NUTRAGE
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WP7

Partecipazione pro-attiva sesso-specifica ed età-dipendente del tessuto adiposo nella risposta alla neuropatia in modelli preclinici: nuovi target terapeutici e nutraceutici

SARA MARINELLI, PhD
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INCIDENZA E PREVALENZA DEL DOLORE NEUROPATICO

Il dolore neuropatico: è di tipo cronico ed è definito come una sintomatologia nevralgica lancinante e intermittente strettamente correlata a un'alterazione delle normali connessioni nervose periferiche o centrali.

- Gli esempi più tipici sono rappresentati da:

-dolore neuropatico di origine: meccanica, metabolica, iatrogena, genetica

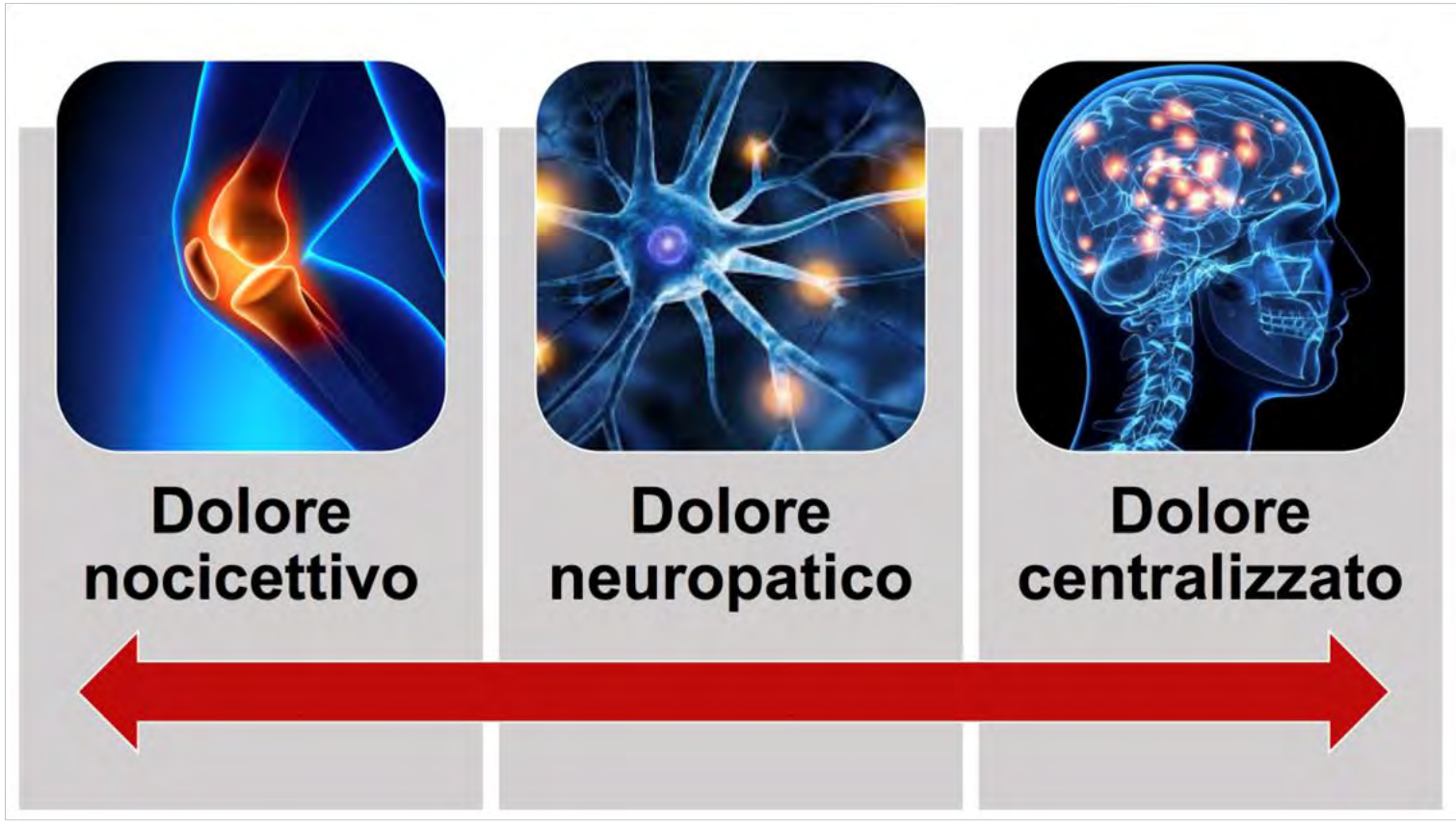
-dolore da deafferentazione,

-nevralgia post-herpetica,

-lesione del SNC, del midollo spinale,

-sindrome da arto fantasma,

-neoplasie dei nervi, del midollo, dell'encefalo.



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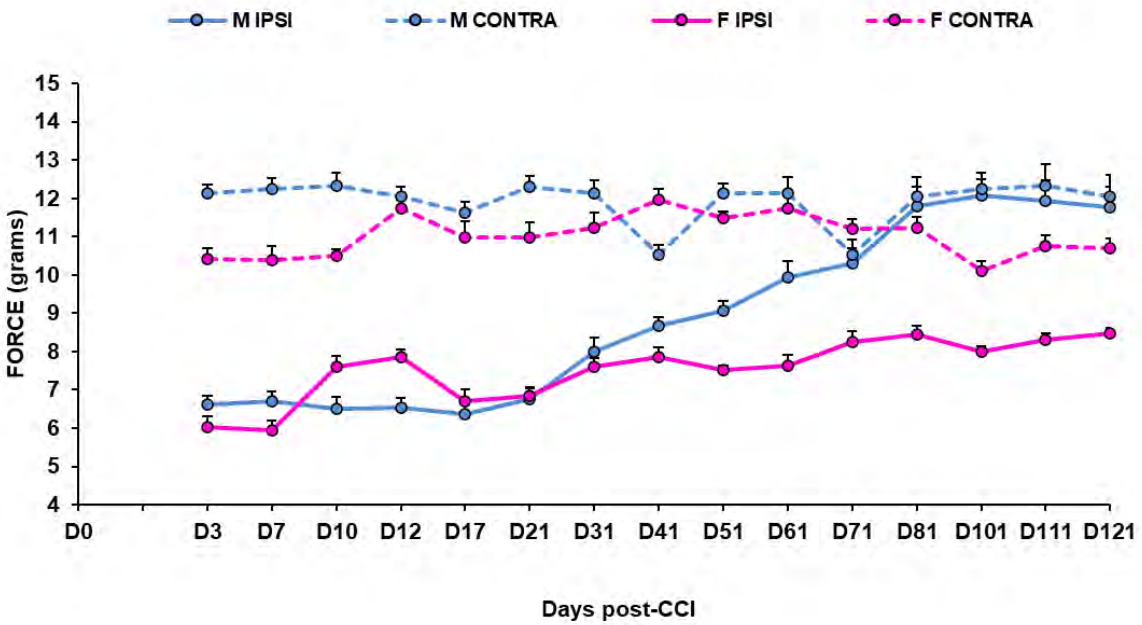
DOLORE NEUROPATICO NEL MODELLO PRECLINICO
DIFFERENZE DI GENERE E INVECCHIAMENTO

Vacca et al. / PAIN 155 (2014) 388–402
Vacca et al. iScience 26, 107914, (2023)



