STZ) or a late (24 h after the last STZ injection) prophylactic treatment for 14 consecutive days. Control, Mice without STZ. Blood glucose levels were determined through weekly measurements (A) or 12 d after receiving STZ (C). Histopathological analyses of pancreata from C57BL/6 mice (D) and CBA/H mice (E) are presented as insulitis scores. *, *P* 0.05 refers to corresponding STZ or STZ-IgG animals.



Neutralization of MIF activity reduces the production of

TNF-α.

SMNC(A),PC(B), and pancreatic islets (C) were isolated from the same groups of mice as described previously on d 15 after DM induction. TNF production was measured in the 48-h culture supernatants. Results are presented as the mean +/- SD of three independent experiments with similar results.

*$P<0.05$ refers to corresponding STZ-IgG or STZ animals.

J Neuroimmunol. 2005 Nov;168(1-2):168-74.

Macrophage migration inhibitory factor (MIF) seems crucially involved in Guillain-Barré syndrome and experimental allergic neuritis.

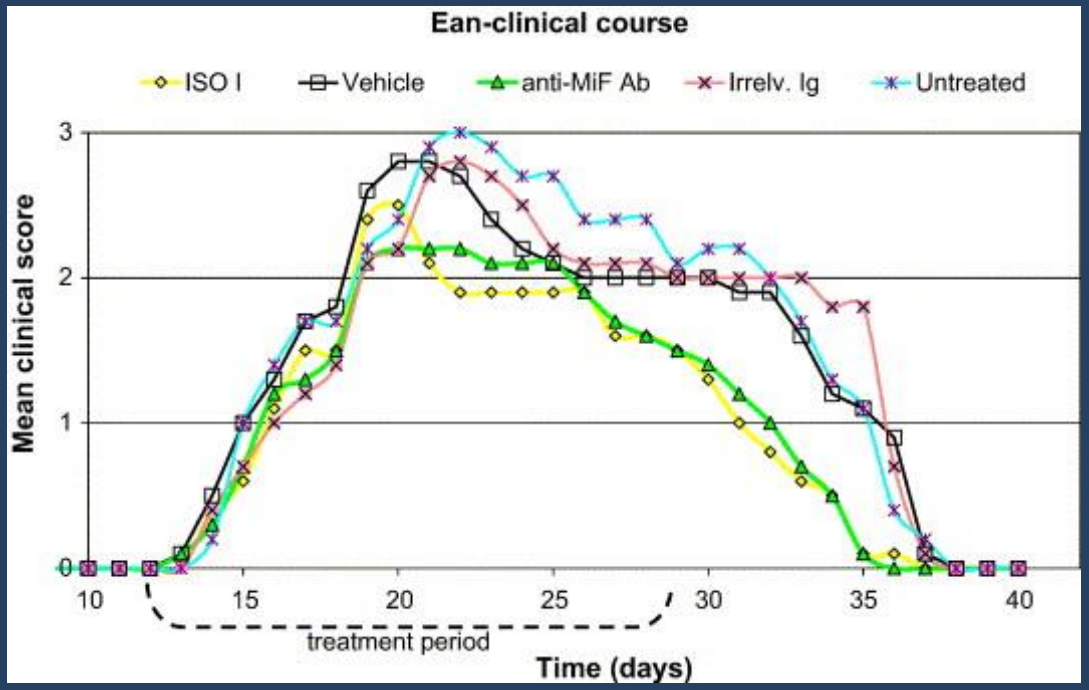
Nicoletti F[1], Créange A, Orlikowski D, Bolgert F, Mangano K, Metz C, Di Marco R, Al Abed Y.

