SCHWANN CELL, MICROENVIRONMENT AND TUMOR: shaping their role in vestibular schwannoma and schwannomatosis

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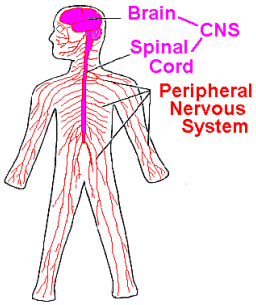
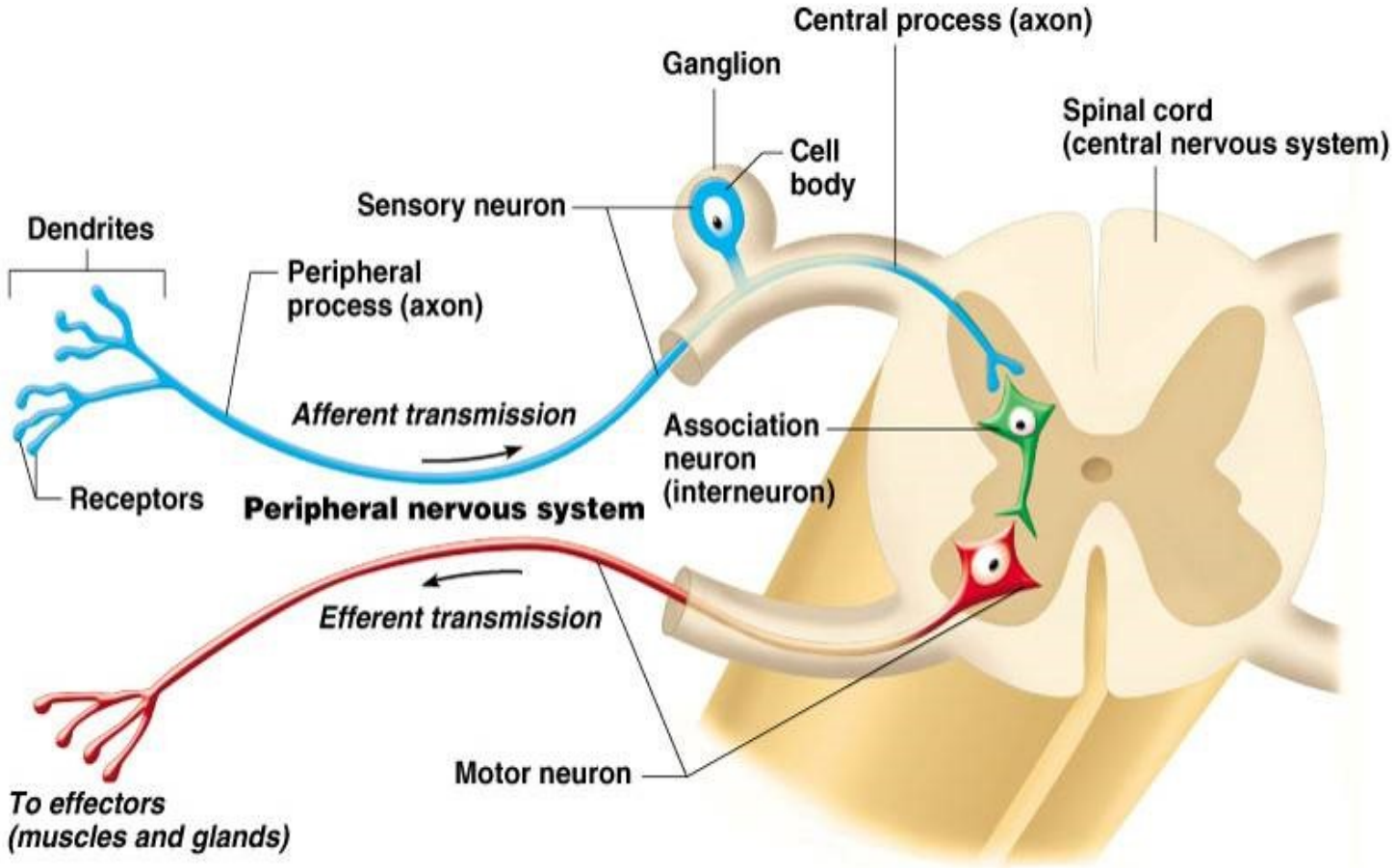
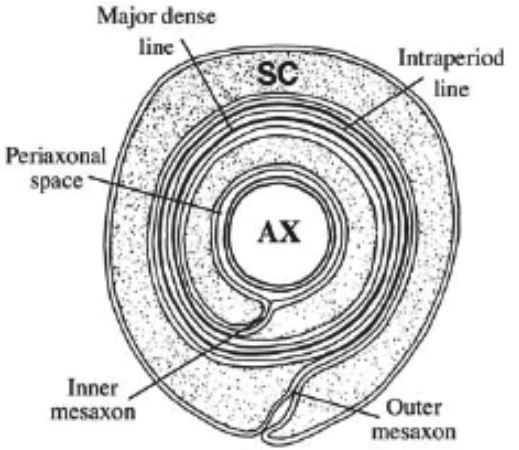
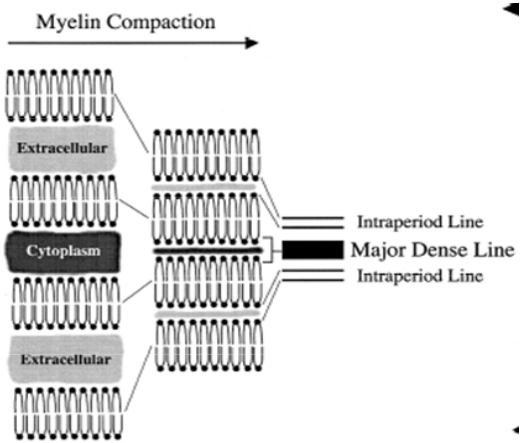
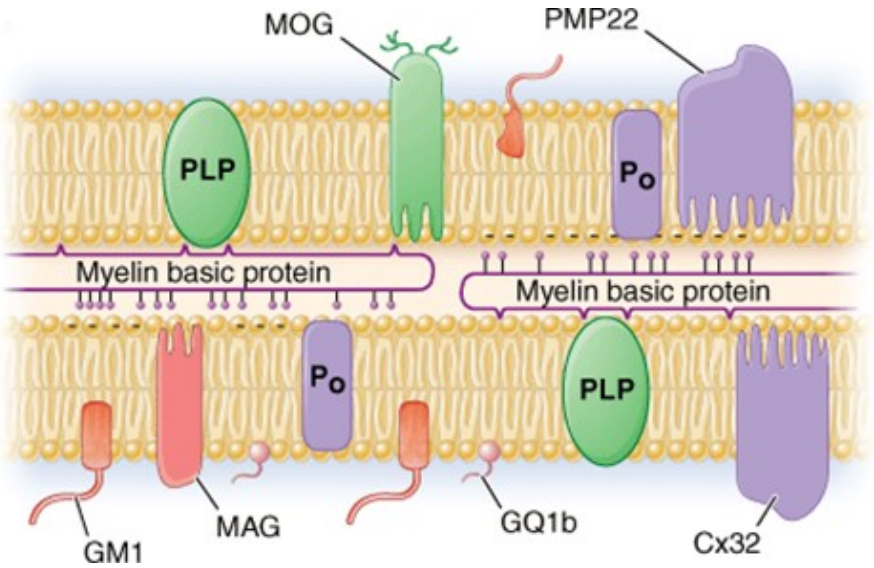
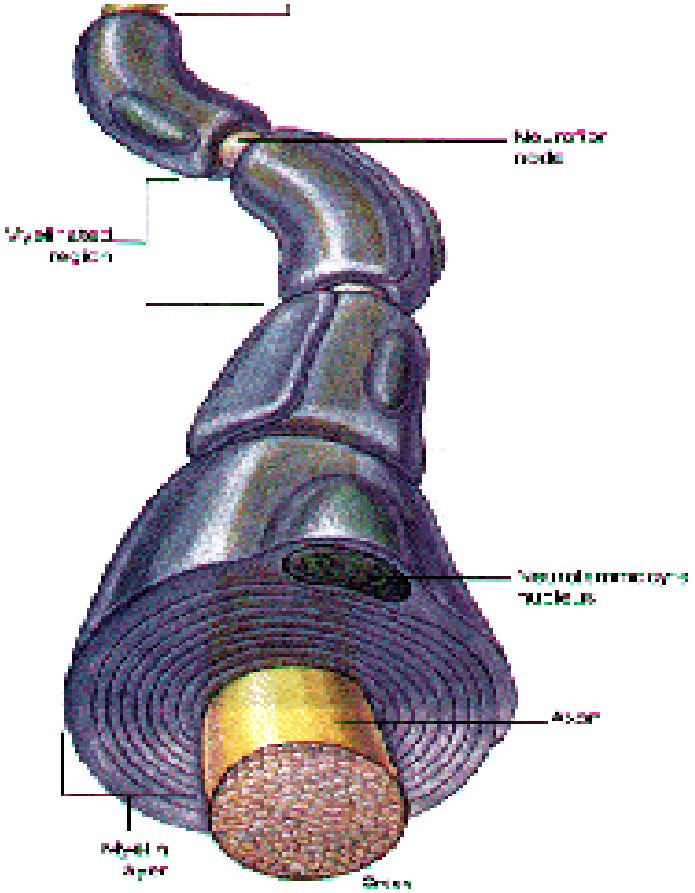

Brain
CNS
Spinal Cord
Peripheral Nervous System

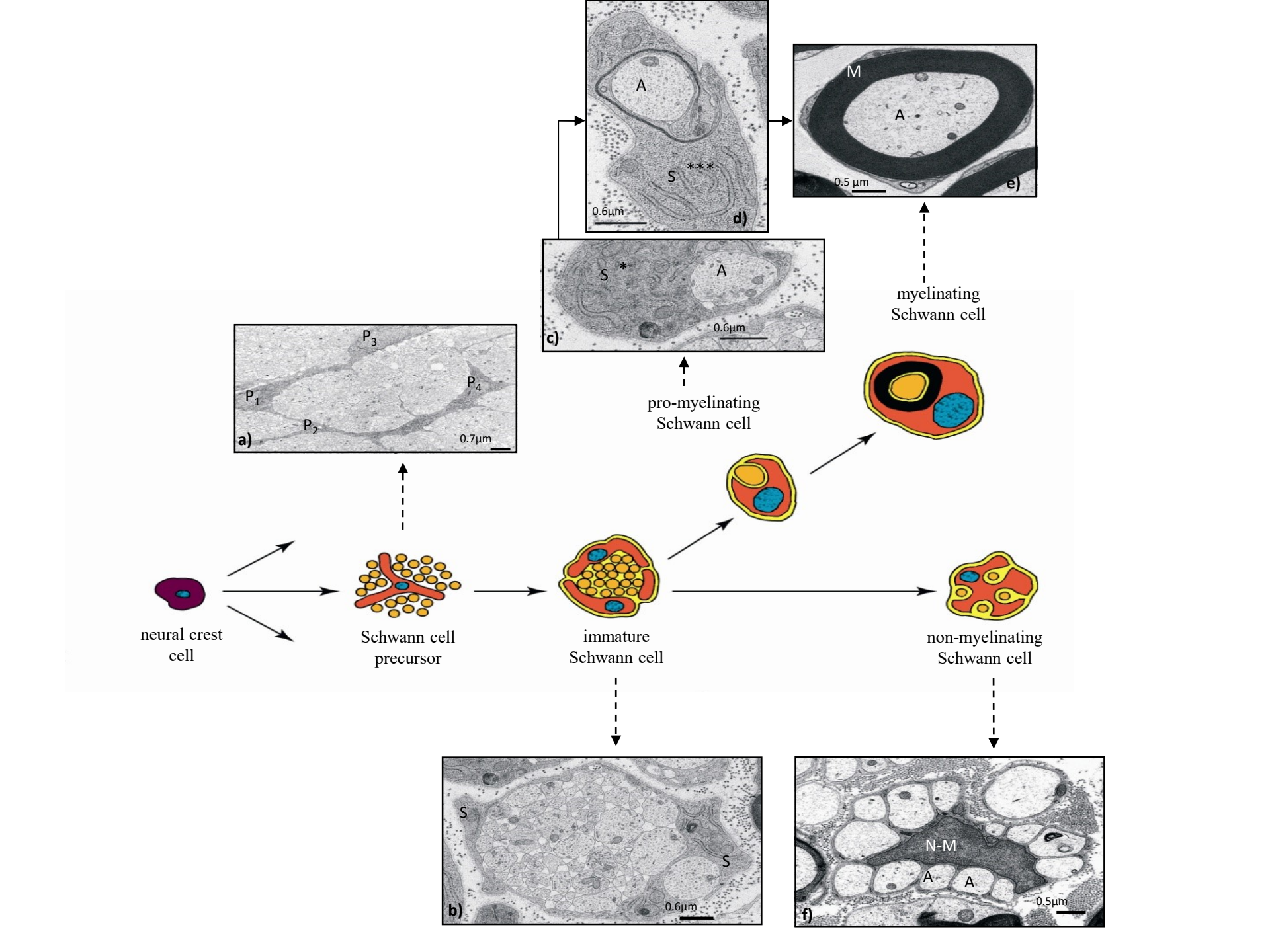

Central process (axon)
Ganglion
Spinal cord (central nervous system)
Cell body
Sensory neuron
Dendrites
Peripheral process (axon)
Afferent transmission
Association neuron (interneuron)
Receptors
Peripheral nervous system
Efferent transmission
Motor neuron
To effectors (muscles and glands)