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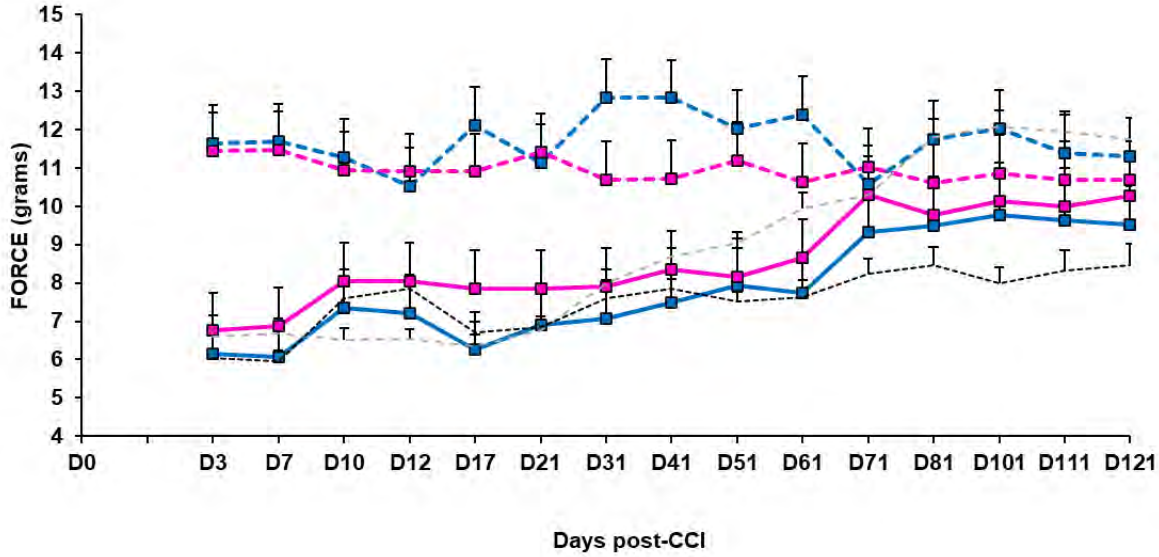

TOPI MASCHI ADULTI dopo una lesione nervosa periferica sviluppano dolore neuropatico che si risolve in 60 giorni

TOPI FEMMINE ADULTE dopo la lesione nervosa hanno un'iniziale Maggiore resistenza al dolore neuropatico sebbene non abbiano un recupero completo mostrando una cronicizzazione del dolore.

TOPI ANZIANI dopo una lesione nervosa periferica sviluppano dolore neuropatico che migliora ma non si risolve verso I 70 giorni

TOPI ANZIANI dopo la lesione nervosa periferica sviluppano dolore neuropatico che si risolve completamente in 70 giorni

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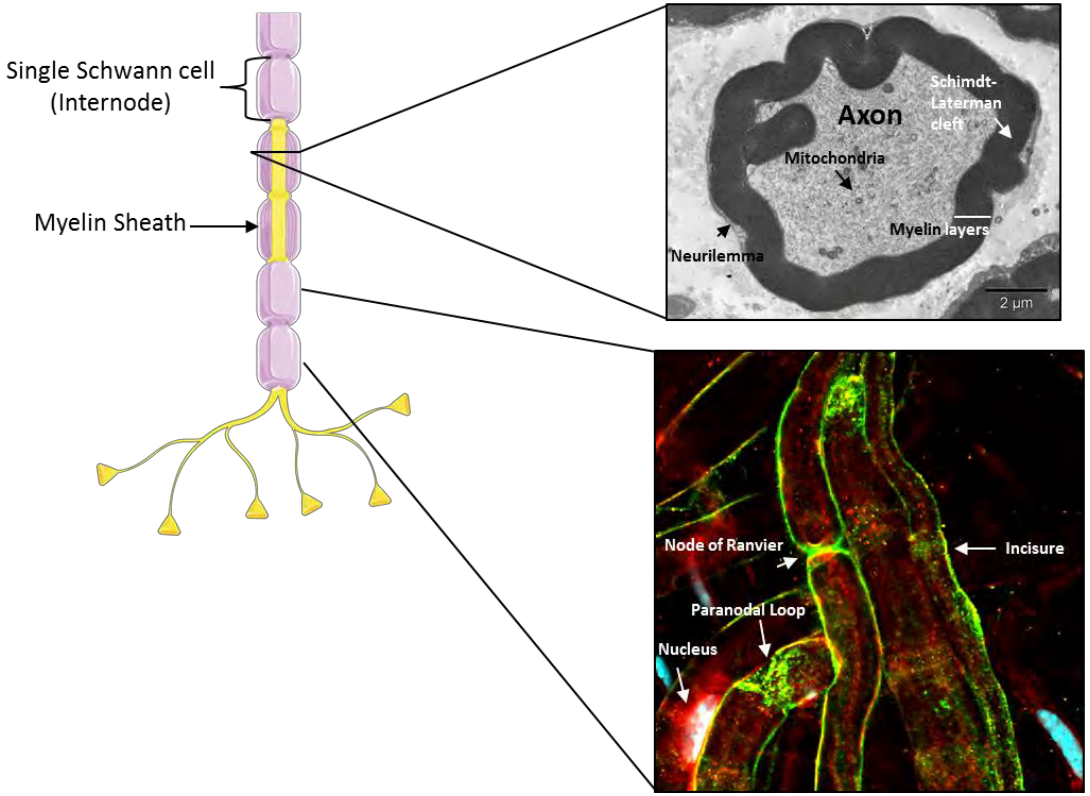
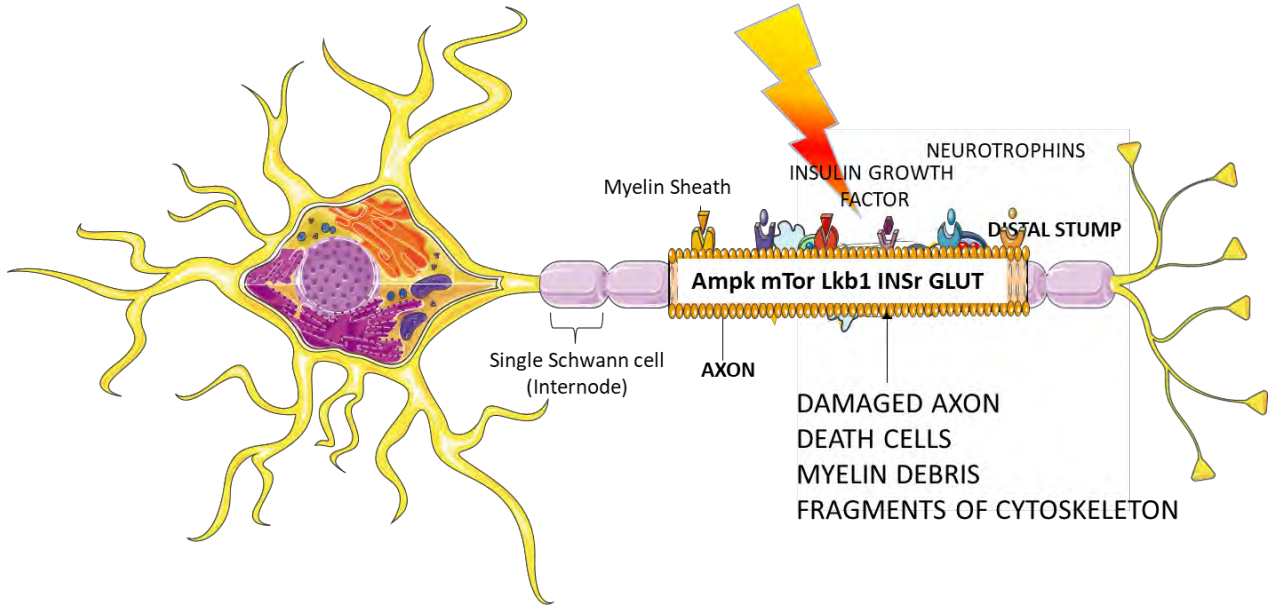
Peripheral Neuropathy and Neuropathic Pain



WALLERIAN DEGENERATION FIRST STEPS: Schwann cells, macrophages and mast cells activation

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ARTICLES

Schwann cell autophagy counteracts the onset and chronification of neuropathic pain

Marinelli, Sara[a,b]; Nazio, Francesca[b]; Tinari, Antonella[c]; Ciarlo, Laura[d]; D'Amelio, Marcello[b,e]; Pieroni, Luisa[b,f]; Vacca, Valentina[a,b]; Urbani, Andrea[b,f]; Cecconi, Francesco[b,g]; Malorni, Walter[d,h,i]; Pavone, Flaminia[a,b,*]


PLOS ONE

OPEN ACCESS · PEER-REVIEWED

RESEARCH ARTICLE

Effects of caloric restriction on neuropathic pain, peripher nerve degeneration and inflammation in normometabolic and autophagy defective prediabetic Ambra1 mice

Roberto Coccurello, Francesca Nazio, Claudia Rossi, Federica De Angelis, Valentina Vacca, Giacomo Giacovazzo, Patrizia Procacci, Valerio Magnaghi, Domenico Ciavardelli, Sara Marinelli