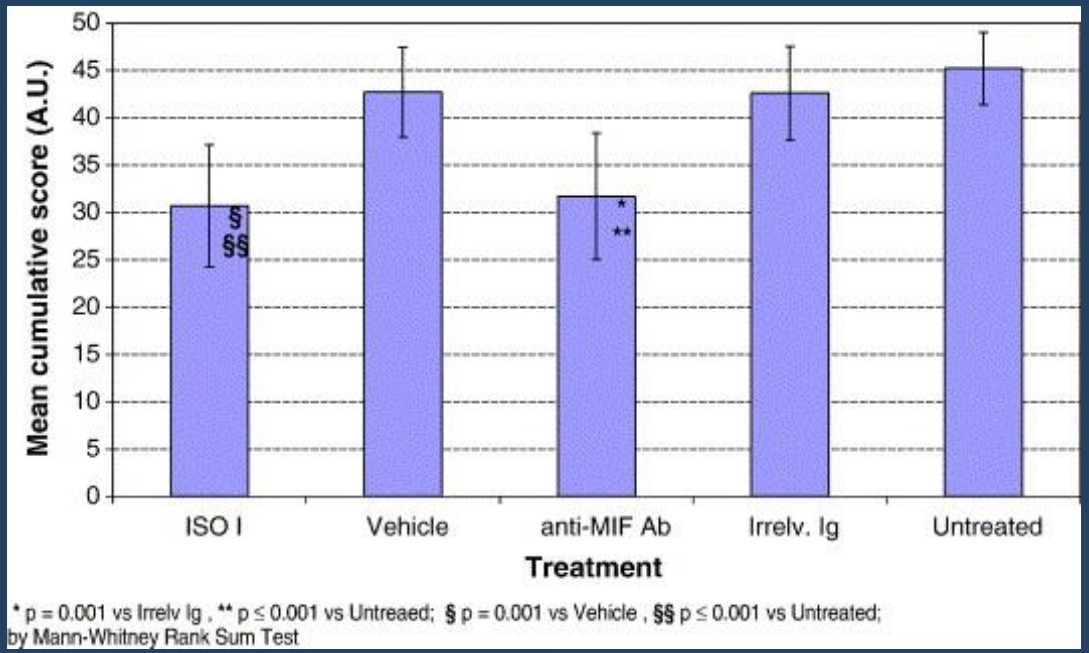
Author information

Abstract

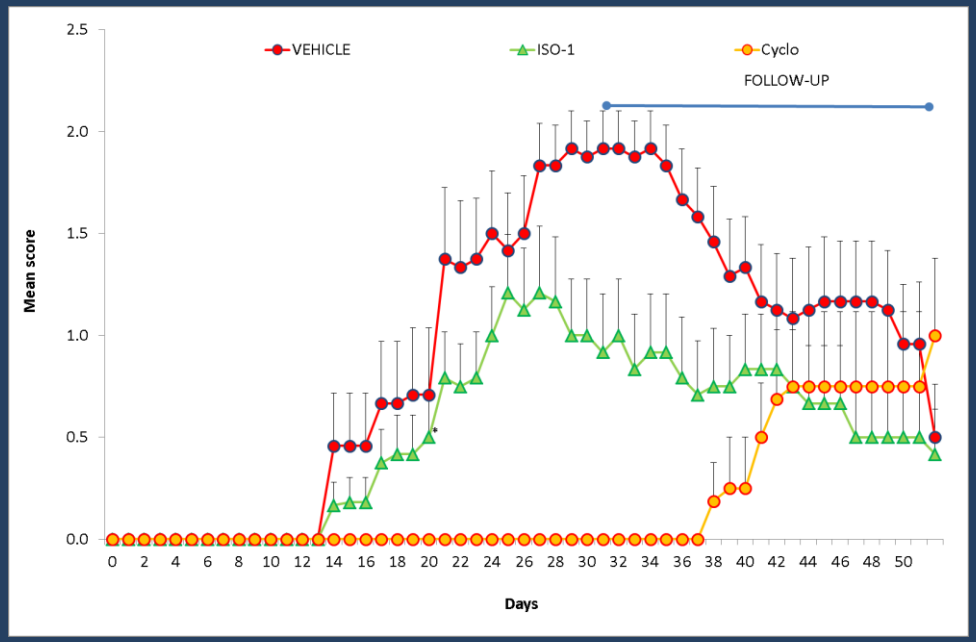
Macrophage migration inhibitory factor (MIF) is a proinflammatory type 1 cytokine that plays a pathogenic role in several inflammatory and autoimmune diseases. The role of this cytokine in peripheral nerve inflammatory disease has not been evaluated. Therefore, to evaluate the role of macrophage migration inhibitory factor (MIF) in Guillain-Barré syndrome (GBS) and experimental allergic neuritis (EAN), we determined MIF circulating levels in a series of patients with GBS and healthy subjects with ELISA and evaluated the effect of two specific inhibitors of MIF, a neutralizing monoclonal antibody or a chemical inhibitor ISO1 on the course of murine EAN. The data show increased MIF plasma levels in GBS patients as compared to healthy controls ($p<0.0001$) and a progressive increase of MIF circulating concentration with patient's disability ($p<0.0001$). Both anti-MIF mAb and ISO1 favorably influenced the course of EAN. Treated mice had a lower cumulative severity score ($p=0.001$) and reduced disease duration than the control mice ($p<0.03$). MIF may promote immune reaction in GBS. Therapeutic effects of both anti-MIF mAb and ISO1 in EAN suggest that MIF could be a promising therapeutic target in inflammatory demyelinating peripheral nerve disorders.