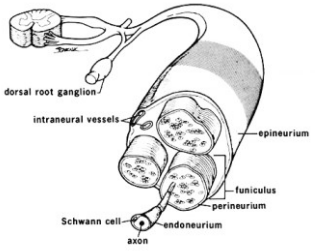

Major dense line
SC
Intraperiod line
Periaxonal space
AX
Inner mesaxon
Outer mesaxon

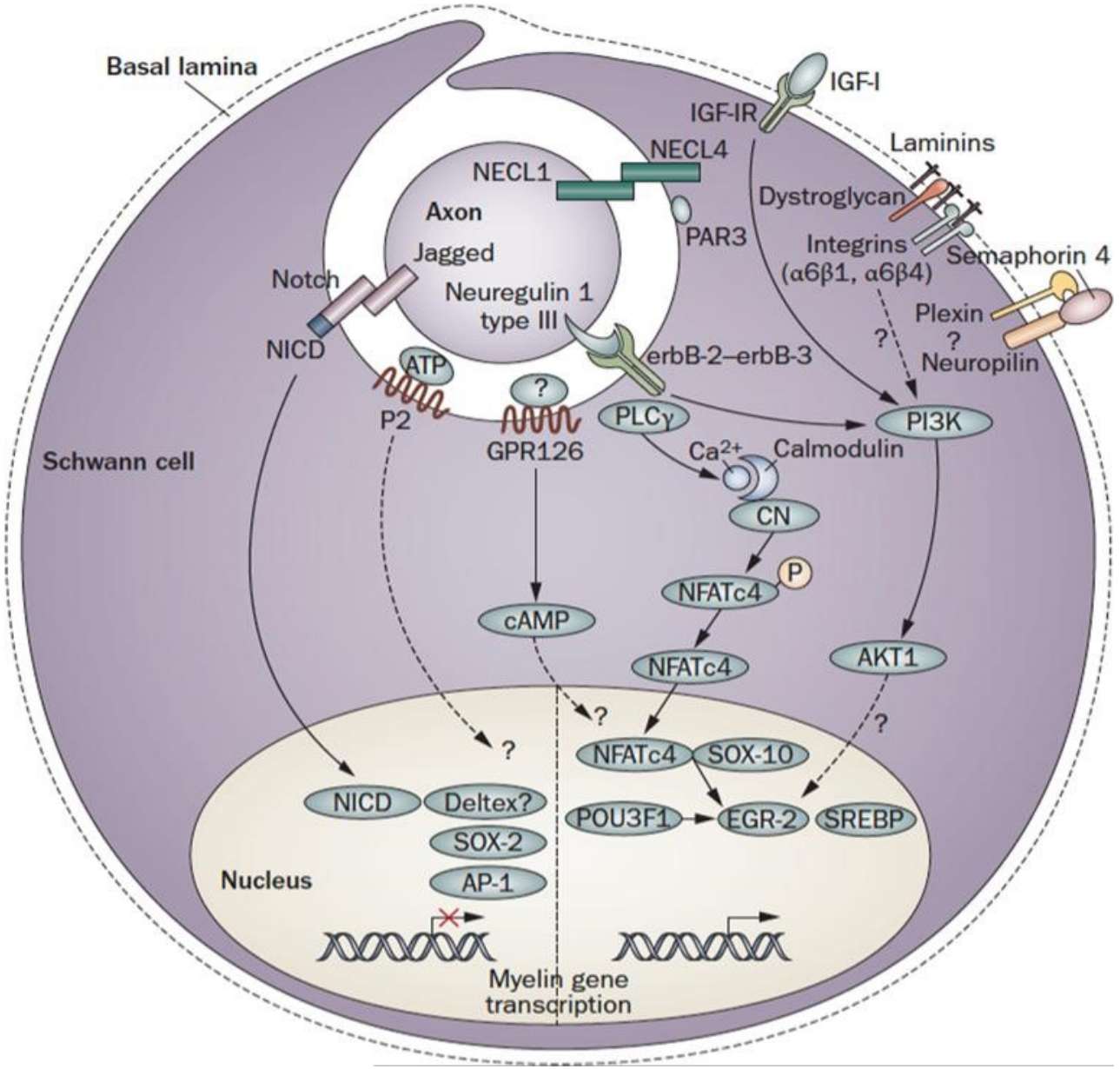

Myelin Compaction
Extracellular
Cytoplasm
Extracellular
Intraperiod Line
Major Dense Line
Intraperiod Line


MOG
PMP22
PLP
Po
Myelin basic protein
Myelin basic protein
Po
PLP
GM1
MAG
GQ1b
Cx32

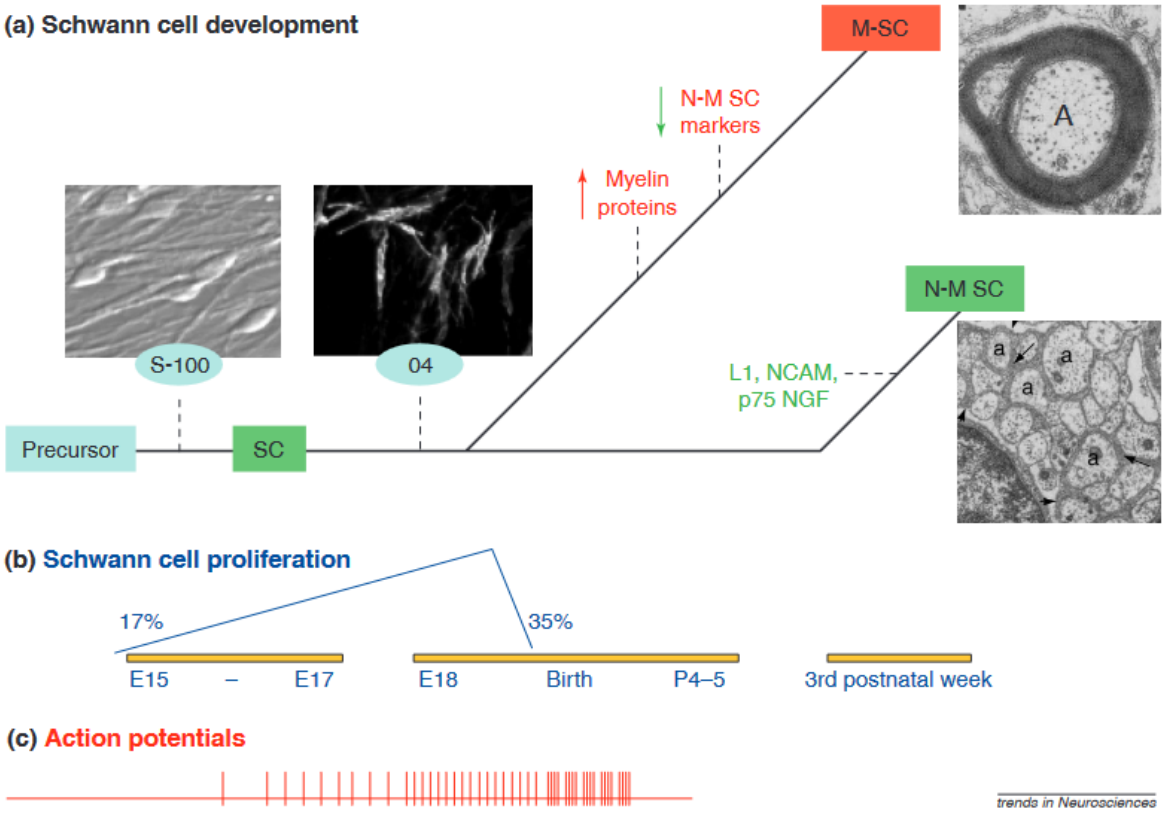



A
S
***
0.6µm
d)
M
A
0.5 µm
e)
S
*
A
0.6µm
c)
myelinating
Schwann cell
pro-myelinating
Schwann cell
P3
P1
P4
P2
a)
0.7µm
neural crest
cell
Schwann cell
precursor
immature
Schwann cell
non-myelinating
Schwann cell
S
S
0.6µm
b)
N-M
A
A
0.5µm
f)





Taveggia et al. Nature Rev. Neurol. 2010



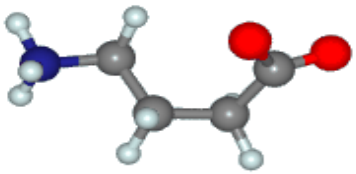
ATP: an extracellular signaling molecule between neurons and glia

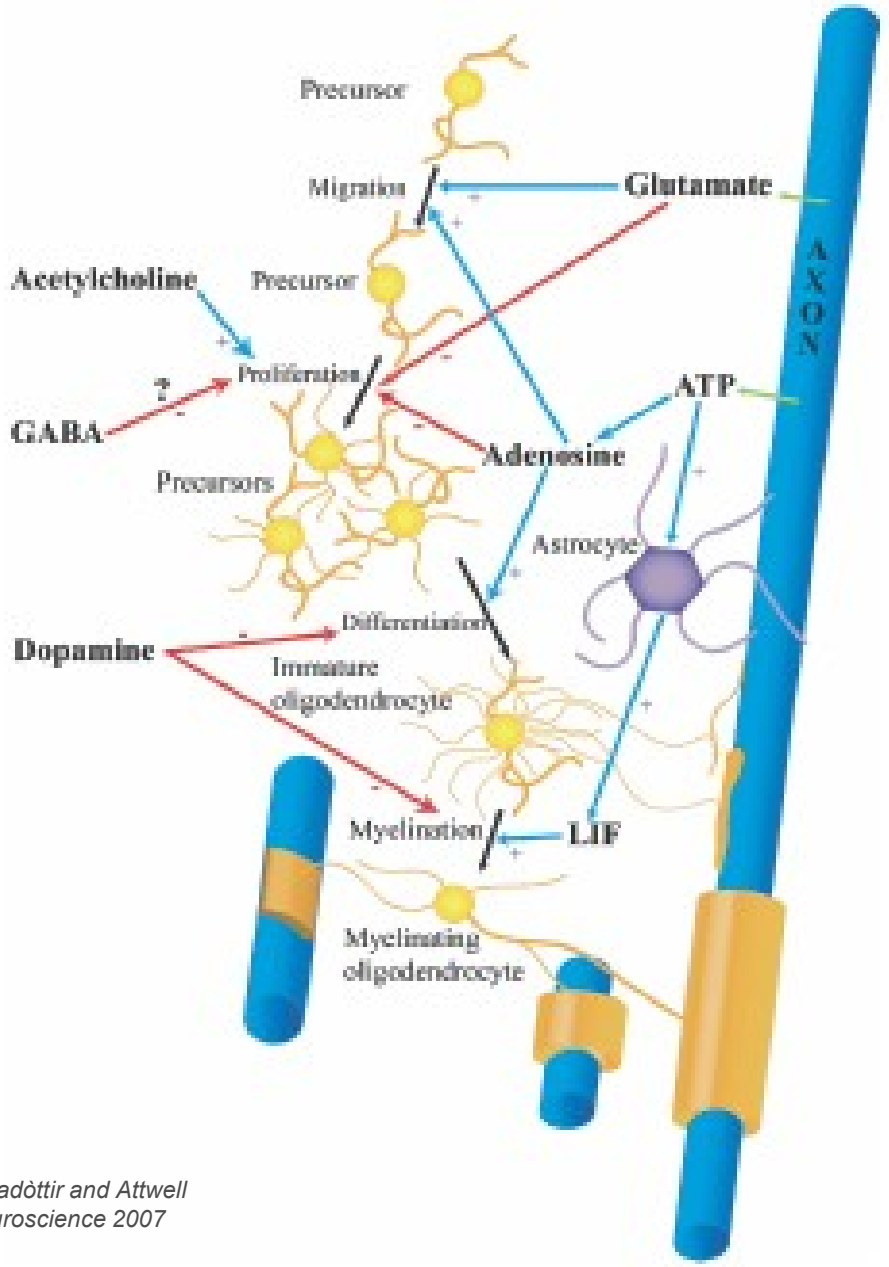
R. Douglas Fields and Beth Stevens

Recent studies on Schwann cells at the neuromuscular junction and non-synaptic regions of premyelinated axons indicate that extracellular ATP can act as an activity-dependent signaling molecule in communication between neurons and glia. Several mechanisms have been observed for the regulated release of ATP from synaptic and non-synaptic regions, and a diverse family of receptors for extracellular ATP has been characterized. The findings suggest functional consequences of neuron–glial communication beyond homeostasis of the extracellular environment surrounding neurons, including regulating synaptic strength, gene expression, mitotic rate, and differentiation of glia according to impulse activity in neural circuits.