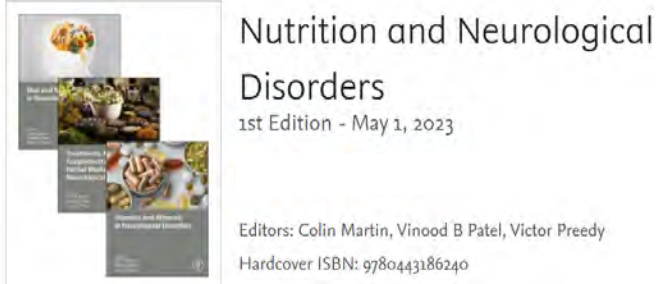

EJP European Journal of Pain

EFIC

SHORT COMMUNICATION

Impact of caloric restriction on peripheral nerve inju induced neuropathic pain during ageing in mice

Federica De Angelis, Valentina Vacca, Flaminia Pavone, Sara Marinelli



Elsevier, Part XI - Peripheral neuropathy, CH41. Caloric restriction as a nutrition strategy in counteracting peripheral neuropathies. *Marinelli S*

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BIOMARCATORI METABOLICI DI NEUROPATIA SESSO SPECIFICI E CORRELATI ALL'ETA'

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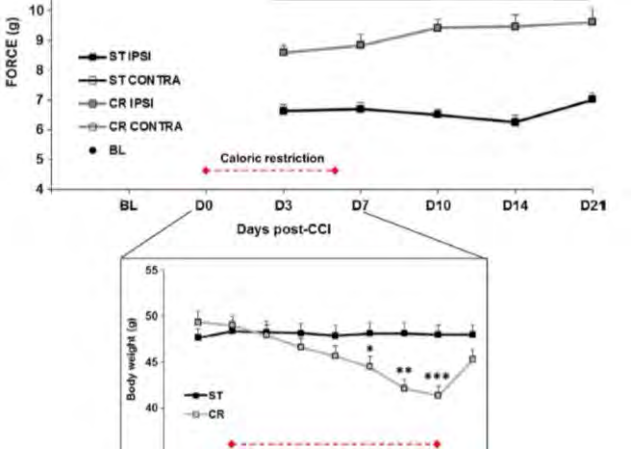
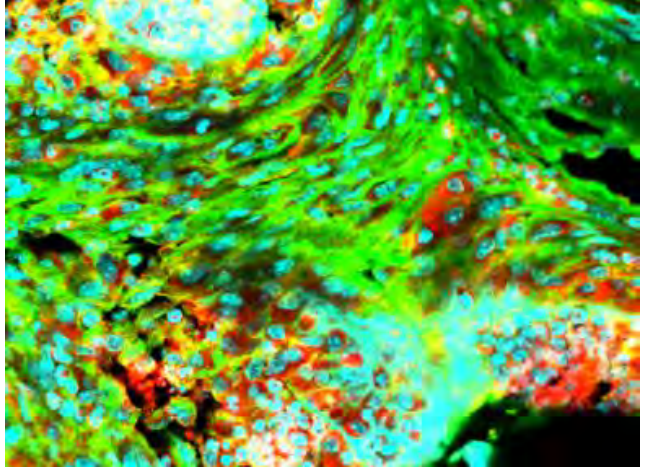
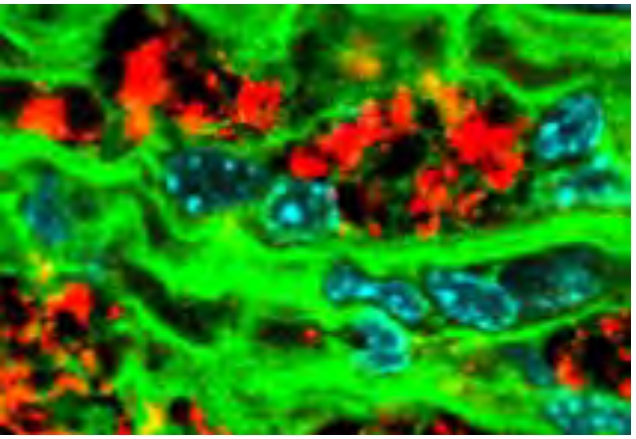
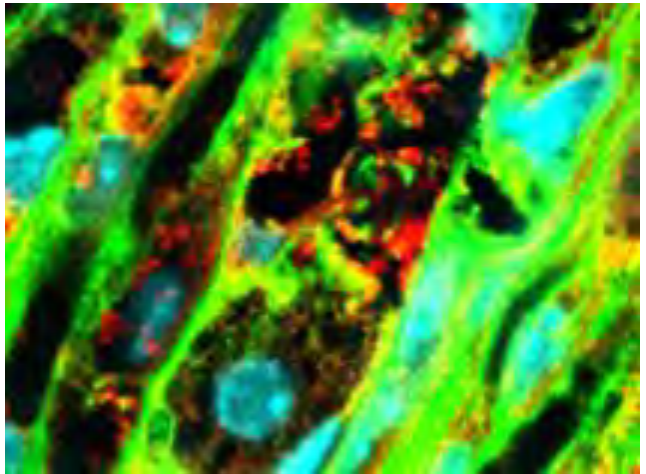






GM-CSF	Granulocyte-macrophage colony-stimulating factor	91,71 ± 14,84	134,47 ± 5,45	77,61 ± 3,25
IFNg	Interferon gamma	133,95 ± 6,32	122,09 ± 22,90	136,29 ± 3,13
IL–1a	Interleukin 1 alpha	22,75 ± 6,50	3,06 ± 0,58	13,15 ± 1,61
IL–1 b	Interleukin 1 beta	17,41 ± 3,13	3,06 ± 0,58	12,94 ± 2,75
IL–2	Interleukin 2	88,88 ± 2,08	85,48 ± 0,14	111,62 ± 3,06
IL–3	Interleukin 3	123,56 ± 10,71	64,68 ± 3,75	139,63 ± 6,32
IL–4	Interleukin 4	142,99 ± 0,57	84,20 ± 0,81	177,25 ± 5,06
IL–6	Interleukin 6	100,44 ± 2,27	79,99 ± 2,21	113,76 ± 7,09
IL–9	Interleukin 9	127,62 ± 3,53	91,47 ± 2,21	131,20 ± 3,34
IL–10	Interleukin 10	69,29 ± 6,80	98,49 ± 4,71	68,41 ± 1,41
IL–12p40p70	Interleukin 12	96,32 ± 2,49	118,9 ± 2,35	88,70 ± 0,41
IL–12p70	Interleukin 12	82,23 ± 0,13	79,99 ± 13,84	138,40 ± 25,44
IL–13	Interleukin 13	21,44 ± 4,29	8,03 ± 18,56	10,17 ± 0,42
IL–17	Interleukin 17	169,95 ± 6,38	104,48 ± 19,88	142,47 ± 2,29
I-TAC	chemokine ligand 11 (CXCL11)	14,89 ± 4,85	1,14 ± 0,22	13,08 ± 3,68
KC	Neutrophil chemokine, (CXCL1)	25,46 ± 1,71		32,00 ± 0,62
Leptin	adipokine	75,68 ± 3,07	244,57 ± 21,43	40,31 ± 5,02
LIX	Lipopolysaccharide-induced CXC chemokine	165,67 ± 7,40	133,19 ± 14,14	186,81 ± 4,21
Lymphotactin	Chemokine (C motif) ligand (XCL1)	79,93 ± 5,52	59,70 ± 1,98	107,89 ± 6,57
MCP–1	Monocyte chemoattractant protein 1	100,50 ± 10,67	70,04 ± 5,59	110,21 ± 0,90
MCSF	macrophage-chemotactic factor	15,42 ± 3,79	40,95 ± 7,88	29,59 ± 9,84
MIG	Monokine induced by gamma interferon	39,40 ± 1,49	51,67 ± 9,94	112,76 ± 3,08
MIP–1a	macrophage inflammatory protein 1-alpha (CCL3)	7,77 ± 3,04	4,97 ± 1,10	15,26 ± 3,46