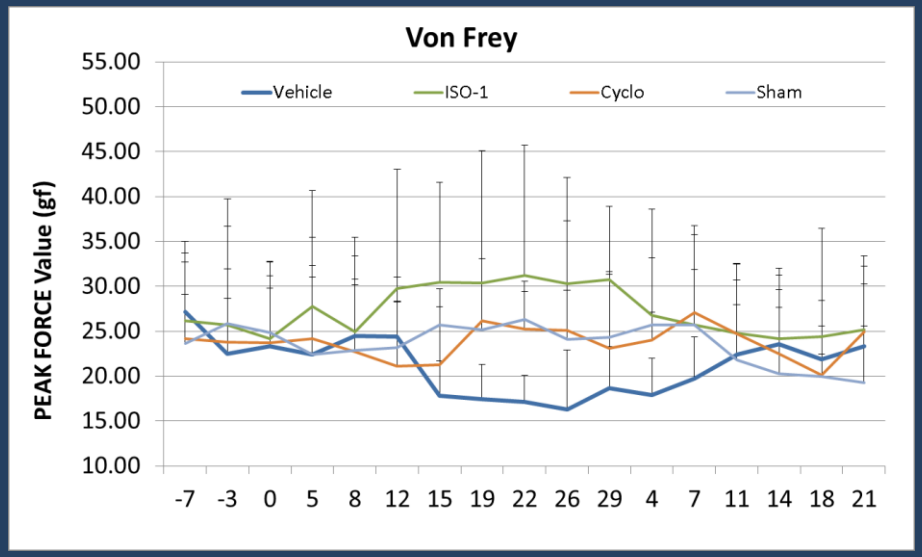
PMID: 16171874 DOI: 10.1016/j.jneuroim.2005.07.019





Nicoletti et al., 2005


VEHICLE
ISO-1
Cyclo
FOLLOW-UP
Mean score
Days
2.5
2.0
1.5
1.0
0.5
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50
*


Von Frey
Vehicle
ISO-1
Cyclo
Sham
PEAK FORCE Value (gf)
55.00
50.00
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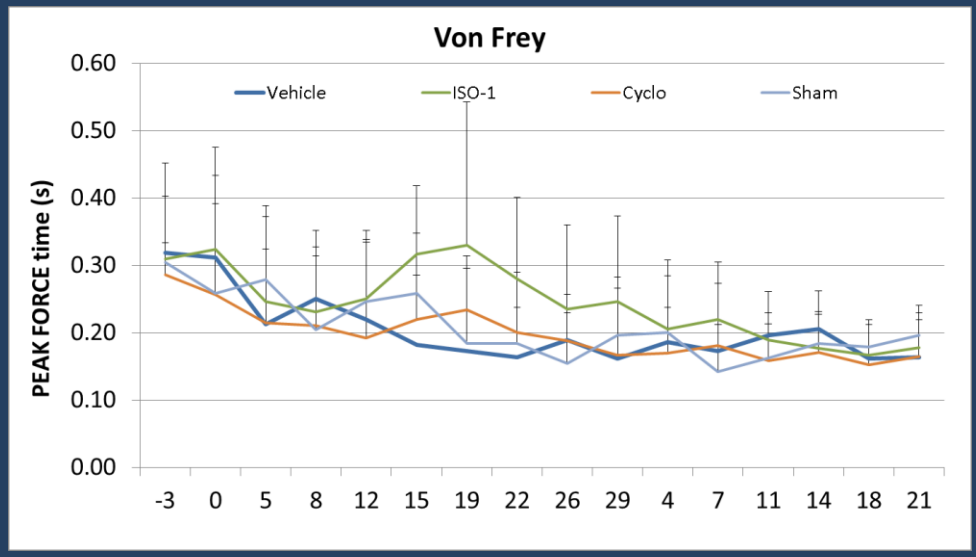
25.00
20.00
15.00
10.00
-7 -3 0 5 8 12 15 19 22 26 29 4 7 11 14 18 21


Von Frey
Vehicle
ISO-1
Cyclo
Sham
PEAK FORCE time (s)
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-3 0 5 8 12 15 19 22 26 29 4 7 11 14 18 21

Conclusioni

- Studi condotti nell'ultimo decennio sottolineano il ruolo patogenetico importante svolto dai recettori Toll-like del sistema dell'immunità innata nella patogenesi del dolore neuropatico.
- I recettori Toll-like 2, 4, e 5 sembrano quelli maggiormente coinvolti nell'amplificazione della nocicezione, e il loro blocco con inibitori specifici o tramite delezione genica, migliora la risposta allodinica indotta con stimolo meccanico.
- Il CXCR4 è un altro recettore espresso dalle cellule del Sistema Immune, che sembra agire in sinergia con i recettori Toll-like nella patogenesi del dolore neuropatico.
- Un noto agonista endogeno del CXCR4 è la citochina proinfiammatoria MIF. Il blocco del MIF con inibitori specifici, come la small molecule ISO-1, migliora la risposta allodinica meccanica in modelli sperimentali.
- Antagonisti specifici del MIF o del CXCR4 o dual o triple inhibitors dei recettori Toll-like meritano ulteriori studi per l'utilizzo come farmaci «pathogenetic-tailored» per il trattamento del dolore neuropatico.

«Due cose contribuiscono ad avanzare: andare più rapidamente degli altri o andare per la buona strada»

Cartesio

Ringraziamenti