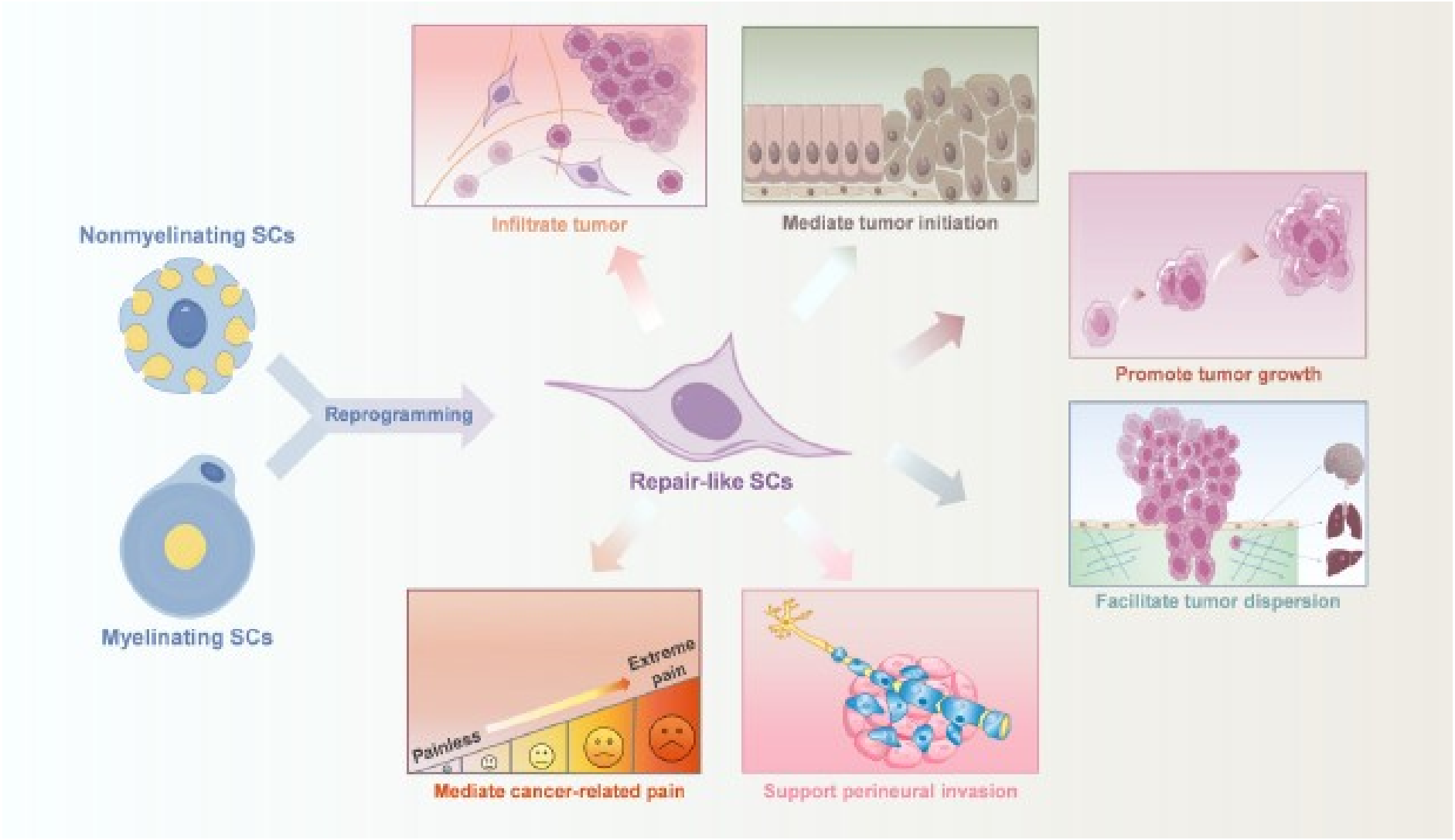
Trends Neurosci. (2000) 23, 625–633

Fig. 2. *Correlation between Schwann cell development and changes in neural impulse activity in dorsal root ganglion neurons of mouse during the perinatal period.* (a) Schwann cells precursors migrate out with the neural crest and begin to express the S-100 antigen. As they develop into immature Schwann cells they begin to express the 04 antigen, and then differentiate into either myelinating (M SC) or non-myelinating phenotypes (NM SC)[27]. (b) The rate of Schwann cell proliferation increases in late fetal development and begins to decrease near the time of birth[27]. (c) Action potentials from dorsal root ganglion (DRG) neurons show the onset of active spontaneous and sensory-evoked activity in DRG neurons coincides with the decrease in Schwann cells proliferation and differentiation[27]. ATP that is released by DRG neurons in culture inhibits Schwann cells proliferation and arrests development at a stage before development of the 04 antigen[7]. These correlations have yet to be tested in vivo, but suggest that impulse activity could stop proliferation and prevent terminal differentiation of Schwann cells until exposure to appropriate axon-specific differentiation signals. Adapted, with permission, from Ref. 51 and Ref. 68.





Kàradòttir and Attwell
Neuroscience 2007



The Emerging Role of Schwann Cells in the Tumor Immune Microenvironment and Its Potential Clinical Application

Shan Zhang [1,†], Jing Chen [1,†], Fanjun Cheng [1,*] and Fang Zheng [2,*]

Int. J. Mol. Sci. **2024**, *25*, 13722. https://doi.org/10.3390/ijms252413722

Journal of Oncology
Volume 2022, Article ID 1058667, 10 pages
https://doi.org/10.1155/2022/1058667

Schwann Cells in the Tumor Microenvironment: Need More Attention

Leqi Sun,[1] Shuhai Chen,[2] and Mingyou Chen[3]

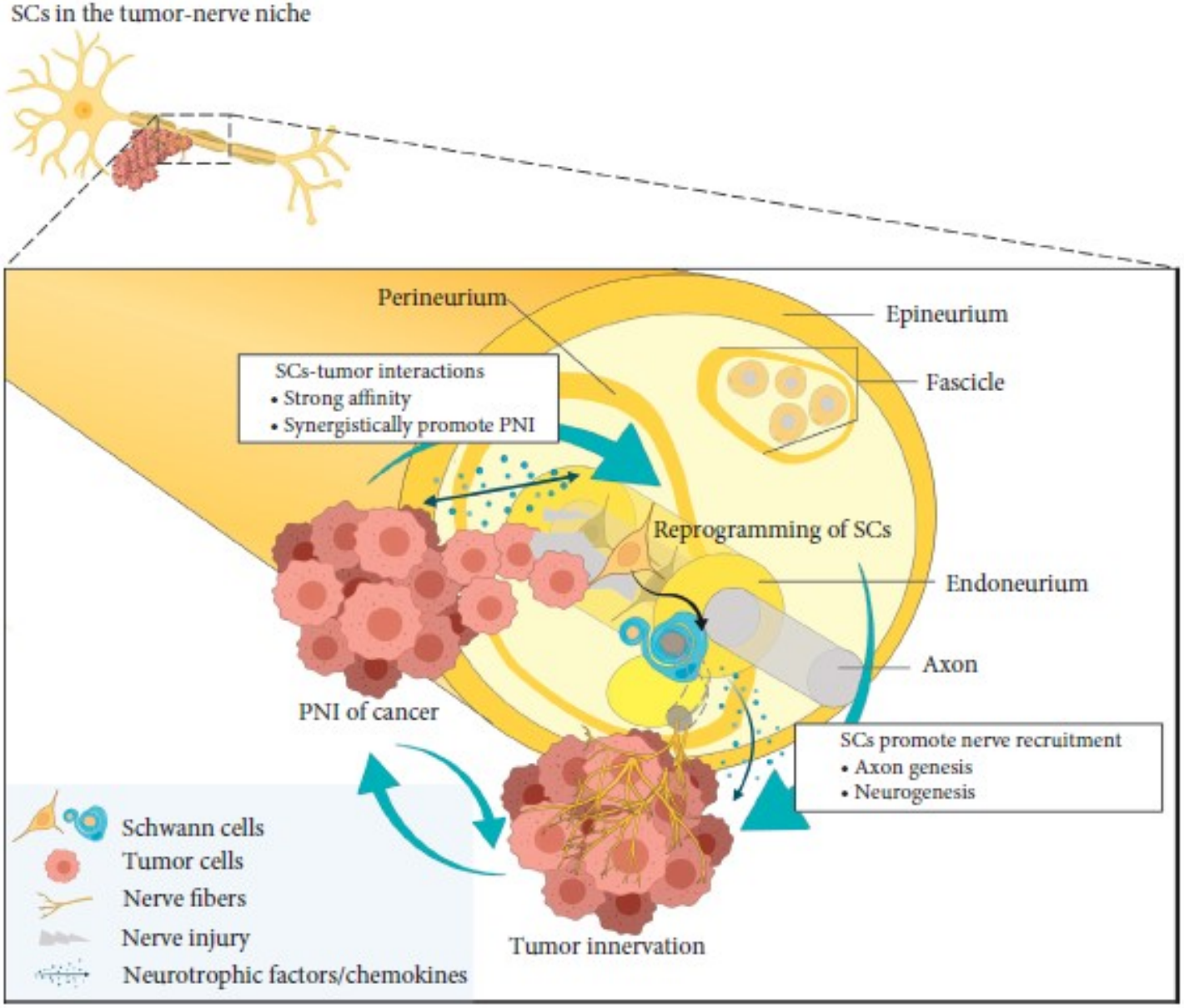


FIGURE 1: Schematic diagram of how Schwann cells (SCs) undergo reprogramming and facilitate perineural invasion (PNI) and tumor innervation. SCs show a strong affinity with cancer cells, even in the early stage of tumorigenesis. Tumors attracted by SCs (nerve) or developed actively invade the nerves to form the tumor-nerve niche, and SCs in this microenvironment undergo reprogramming. Reprogrammed SCs further promote nerve recruitment through axon genesis and follow neurogenesis, which finally induce the tumor innervation. Reprogrammed SCs can also synergistically promote PNI, thus constituting positive feedback of cancer-nerve crosstalk. Abbreviation: PNI, perineural invasion; SCs, Schwann cells.