De Angelis et al. EJN 2019



ANZIANI DOLORE NEUROPATICO E RESTRIZIONE CALORICA

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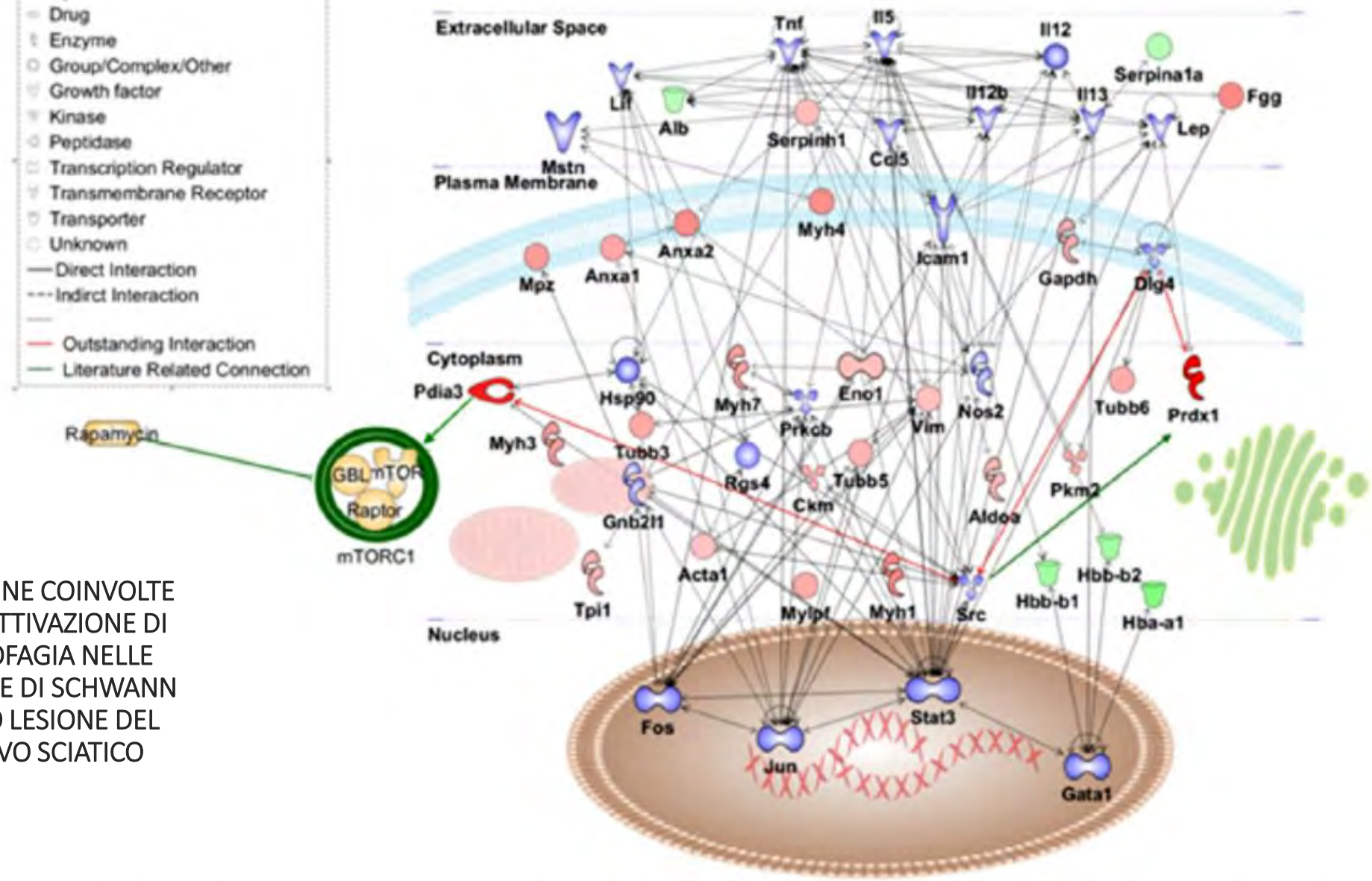
		FI VALUES		FI VALUES	
MEDIATOR	NAME and FUNCTION	NAIVE M	CCI D7 M	NAIVE F	CCI D7 F
CD30L	tumor necrosis factor ligand superfamily member 8	3239,11 ± 145,84	3202,57 ± 178,68	8,16 ± 0,67	50,85 ± ** 1,16
Eotaxin-1	C-C motif chemokine 11; eosinophil chemotactic protein	44572,06 ± 558,62	86503,33 ±** 1113,81	1136,88 ± 91,29	8543,73±** 203,06
Eotaxin-2	C chemokine selective for the chemokine receptor CCR	65439,39 ± 707,19	62086,92 ± 1392,43	368,33 ± 22,90	920,55 ±** 6,64
FAS ligand	type-II transmembrane protein tumor necrosis factor (TNF) family; apoptosis	2678,89 ± 419,10	2188,06 ± 19,53	5,58 ± 0,24	17,40 ± ** 1,02
G-CSF	Granulocyte colony-stimulating factor	4717,01 ± 622,37	9196,65 ±** 4132,10	19,01 ± 2,01	152,38 ± ** 5,10
IL1-beta	interleukine, inflammtory cytokine	2545,66 ± 203,90	4826,89 ± ** 877,03	11,98 ± 1,15	19,40 ± 0,77
IL2	interleukine activateing cytotoxic T cells and NK cells	3680,88 ± 28,07	5848,85 ± * 758,01	65,87 ± 6,45	82,10 ± 7,06
IL3	interleukine, multicolony-stimulating factor	3956,59 ± 12,65	5625,25 ± * 673,60	67,37 ± 0,65	104,35 ± * 4,68
IL4	interleukine, prototypic immunoregulatory cytokine.	4695,06 ± 21,11	5408,58 ± 400,68	75,66 ± 4,43	111,38 ± * 4,51
IL6	pro-inflammatory cytokine and an anti-inflammatory myokine	3126,88 ± 57,67	6946,52 ** ±302,31	73,17 ± 6,16	98,85 ± * 5,46
IL9	interleukine, T cell growth factor	4778,08 ± 25,16	4012,32 ± 61,27	88,53 ± 7,48	124,79 ± * 1,26
IL10	interleukine, cytokine synthesis inhibitory factor (CSIF), anti-inflammatory cytokine	3486,74 ± 285,06	2664,39 ± * 81,40	47,91 ± 4,95	74,77 ± * 1,71
IL12-p40/p70	produced mainly by macrophages, induction of NK cells, elaboration of IFN-γ,	3365,14 ± 469,47	2461,49 ± 68,61	8,13 ± 0,21	44,193 ± ** 1,27
IL13	immunoregulatory cytokine, regulating function of human B cells and monocytes (but only macrophages in the mouse).	2310,25 ± 35,07	2216,17 ± 19,33	1,52 ± 0,15	17,17 ± ** 1,45
IL17	interleukine, links T cell activation to neutrophil mobilization and activation	4972,98 ± 588,04	3400,63 ± * 34,76	116,98 ± 8,67	106,50 ± 7,33
I-TAC	CXCL11, interferon-inducible T cell alpha chemoattractant	3499,39 ± 193,76	2975,77 ± * 122,78	7,45 ± 2,57	11,06 ± 0,10
Leptin	Hormone, increasing the cytotoxicity of natural killer (NK) cells, activation of granulocytes, macrophages	2236,96 ± 76,20	2199,3 ± 25,46	7,39 ± 0,81	17,55 ± ** 0,86
LIX	Chemokine (C-X-C motif) ligand 5 (CXCL5), induced IL-1beta and TNF-alpha promoter activity	3121,82 ± 80,72	3295,84 ± 102,97	21,53 ± 5,79	57,20 ± ** 2,28
M-CSF	Macrophage colony-stimulating factor, regulating monocytes proliferation, differentiation, activation	3853,74 ± 51,24	3836,77 ± 61,51	5,60 ± 0,35	24,59 ± ** 1,03
MIG	Chemokine (C-X-C motif) ligand 9 (CXCL9) recruitment of activated T-cells to sites of infection	2170,33 ± 74,10	2392,14 ± 40,75	14,21 ± 1,03	32,54 ± * 2,93
MIP-1-gamma	Macrophage inflammatory protein-1 gamma	325343,87 ± 1176,85	479722,61 ± 29450,37	3762,50 ± 91,22	12080,64 ** 679,14
RANTES	Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted (CCL5)	3256,60 ± 230,71	2755,26 ± 51,61	4,36 ± 1,36	13,62 ± ** 0,81
TECK	Thymus-Expressed Chemokine (CCL25)	4015,28 ± 156,62	3477,89 ± 17,08	79,31 ± 1,26	174,88 ± * 7,61
TIMP-1	Tissue inhibitors of metalloproteinases	3027,73 ± 59,31	14256,16 ± ** 41,94	7,38 ± 0,22	478,07 ± ** 24,07
TIMP-2	Tissue inhibitors of metalloproteinases	2788,91 ± 114,53	2700,57 ± 39,73	33,98 ± 5,18	73,65 ± * 5,42
sTNF RI	Soluble Tumor Necrosis Factor Receptor I	40114,16 ± 729,10	104619,27 ± * 4737,74	618,50 ± 16,74	1462,48 ** 90,02±
sTNF RII	Soluble Tumor Necrosis Factor Receptor II	8069,29 ± 156,29	11281,71 ± * 1115,63	139,88 ± 0,22	165,51 ± 13,87

De Angelis, F et al.. Int. J. Mol. Sci. 2022, 23, 14503.