Neurosurgery 88:234–243, 2021 DOI:10.1093/neuros/nyaa455

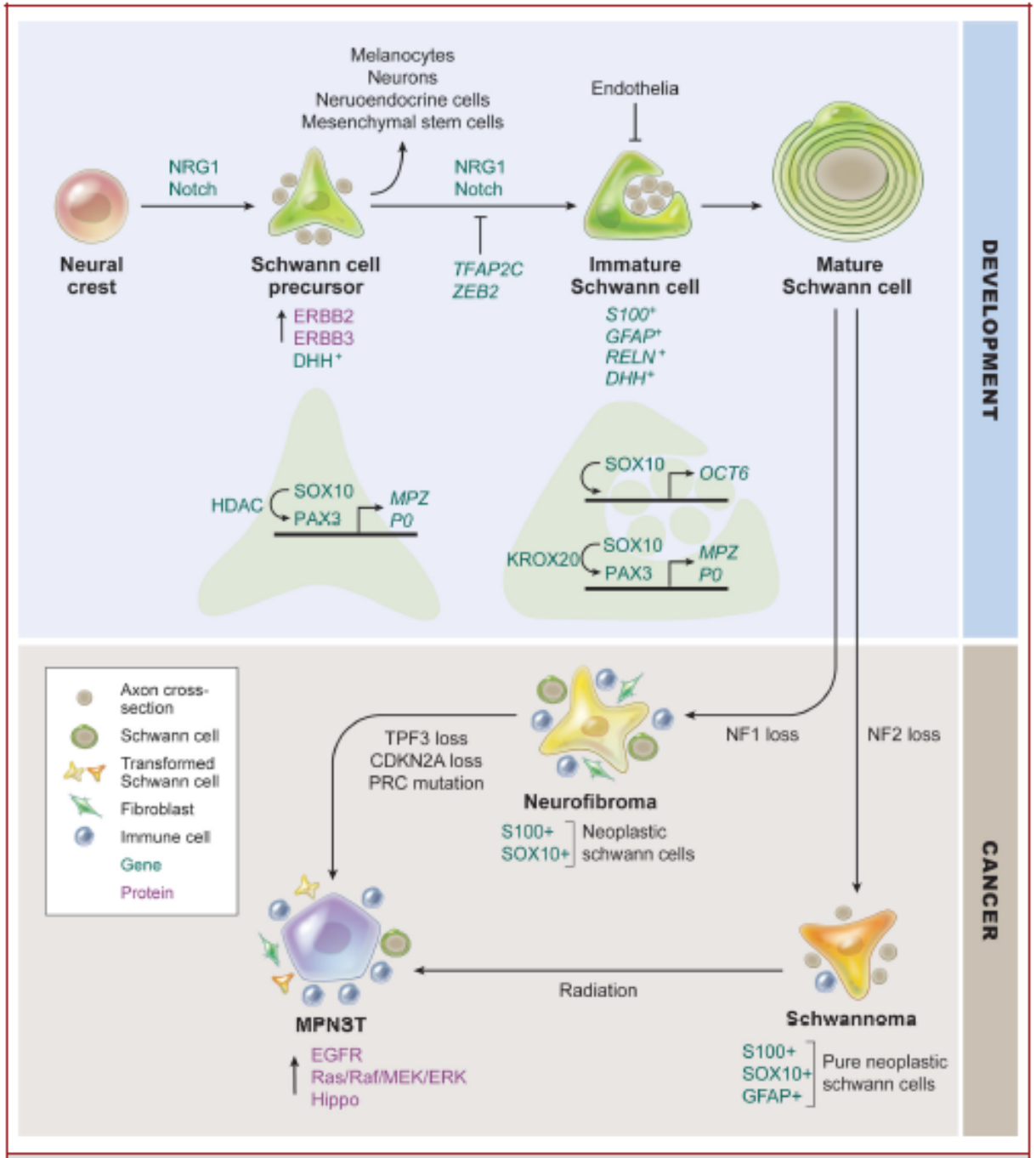
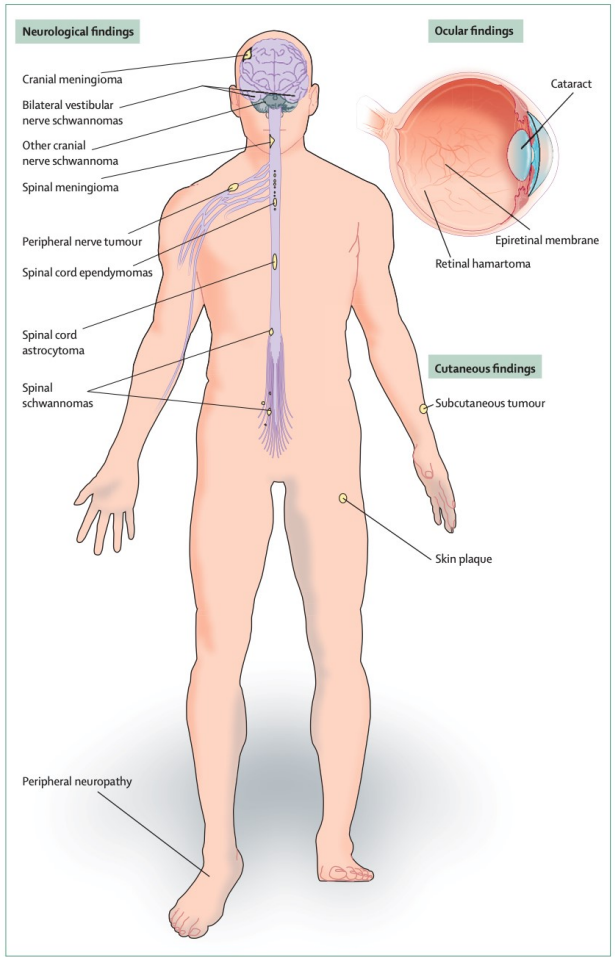


FIGURE 1. *Overview of normal Schwann cell development and transformation to peripheral nerve tumors.*

Neurofibromatosis Type 2 (NF2)



Clinical manifestations of neurofibromatosis type 2 (Asthagiri et al., 2009)

NF2 is characterized by the development of multiple schwannomas, meningiomas and spinal cord ependymomas.

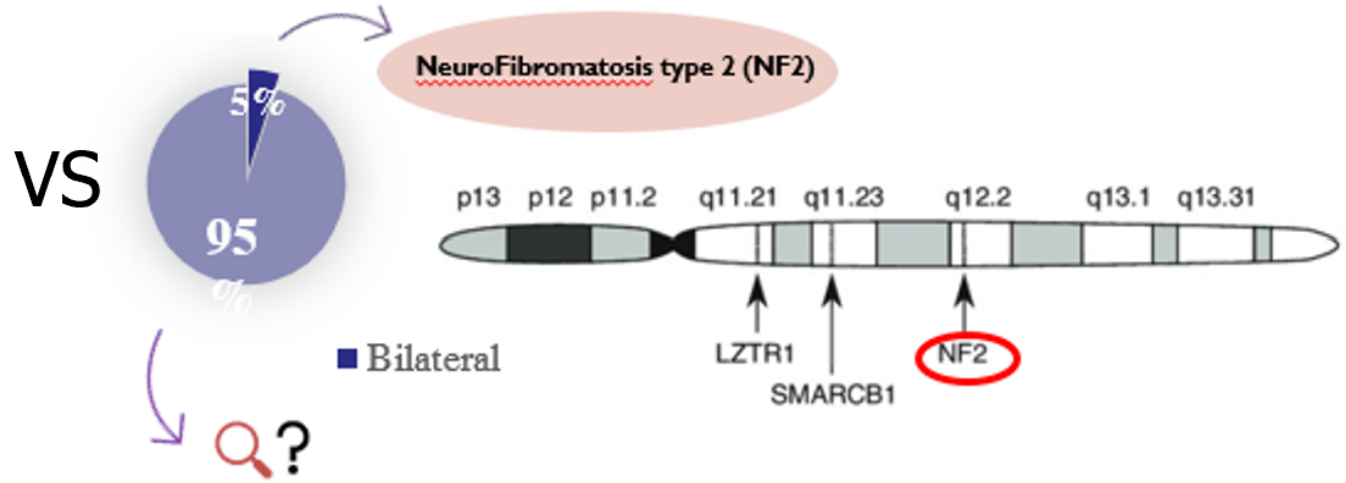
Defects in the ***NF2 gene*** located on chromosome 22q12 and the consecutive loss of its protein **merlin.**

Hallmark of NF2 is bilateral **VESTIBULAR SCHWANNOMA**, present in almost all patients.

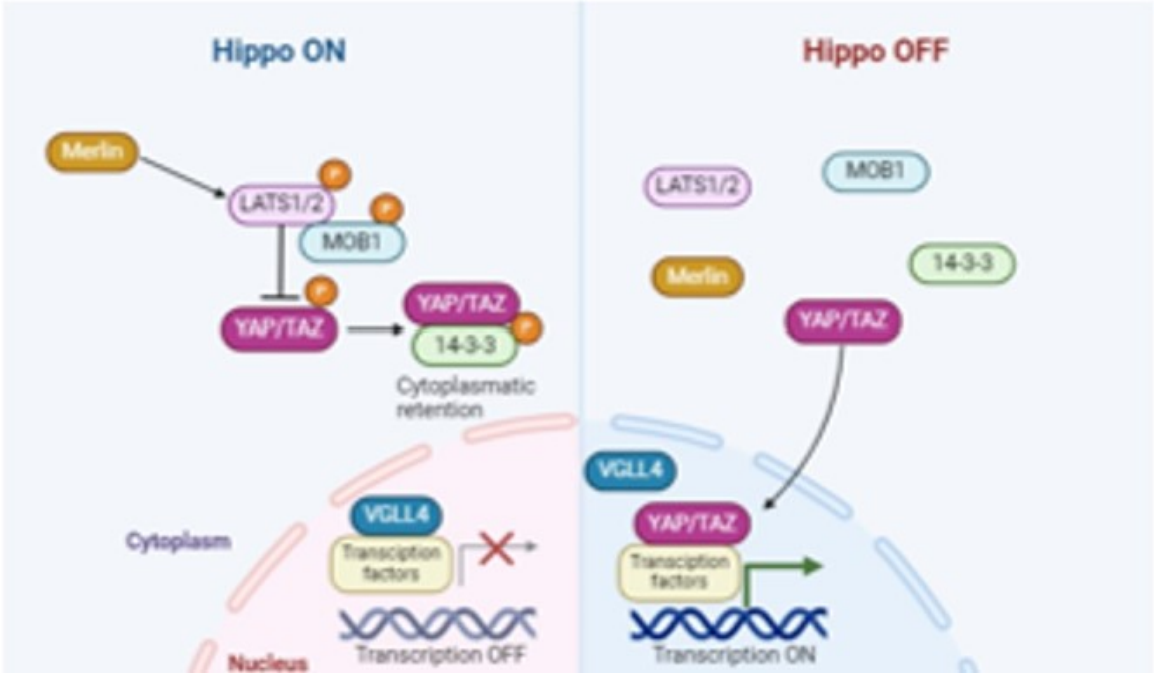
Symptoms: hearing loss, tinnitus, imbalance, dizziness, nausea, vomiting, or vertigo.

Mutations of the NF2 gene include non-sense (29–39%), splice-site (25%), frameshift (25–27%), and missense (5–7%) mutations (Evans DGR et al., 1999).

Treatment: surgery is the preferred therapy for VS with a diameter greater than 3 cm.
Not **applicable** in cases where the risk of paralysis of the facial nerve and hearing loss is high.

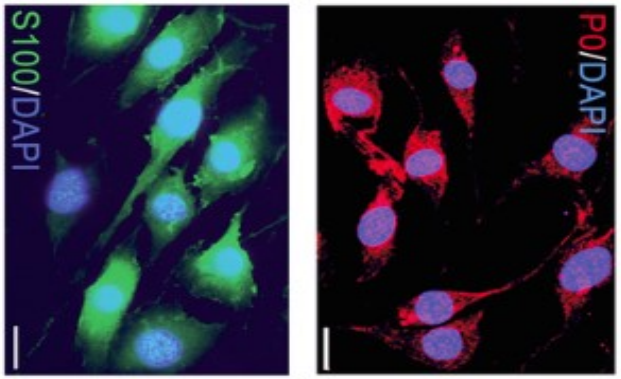

NeuroFibromatosis type 2 (NF2)
VS
5%
95
%
Bilateral
?
p13 p12 p11.2 q11.21 q11.23 q12.2 q13.1 q13.31
LZTR1
SMARCB1
NF2

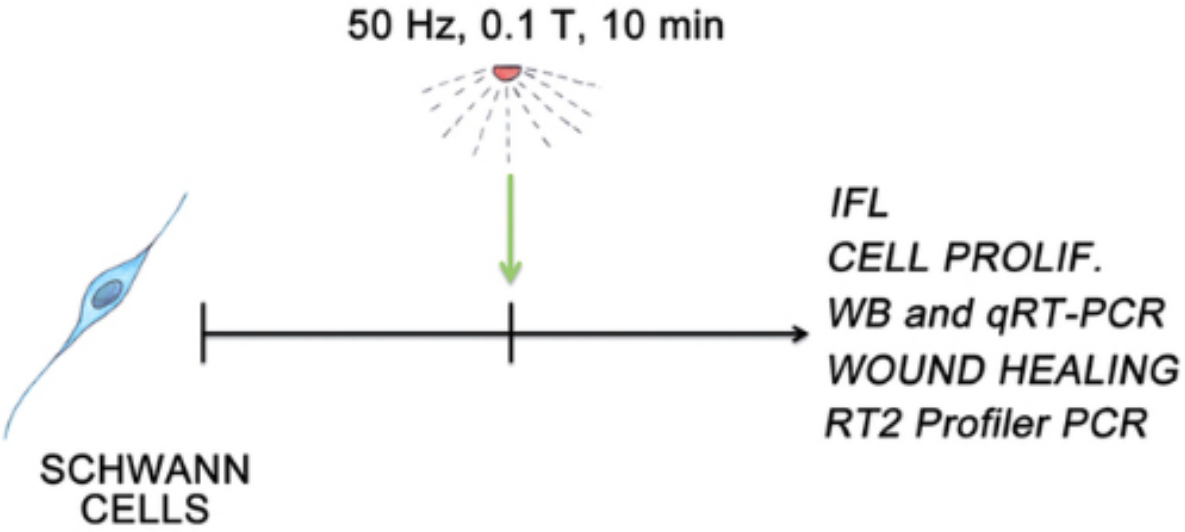
Merlin


Hippo ON
Hippo OFF
Merlin
LATS1/2
MOB1
YAP/TAZ
14-3-3
Cytoplasmatic retention
Cytoplasm
VGLL4
Transcription factors
Transcription OFF
Nucleus
Transcription ON


UNIVERSITÀ DEGLI STUDI MILANO
INVENTARIO N. 4241
CENTRO DI COSTO 669
CAT. 9
Magnetic cell stimulator
mTesla emitted
START
STOP
PAUSE
RS EZM-3735

In vitro Schwann cells exposed to EMF





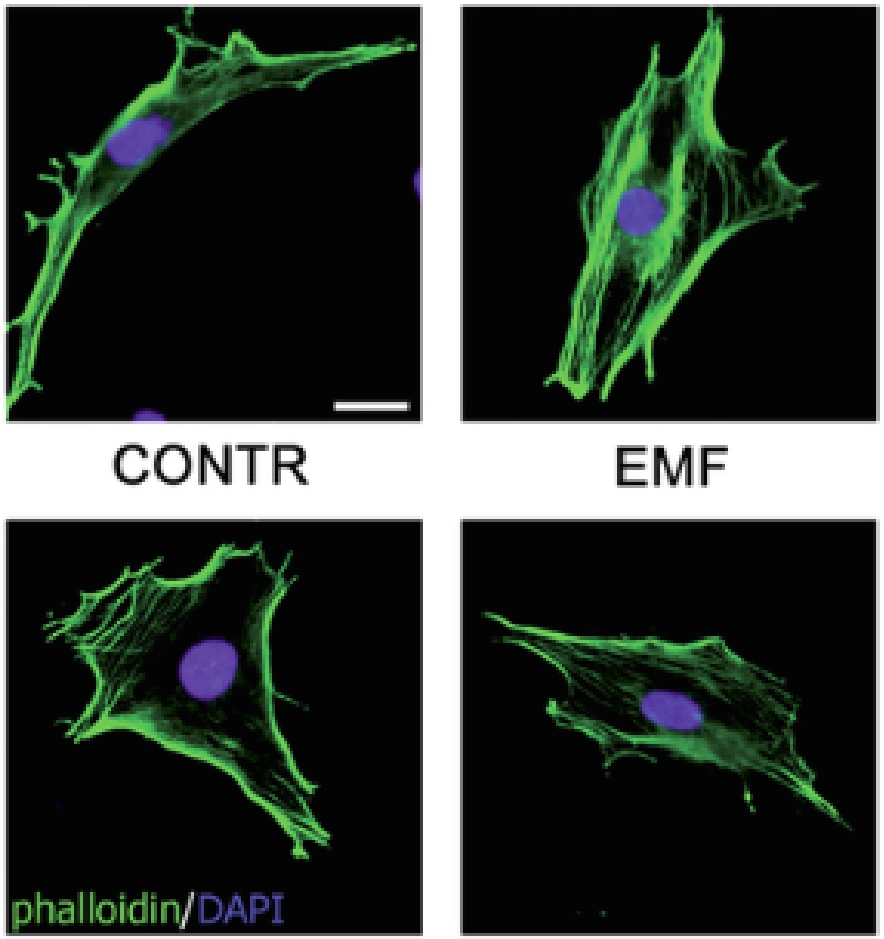
Exp scheme

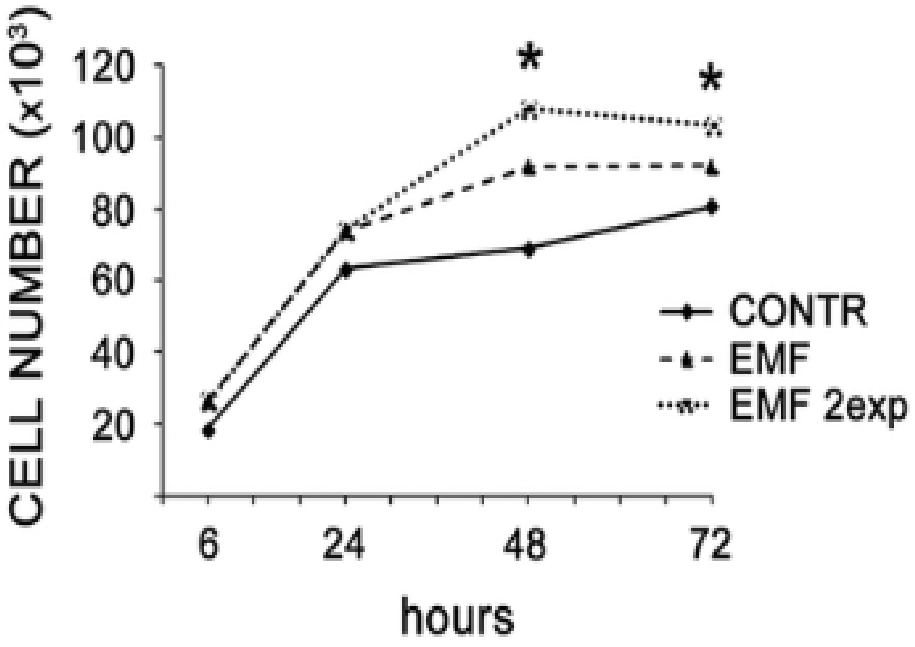
acute →

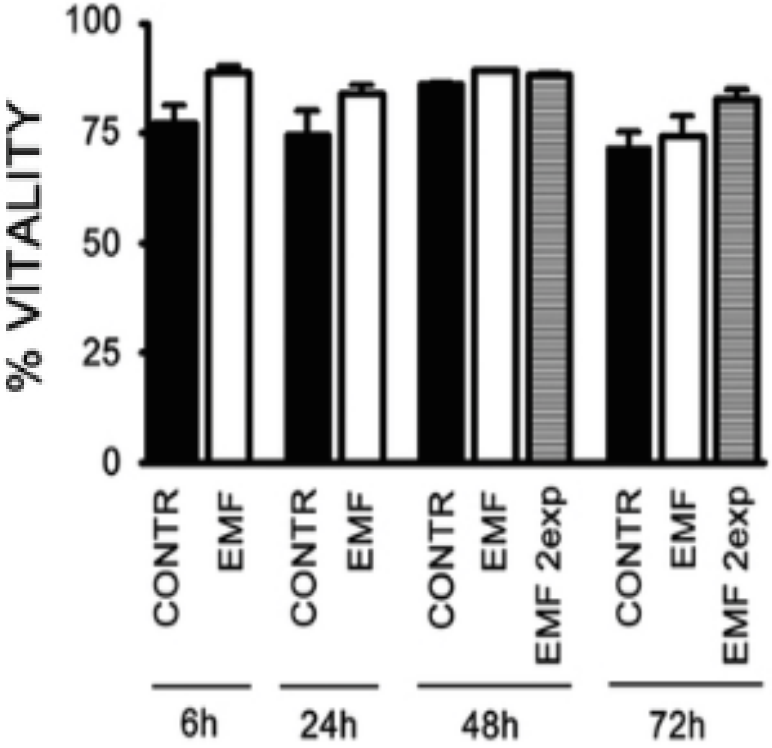
day 1	1 exposure	50 Hz, 0.1 T, 10 min

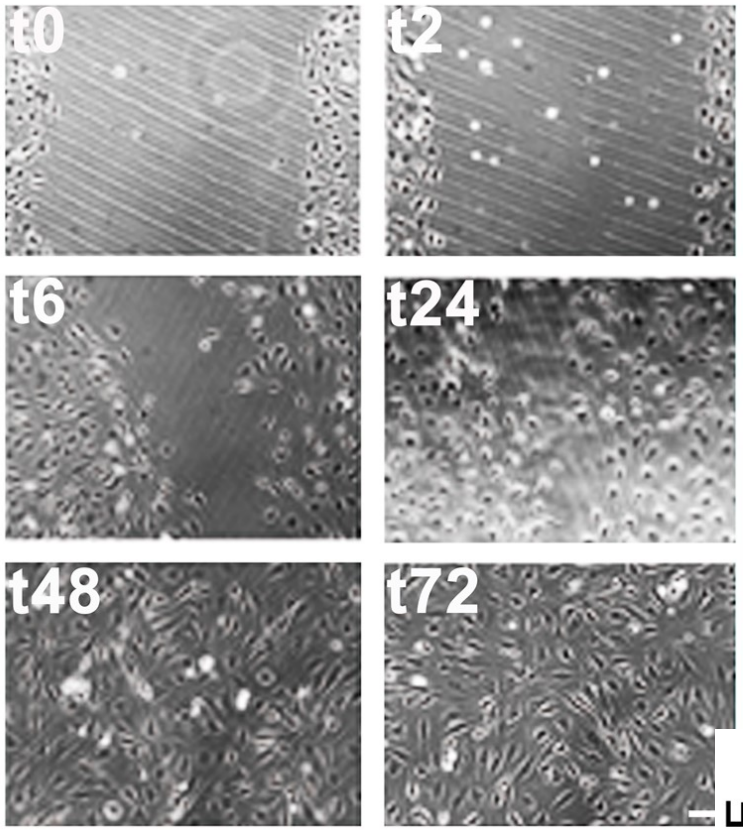
chronic →

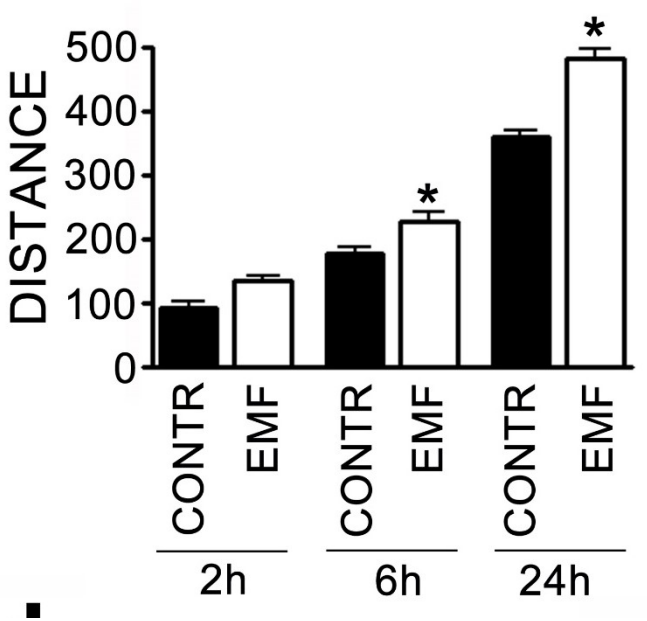
day 1	1 exposure	50 Hz, 0.1 T, 10 min
day 2	1 exposure	50 Hz, 0.1 T, 10 min
day 3	1 exposure	50 Hz, 0.1 T, 10 min
day 4	1 exposure	50 Hz, 0.1 T, 10 min
day 5	1 exposure	50 Hz, 0.1 T, 10 min