PROTEINE COINVOLTE NELL'ATTIVAZIONE DI AUTOFAGIA NELLE CELLULE DI SCHWANN DOPO LESIONE DEL NERVO SCIATICO

Fig. 9. Graphical representation merging of 4 networks built by Ingenuity Pathways Analysis (IPA) filtered for the presence of the most relevant connections. The relationships between molecules revealed by proteomics (described in Table 1) and other proteins are generated by the information contained onto a global molecular network enclosed in the Ingenuity Knowledge Base database. Proteins upregulated and downregulated in dimethyl sulfoxide (DMSO)- vs rapamycin (RAPA)-treated nerves are labelled in red and green, respectively. Colour scale gives an indication of the modulation grade. Selected interacting molecules are coloured in light blue. Connections are indicated by lines. The significant connection between PDIA3 and PRDX1 suggested in Schwann cell autophagic process is highlighted in red; green arrows display a variation designed by the authors.

PROTEINE DIFFERENZIALMENTE ESPRESSE DA MASCHI E FEMMINE NEL NERVO SCIATICO DOPO LESIONE NERVOSA

Accession[a]	Description (gene name)	Highly represented[b]
Q9Z0F7	Gamma-synuclein (Sncg)	Female*
Q9Z331	Keratin type II cytoskeletal 6B (Krt6b)	Female*
P29621	Serine protease inhibitor A3C (Serpina3c)	Female*
Q9JK53	Prolargin (Prelp)	Female*
P04117	Fatty acid binding protein adipocyte (Fabp4)	Female*
P70296	Phosphatidylethanolamine binding protein 1 (Pebp1)	Female*
Q9DCV7	Keratin type II cytos[illegible]	[illegible]
P62259	14 3 3 protein epsilon [illegible]	[illegible]
P48036	Annexin A5 (Anxa5)	Female*
P08228	Superoxide dismutase Cu Zn (Sod1)	Female*
Q3TTY5	Keratin type II cytoskeletal 2 epidermal (Krt2)	Female*
Q19LI2	Alpha 1B glycoprotein (A1bg)	Female*
P35700	Peroxiredoxin 1 (Prdx1)	Female*
P09813	Apolipoprotein A II (Apoa2)	Female*
P45376	Aldose reductase (Akr1b1)	Female*
Q5I2A0	Serine protease inhibitor A3C (Serpina3 g)	Female*

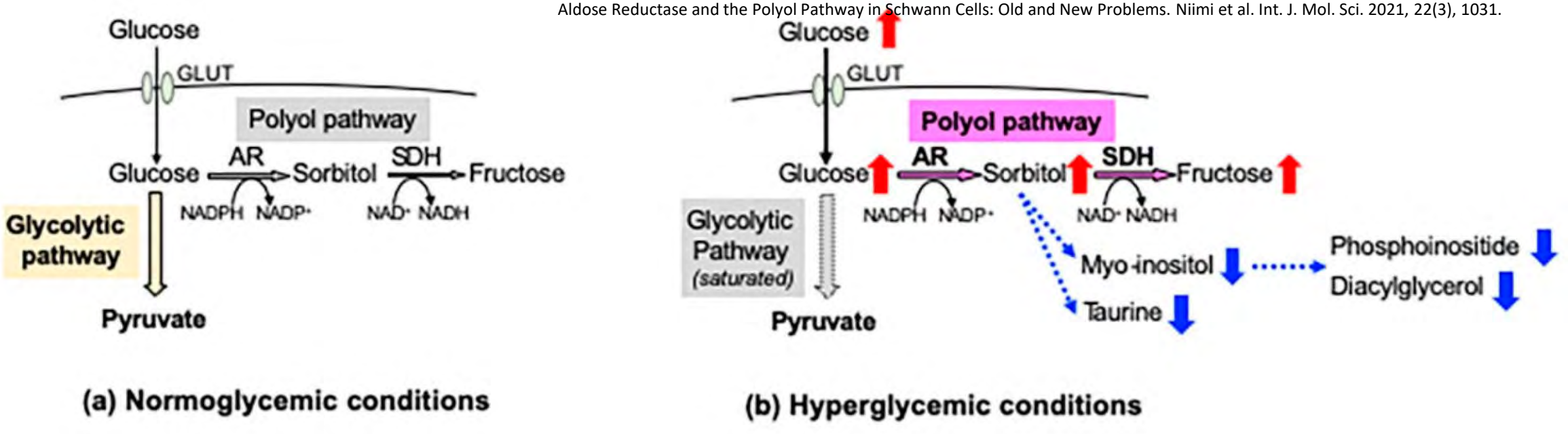
UPREGULATED IN SCI CONDITION

Accession[a]	Description (gene name)	Highly represented[b]
P40142	Transketolase (Tkt)	Female*
O35744	Chitinase 3 like protein 3 (Chi3l3)	Female*
P23953	Liver carboxylesterase N (Es1)	Female*
P29621	Serine protease inhibitor A3C (Serpina3c)	Female*
P21550	Beta enolase (Eno3)	Female*
Q5I2A0	Serine protease inhibitor A3C (Serpina3 g)	Female*
[illegible]	Serum albumin [illegible]	[illegible]
P10126	Elongation factor 1 alpha 1 (Eef1a1)	[illegible]
P52480	Pyruvate kinase isozymes M1 M2 (Pkm2)	[illegible]
P62962	Profilin 1 (Pfn1)	[illegible]
P18760	Cofilin 1 (Cfl1)	[illegible]
Q91X72	Hemopexin (Hpx)	[illegible]
P27773	Protein disulfide isomerase A3 (Pdia3)	[illegible]
P20029	78 kDa glucose regulated protein (Hspa5)	[illegible]

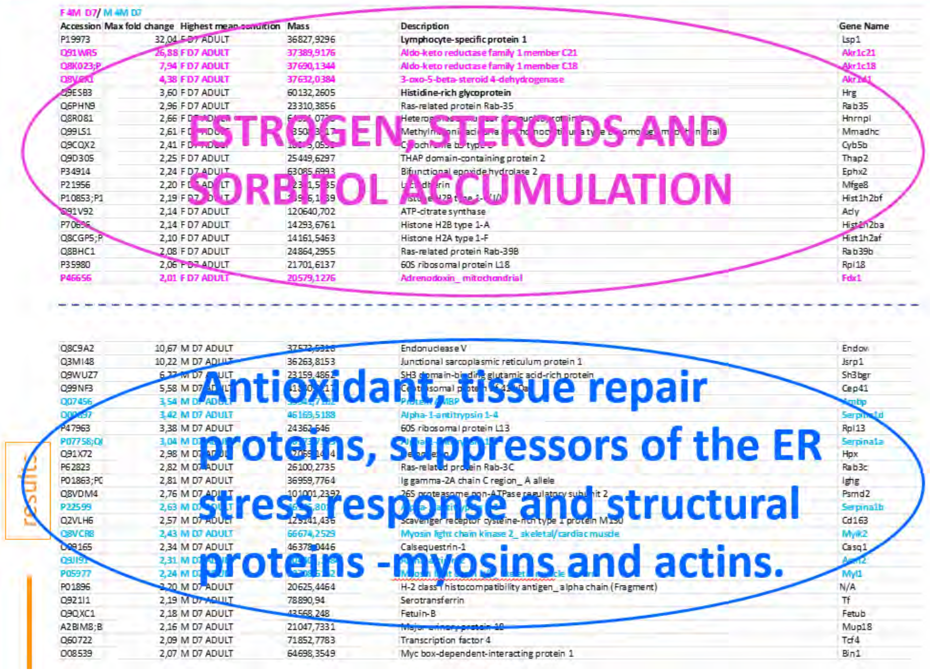
DOWNREGULATED IN SCI CONDITION

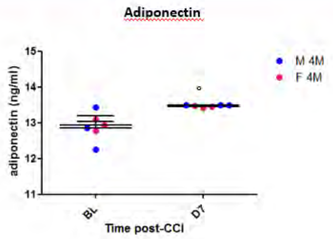
REDOX STATE AND GLUCOSE METABOLISM

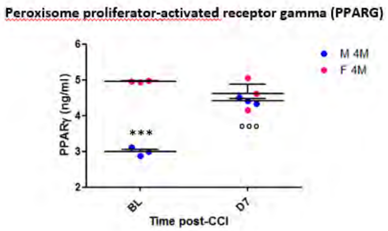
Aldose Reductase and the Polyol Pathway in Schwann Cells: Old and New Problems. Niimi et al. Int. J. Mol. Sci. 2021, 22(3), 1031.



TESSUTO ADIPOSO IN RISPOSTA ALLA NEUROPATIA: DIFFERENZE DI GENERE







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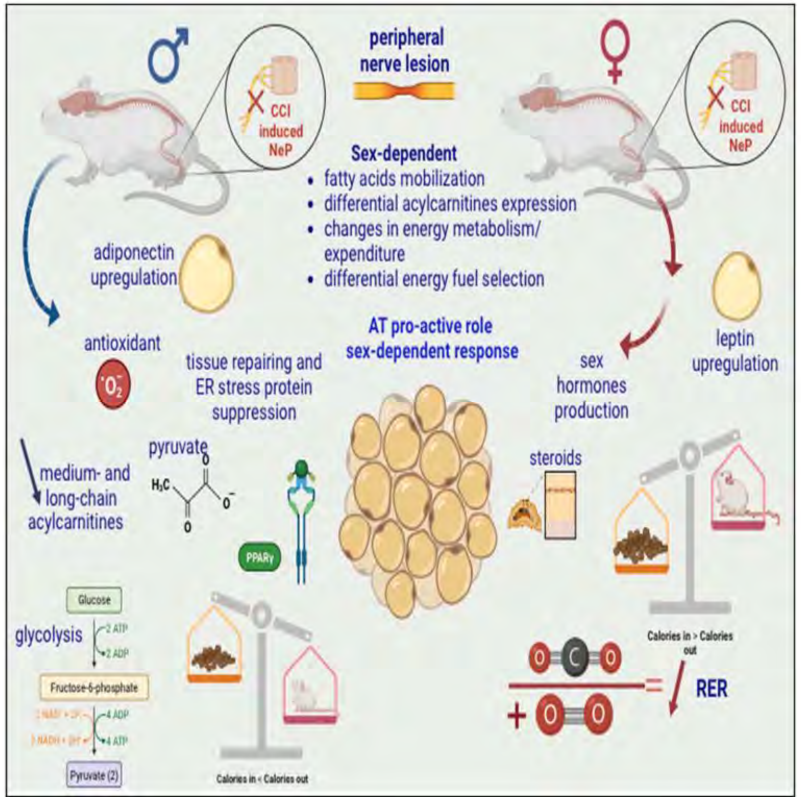
Article

Sex-specific adipose tissue's dynamic role in metabolic and inflammatory response following peripheral nerve injury



peripheral nerve lesion
CCI induced NeP
Sex-dependent
fatty acids mobilization
differential acylcarnitines expression
changes in energy metabolism/ expenditure
differential energy fuel selection
adiponectin upregulation
antioxidant
tissue repairing and ER stress protein suppression
AT pro-active role sex-dependent response
sex hormones production
leptin upregulation
steroids
medium- and long-chain acylcarnitines
pyruvate
PPARγ
glycolysis
Glucose
Fructose-6-phosphate
Pyruvate (2)
RER
Calories in > Calories out
Calories in < Calories out

Valentina Vacca, Claudia Rossi, Luisa Pieroni, ..., Flaminia Pavone, Roberto Coccurello, Sara Marinelli

sara.marinelli@cnr.it

Highlights

Female sex is linked to higher neuropathic pain incidence

Neuropathy prompts sex-related metabolic rates

Differential fatty acid, acylcarnitine, energy responses by sex pre- and post-injury

Adipose tissue's active role in sex-specific nerve injury response

TESSUTO ADIPOSO NELLE FEMMINE ANZIANE DOPO NEUROPATIA

Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Gluconeogenesis	14 / 49	0.003	6.66e-16	4.50e-13	9 / 26	0.002
Glucose metabolism	15 / 115	0.006	4.28e-12	1.45e-09	16 / 50	0.003
Glycolysis	12 / 81	0.004	1.50e-10	3.38e-08	7 / 24	0.002
Striated Muscle Contraction	9 / 36	0.002	3.51e-10	5.93e-08	4 / 4	2.72e-04
Metabolism of carbohydrates	22 / 457	0.024	7.85e-09	1.06e-06	35 / 241	0.016
Muscle contraction	19 / 368	0.019	2.95e-08	3.30e-06	13 / 53	0.004
Neutrophil degranulation	21 / 478	0.025	8.06e-08	7.74e-06	7 / 10	6.79e-04
Platelet degranulation	13 / 177	0.009	9.99e-08	8.39e-06	6 / 11	7.47e-04
Response to elevated platelet cytosolic Ca2+	13 / 232	0.012	2.00e-06	1.50e-04	6 / 14	9.51e-04
Post-translational protein phosphorylation	7 / 107	0.006	1.92e-04	0.013	1 / 1	6.79e-05

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TESSUTO ADIPOSO NEI MASCHI ANZIANI DOPO NEUROPATIA

Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Gluconeogenesis	11 / 49	0.003	1.04e-09	9.58e-07	10 / 26	0.002
Neutrophil degranulation	28 / 478	0.025	1.25e-08	5.77e-06	9 / 10	6.79e-04
Platelet degranulation	15 / 177	0.009	4.08e-07	1.25e-04	6 / 11	7.47e-04
mitochondrial fatty acid beta-oxidation of saturated fatty acids	5 / 11	5.77e-04	1.40e-06	3.22e-04	23 / 29	0.002
Beta oxidation of octanoyl-CoA to hexanoyl-CoA	4 / 5	2.62e-04	1.80e-06	3.32e-04	4 / 4	2.72e-04
Beta oxidation of decanoyl-CoA to octanoyl-CoA-CoA	4 / 6	3.15e-04	3.69e-06	5.42e-04	4 / 5	3.40e-04
Attenuation phase	5 / 14	7.34e-04	4.49e-06	5.42e-04	4 / 5	3.40e-04
Glucose metabolism	11 / 115	0.006	4.71e-06	5.42e-04	16 / 50	0.003
Response to elevated platelet cytosolic Ca2+	15 / 232	0.012	1.05e-05	0.001	6 / 14	9.51e-04
Mitochondrial protein degradation	14 / 216	0.011	2.01e-05	0.002	8 / 20	0.001

In preparazione 2024

NUTRIZIONE E INVECCHIAMENTO
WP7

CONCLUSIONI: I NUOVI TARGET per LE NEUROPATIE INDIVIDUATI E I PROSSIMI PASSI

- Stress ossidativo e glucosio-sorbitolo

- TARGET METABOLICI IDENTIFICATI:
  - PRDX1
  - PDIA3
  - AR

- TEST NUTRACEUTICI DIRETTI CONTRO I TARGET

NUTR
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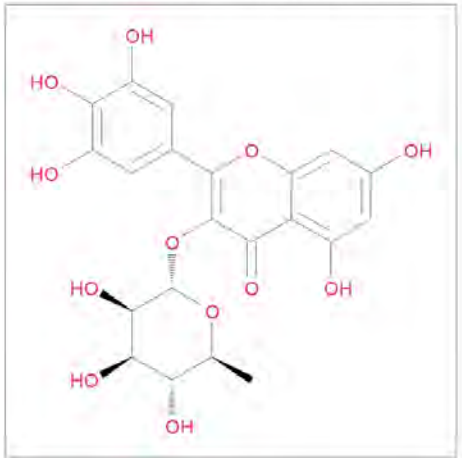
UN'ANTICIPAZIONE.....