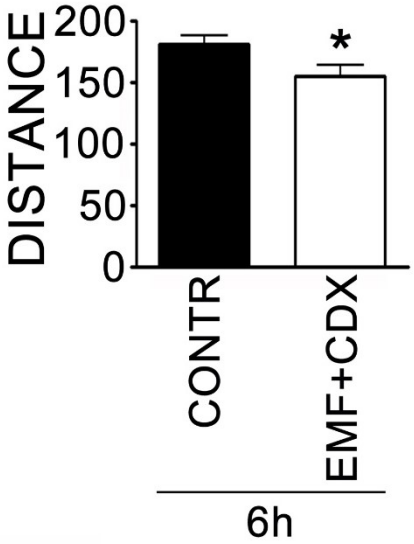

CONTR
EMF
phalloidin/DAPI
EMF
EMF


CELL NUMBER (x10³)
120
100
80
60
40
20
6
24
48
72
hours
*
*
CONTR
EMF
EMF 2exp

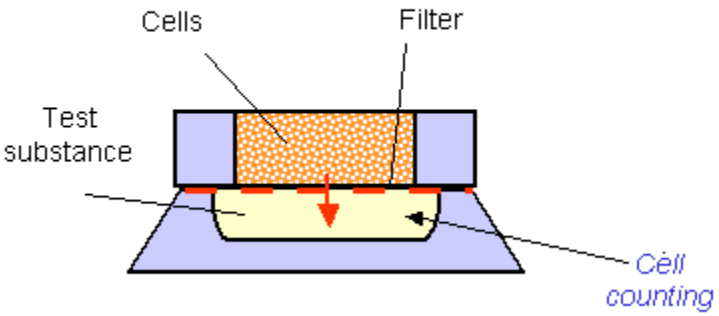

% VITALITY
100
75
50
25
0
CONTR
EMF
CONTR
EMF
CONTR
EMF
EMF 2exp
CONTR
EMF
EMF 2exp
6h
24h
48h
72h

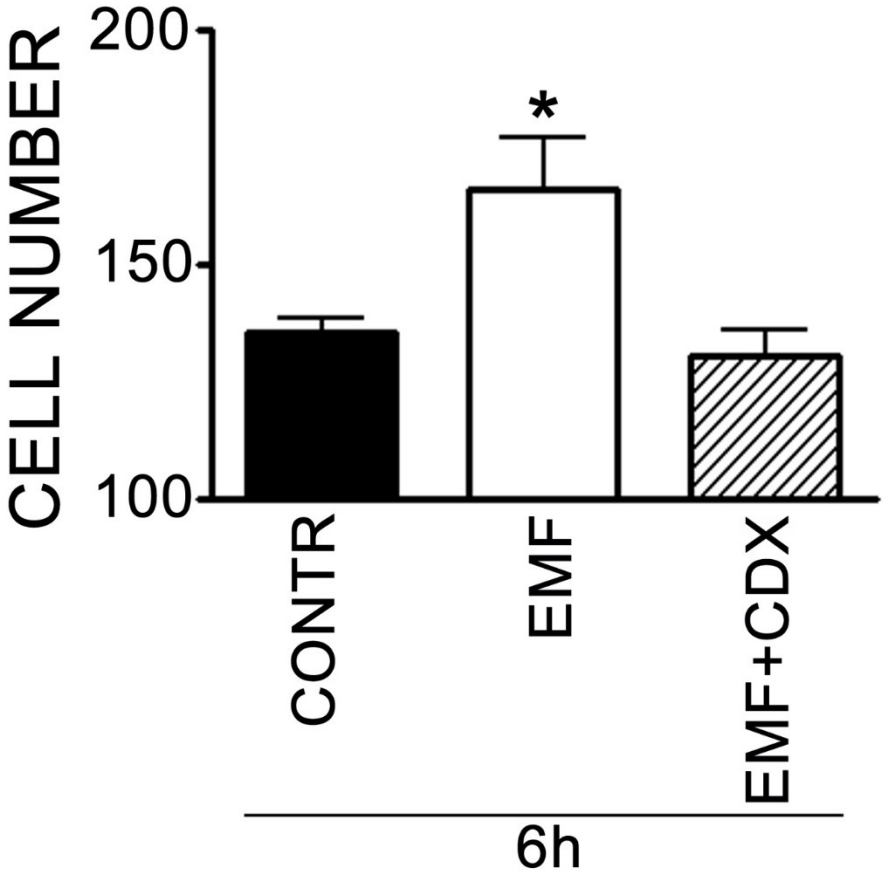

t0
t2
t6
t24
t48
t72

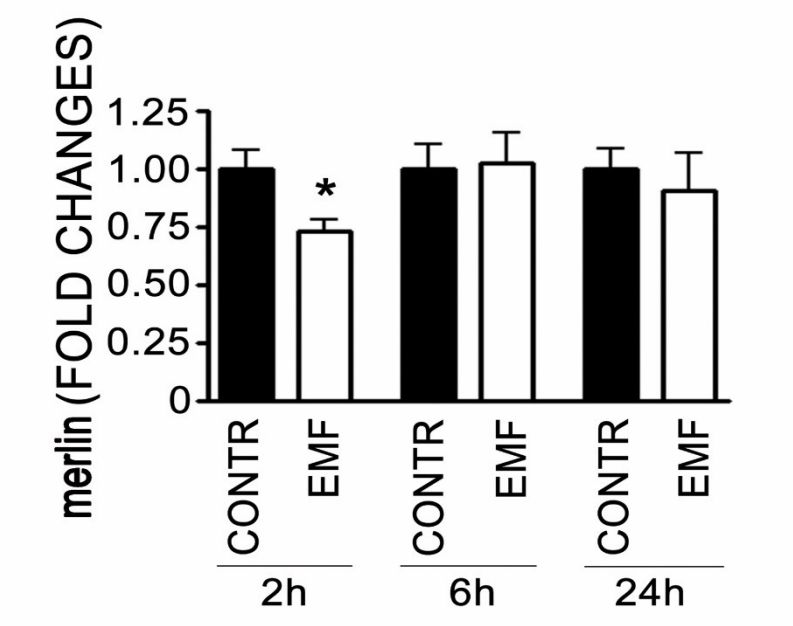

DISTANCE
500
400
300
200
100
0
*
*
CONTR
EMF
CONTR
EMF
CONTR
EMF
2h
6h
24h

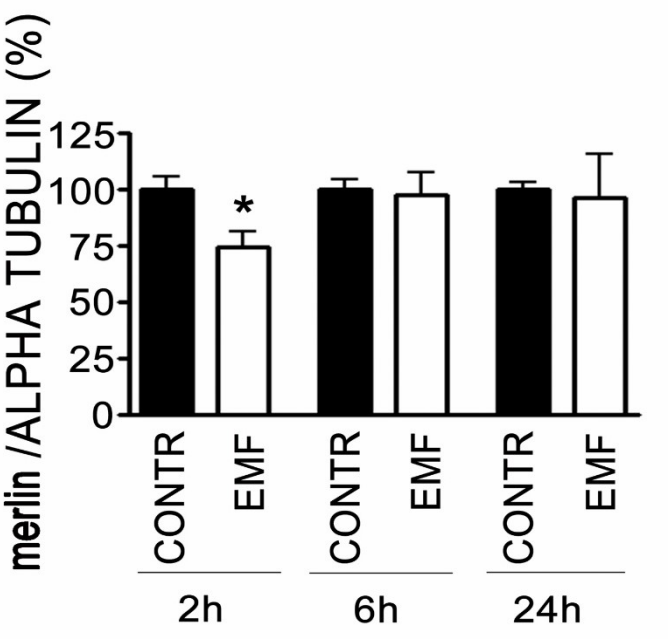

DISTANCE
200
150
100
50
0
*
CONTR
EMF+CDX
6h

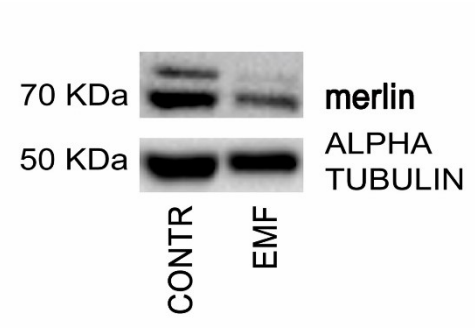
Boyden chamber

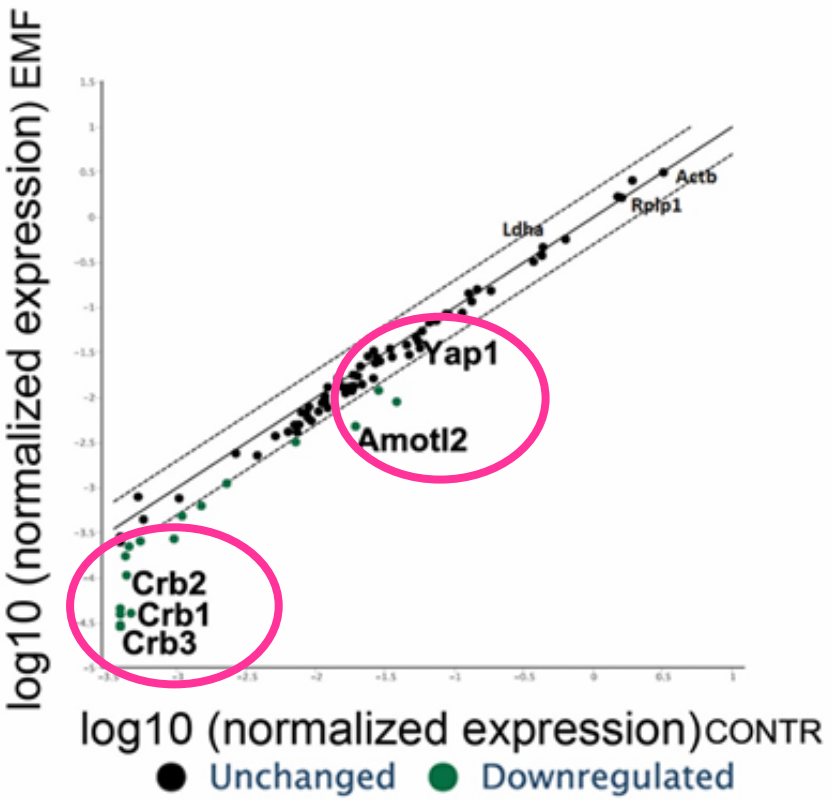


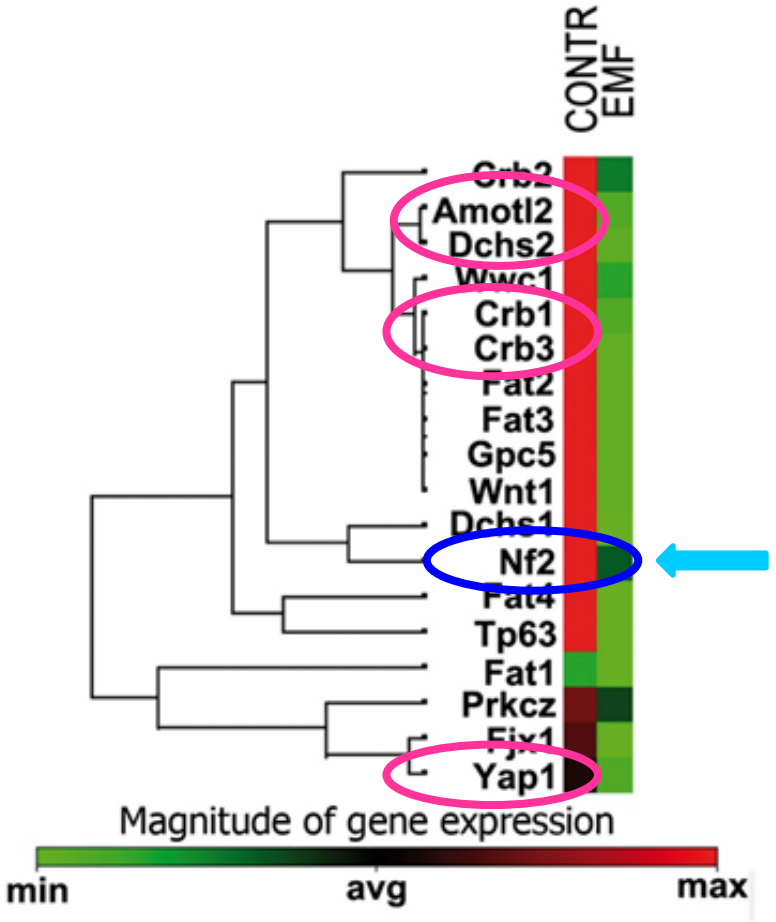


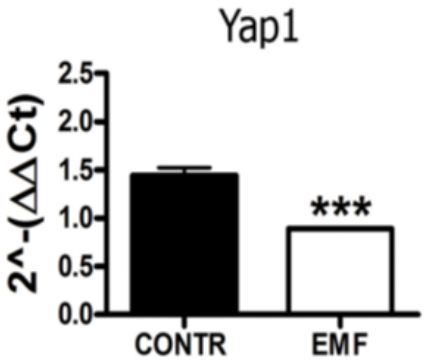

merlin (FOLD CHANGES)
1.25
1.00
0.75
0.50
0.25
0
*
CONTR
EMF
CONTR
EMF
CONTR
EMF
2h
6h
24h