BROAD INSTITUTE Repurposing Data Portal

Compound-level information



Clinical Phase
Preclinical

Disease Area
Not specified

Mechanism of Action
PKC inhibitor

Targets
NOS1 PRKCA

Source: www.sigmaaldrich.com

Broad Compound ID
BRD-K48388905

PubChem CID
5281673

Expected mass
464.095

InChIKey
DCYOADKBABEMIQ-OWMUPTOHSA-N

SMILES
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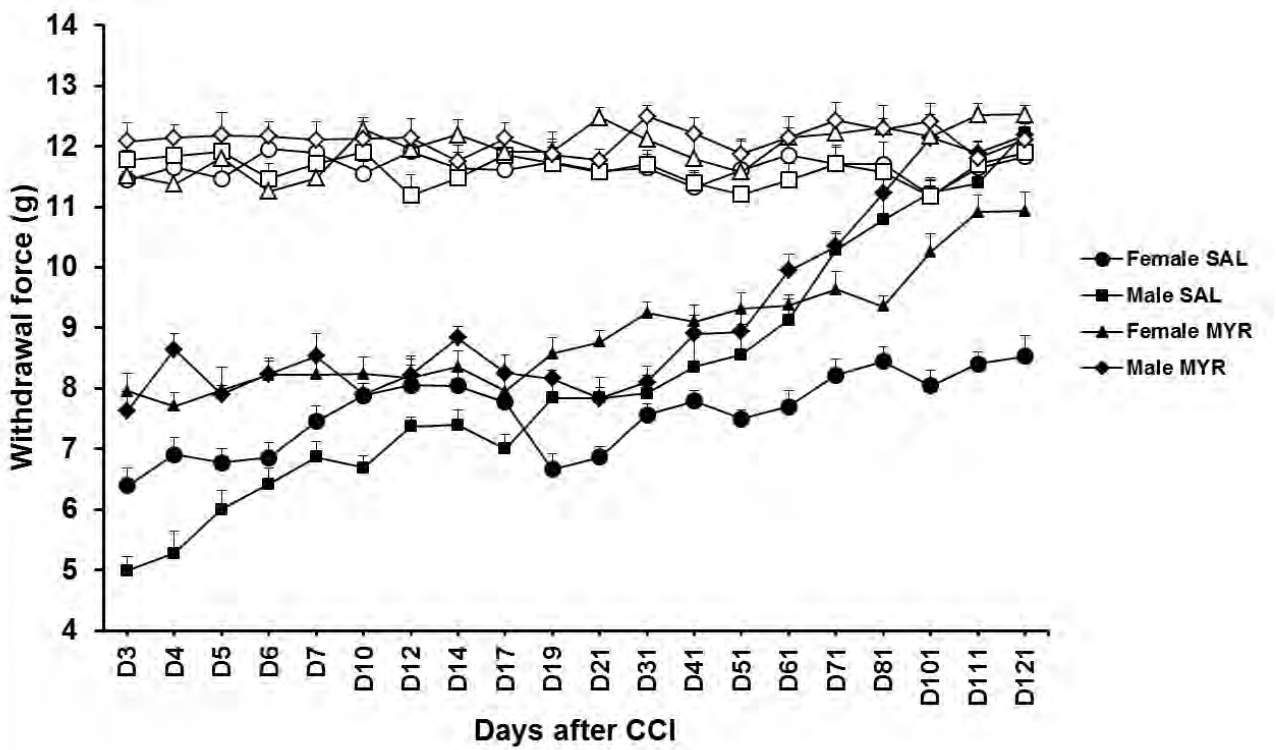
Myrica cerifera (Albero della cera) Visita ›



Blackberries – The Natural Gardener Visita ›

Morella (Myrica) pensylvanica- Northern Bayberry - Visita ›

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Flaminia Pavone
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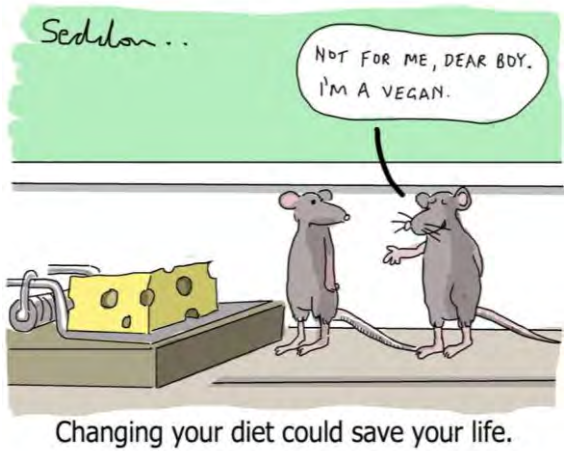
Valentina Mastrorilli



Project granted by

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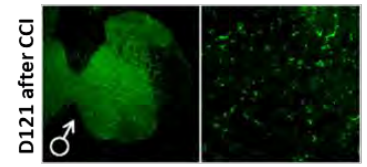
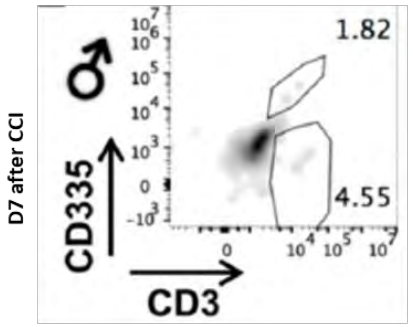
People in NUTRAGE project:
Sara Marinelli IBBC
Chiara Parisi IBBC
Valentina Mastrorilli IBBC

PAIN

Higher pain perception and lack of recovery from neuropathic pain in females: A behavioural, immunohistochemical, and proteomic investigation on sex-related differences in mice

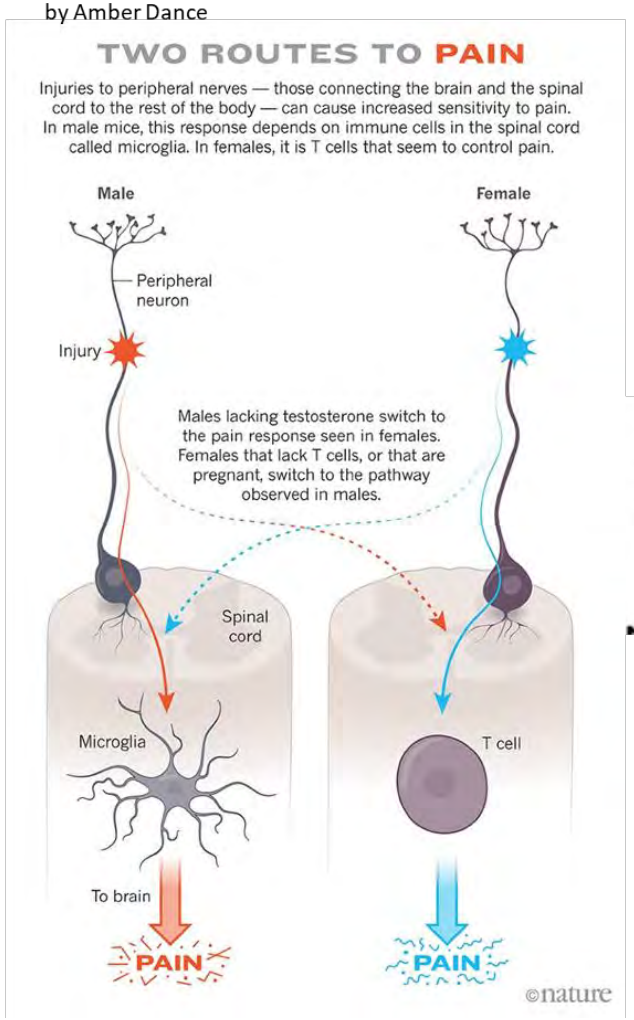


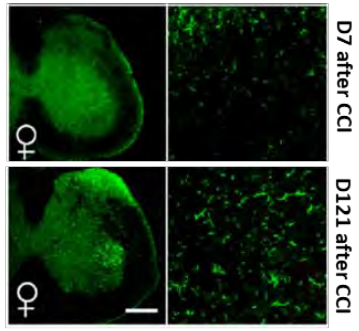
Vacca et al. / PAIN 155 (2014) 388–402

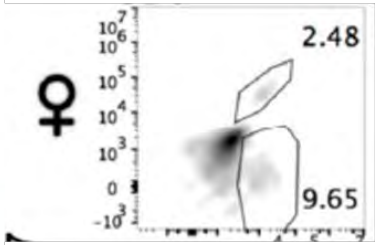


Vacca et al. Int. J. Mol. Sci. (2021), 22, 4397.

NATURE | VOL 567 | 28 MARCH 2019 THE PAIN GAP
by Amber Dance







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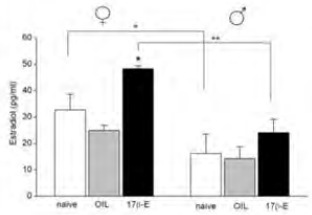
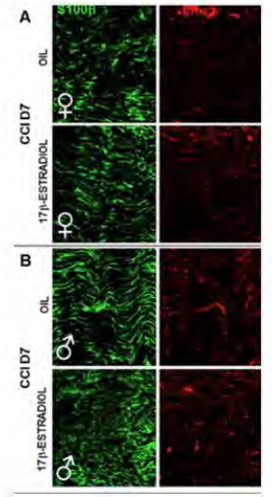
Article | Open access | Published: 06 January 2016

17beta-estradiol counteracts neuropathic pain: a behavioural, immunohistochemical and proteomic investigation on sex-related differences in mice

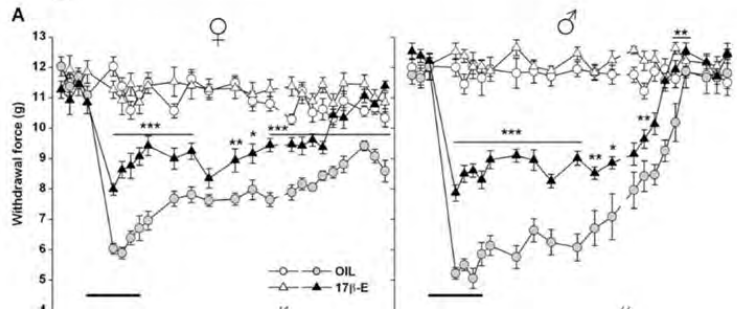
Valentina Vacca, Sara Marinelli, Luisa Pieroni, Andrea Urbani, Siro Luvisetto & Flaminia Pavone





- Decrease in both sexes of estradiol levels after nerve injury,
- Increase in both sexes of estrogen receptors after sciatic nerve lesion
- Oestrus cycle does not interfere with neuropathic pain
- Exogenous estrogen prevents neuropathy and pain chronicization

Vacca et al. 2016 Scientific Reports | 6:18980 | DOI: 10.1038/srep18980



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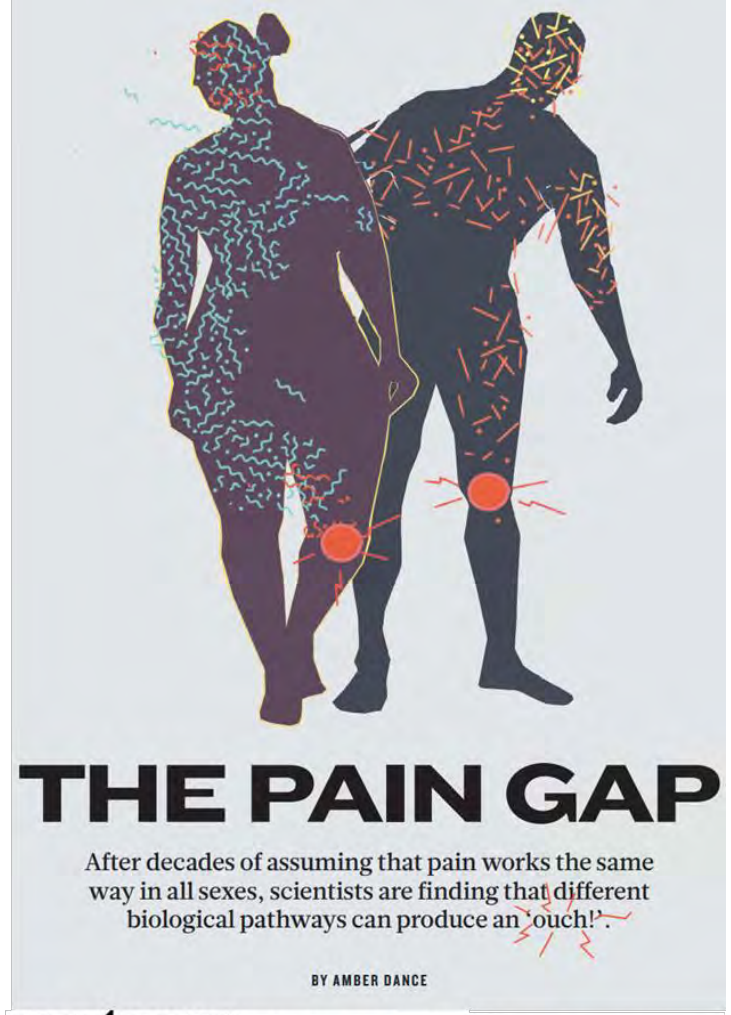
MASCHI vs FEMMINE: NEUROINFIAMMAZIONE, SISTEMA IMMUNITARIO E ORMONI



THE PAIN GAP

After decades of assuming that pain works the same way in all sexes, scientists are finding that different biological pathways can produce an 'ouch!'.

BY AMBER DANCE

nature NEWS FEATURE | 27 March 2019

nature reviews neuroscience

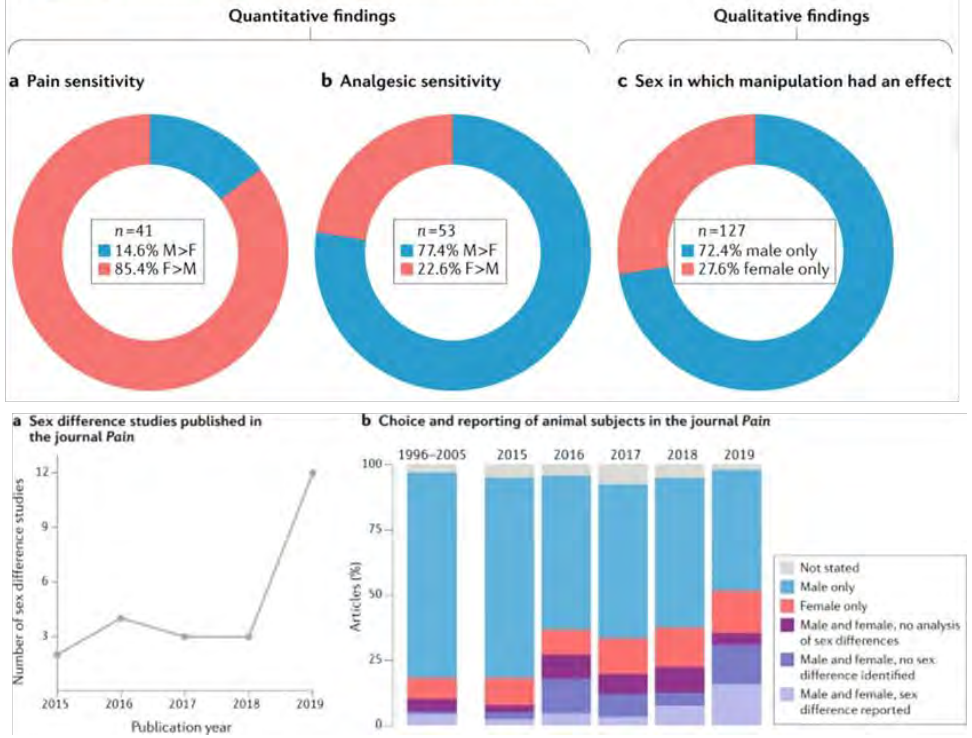
Review Article | Published: 21 May 2020

Qualitative sex differences in pain processing: emerging evidence of a biased literature

Jeffrey S. Mogil

Fig. 1: Analysis of quantitative and qualitative sex differences in the pain literature.

From: Qualitative sex differences in pain processing: emerging evidence of a biased literature



THE GENDER PAIN GAP

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