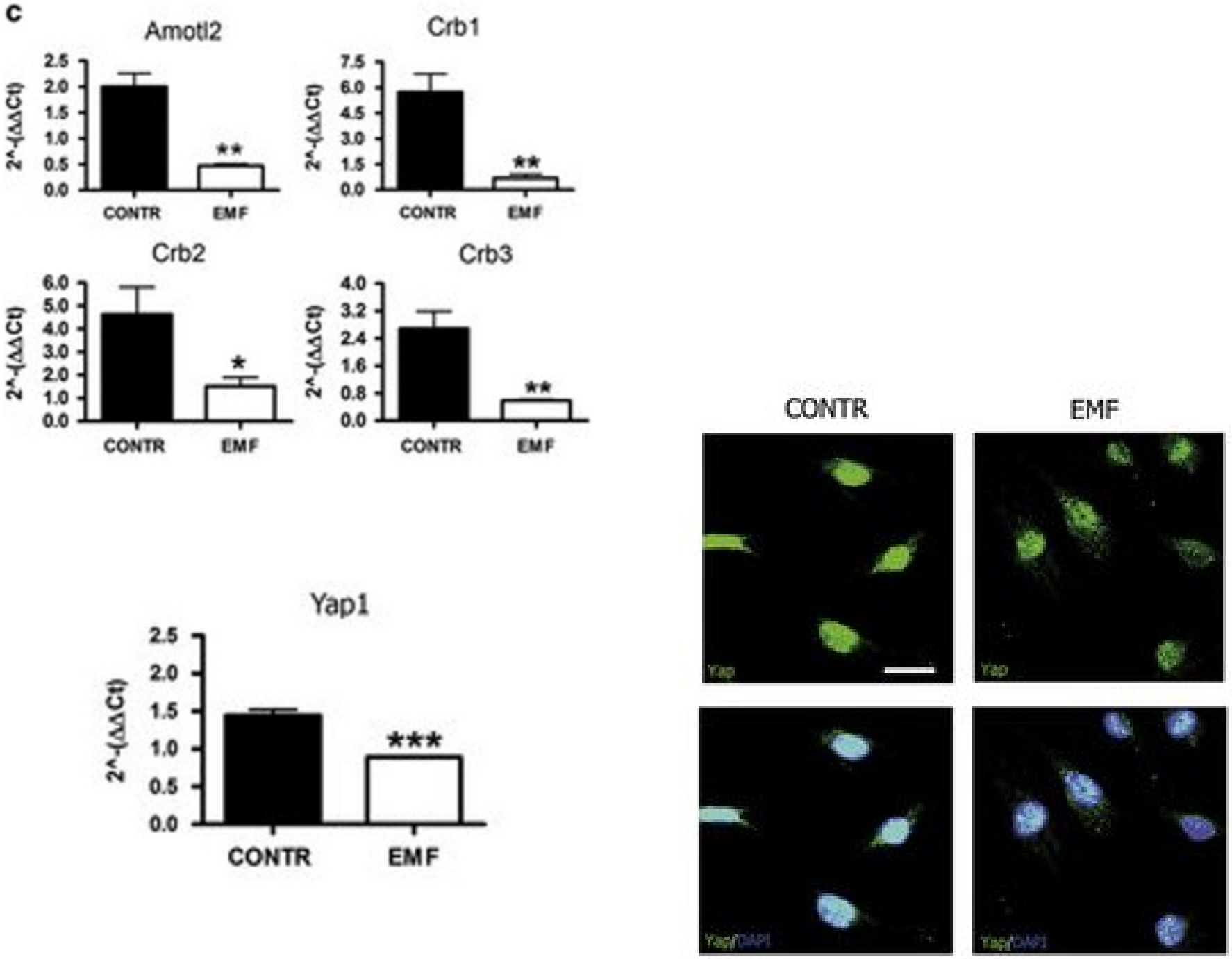

merlin /ALPHA TUBULIN (%)
125
100
75
50
25
0
*
CONTR
EMF
CONTR
EMF
CONTR
EMF
2h
6h
24h

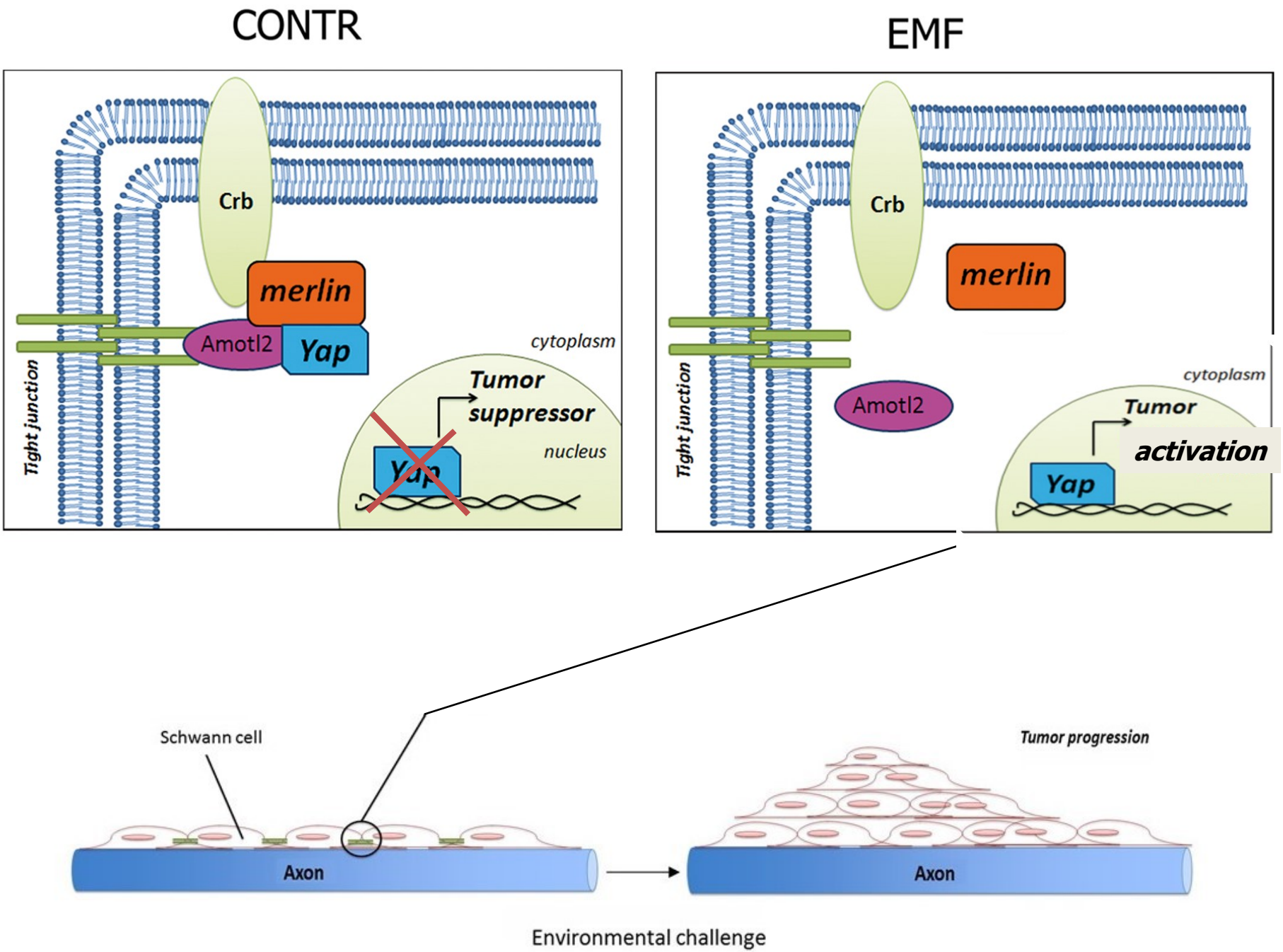

70 KDa
merlin
50 KDa
ALPHA
TUBULIN
CONTR
EMF


log10 (normalized expression) EMF
Actb
Rplp1
Ldha
Yap1
Amotl2
Crb2
Crb1
Crb3
log10 (normalized expression)CONTR
Unchanged
Downregulated


CONTR
EMF
Amotl2
Dchs2
Crb1
Crb3
Fat3
Gpc5
Wnt1
Nf2
Tp63
Fat1
Prkcz
Yap1
Magnitude of gene expression
min
avg
max


Yap1
2^-(ΔΔCt)
2.5
2.0
1.5
1.0
0.5
0.0
***
CONTR
EMF


c
Amotl2
Crb1
Crb2
Crb3
Yap1
2^-(ΔΔCt)
CONTR
EMF
**
*
***
CONTR
EMF
Yap
Yap/DAPI


CONTR
EMF
Crb
merlin
Amotl2
Yap
Tight junction
cytoplasm
Tumor
suppressor
nucleus
Yap
Crb
merlin
Amotl2
Tight junction
cytoplasm
Tumor
activation
Yap
Schwann cell
Axon
Tumor progression
Axon
Environmental challenge

rat SCs exposed to EMFs:

- the oncosuppressor *Nf2*/merlin is decreased, in turn changing the cell phenotype toward a **proliferative/migrating** state;
- the MAPK/ERK signalling, which is mainly involved in cell proliferation, is activated;
- the Hippo intracellular signalling is activated: transcription is OFF…..suppression is ON

We suggest:

….when SCs are altered by EMF exposure, the risk to develop a schwannoma might increase.

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Tumor suppressor Nf2/merlin drives Schwann cell changes following electromagnetic field exposure through Hippo-dependent mechanisms

A Colciago, S Melfi, G Giannotti, V Bonalume, M Ballabio, L Caffino, F Fumagalli & V Magnaghi

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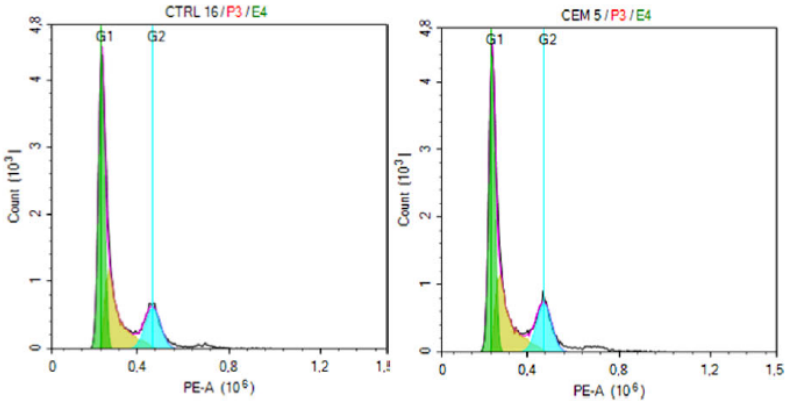
Open Access | Published: 15 October 2015

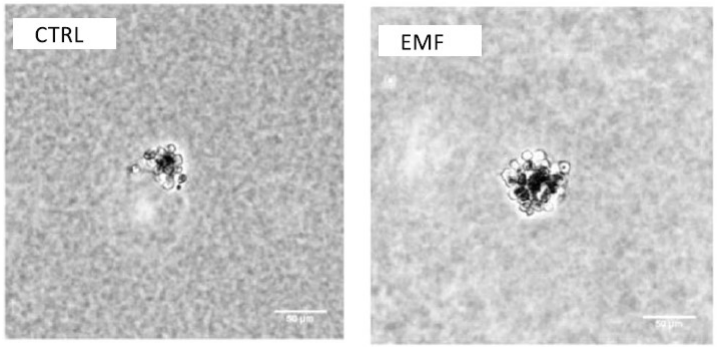
Stressing out the Hippo/YAP signaling pathway: toward a new role in Schwann cells

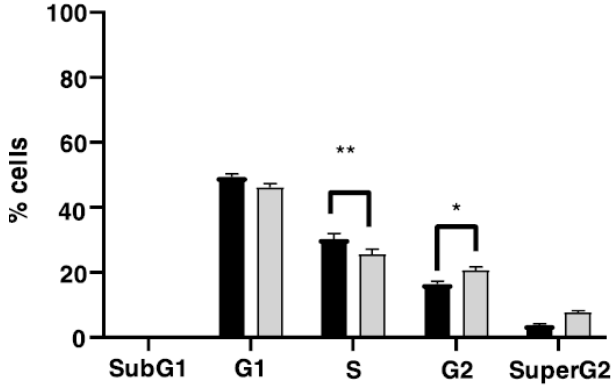
S Melfi, A Colciago, G Giannotti, V Bonalume, L Caffino, F Fumagalli & V Magnaghi

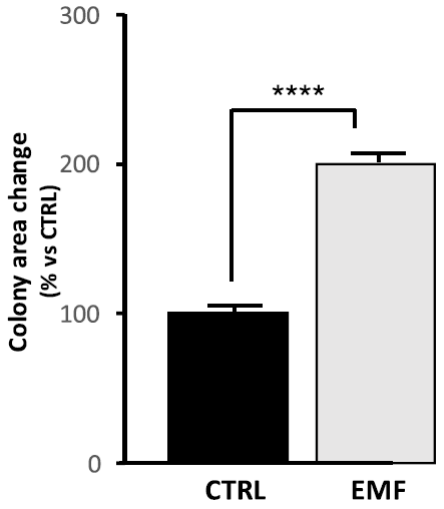
Cell Death & Disease **6**, e1915 (2015) | Cite this article

24 hrs

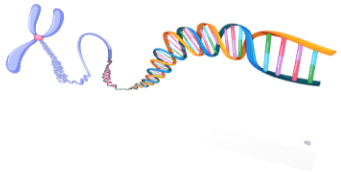

CTRL 16 / P3 / E4
CEM 5 / P3 / E4
G1
G2
Count (10^3)
PE-A (10^6)

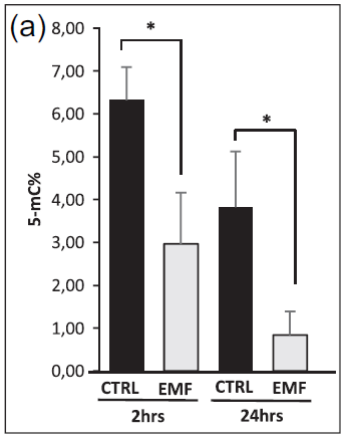

CTRL
EMF

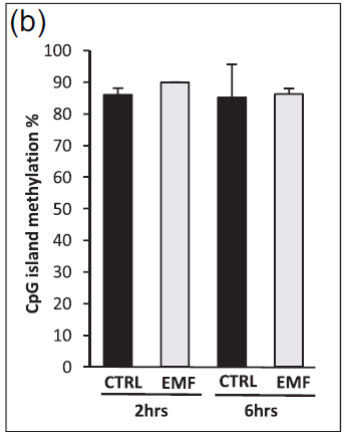

% cells
SubG1
G1
S
G2
SuperG2
**
*

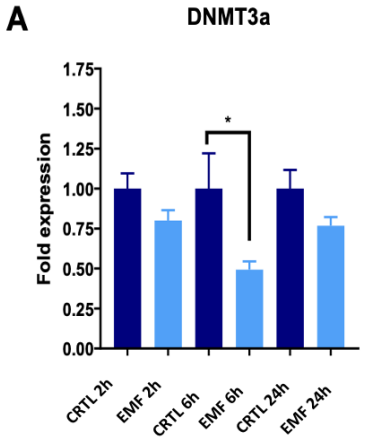

Colony area change (% vs CTRL)
****
CTRL
EMF

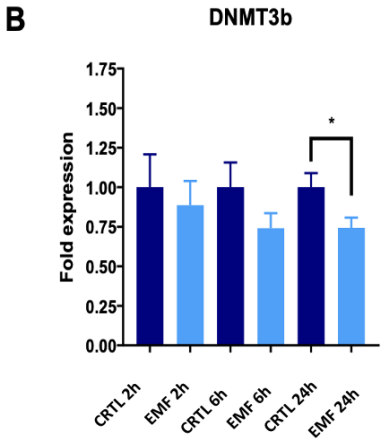
EMF effects on the epigenetic profile of SCs

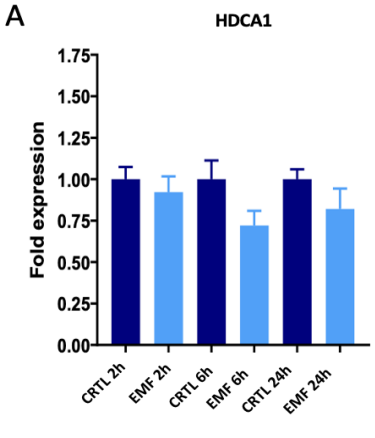


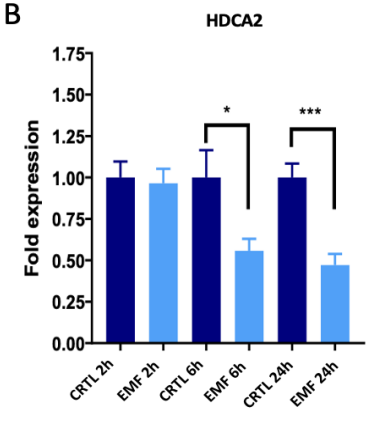




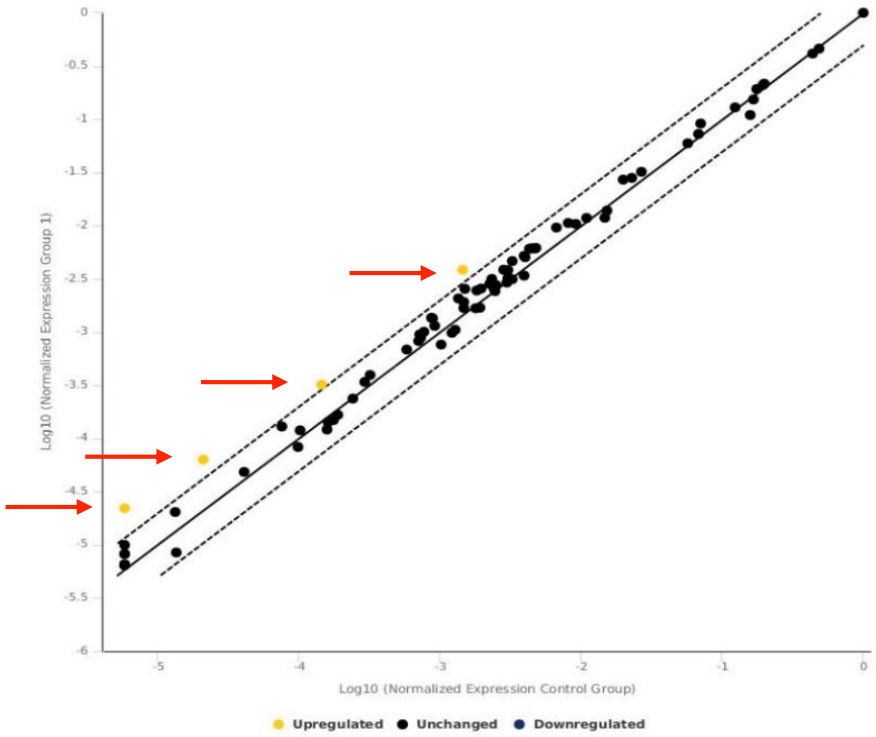


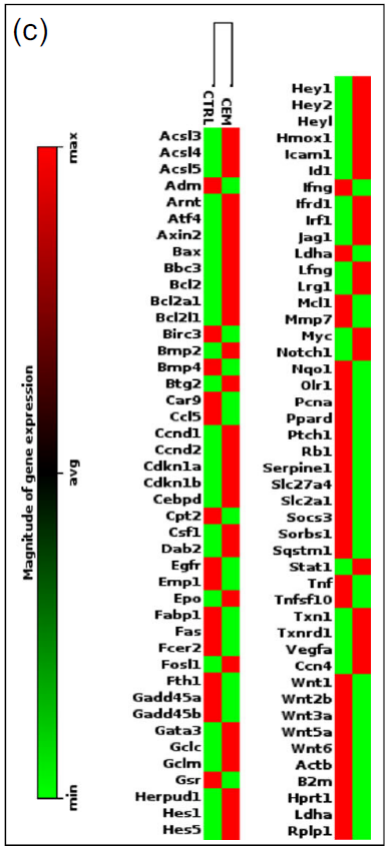






EMFs effects on the expression of some genes

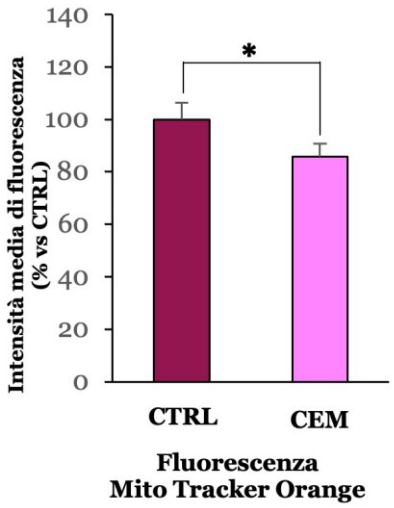


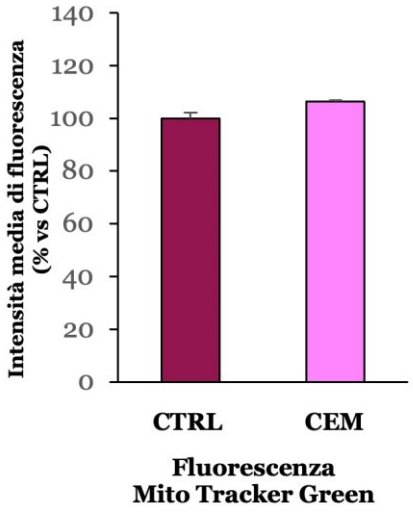


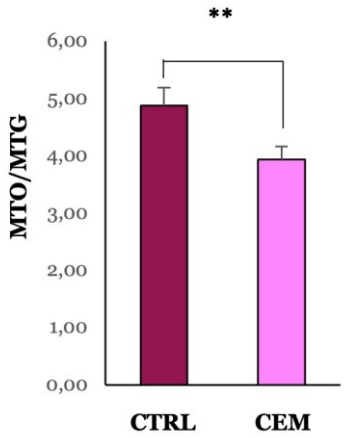
Test group	Control Group	Fold Regulation Threshold	P-value Threshold
Group 1 (EMF)	CTRL	2	0.05

Position	Gene symbol	Fold Regulation
A11	Bcl2a1	2.68
D07	Hes5	3.38
D11	Hmox1	2.35

EMF effects on mithocondrial function







Summary

- **Effects on cell growth:** increased proliferation and anchorage-independent growth.

- **Effects on epigenetic profiling:** increased transcriptional activity and change in differentiation status.

- **Effects on mitochondrial function:** decreased mitochondrial function.

Received: 2 February 2024 | Accepted: 19 June 2024

DOI: 10.1002/jcp.31365

RESEARCH ARTICLE

Journal of Cellular Physiology WILEY

Electromagnetic field-induced adaptive response in Schwann cells through DNA methylation, histone deacetylation, and oxidative stress

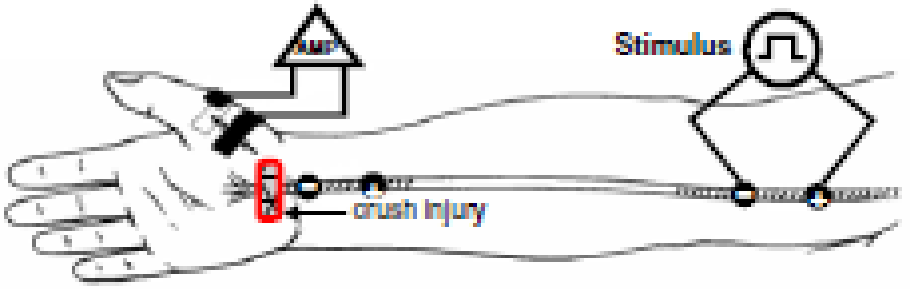
Alessandra Colciago | Tasnim Mohamed | Deborah Colleoni | Valentina Melfi | Valerio Magnaghi

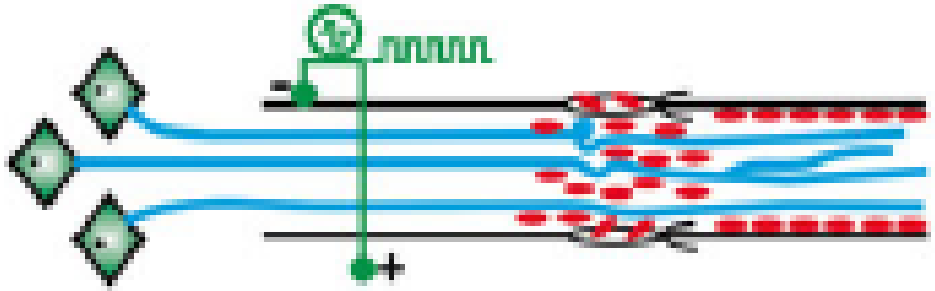
Neurotherapeutics (2016) 13:295–310
DOI 10.1007/s13311-015-0415-1

REVIEW

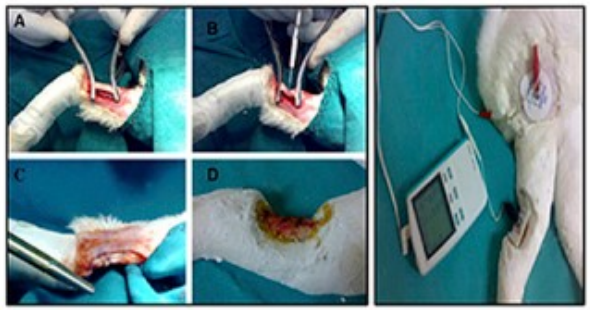
Electrical Stimulation to Enhance Axon Regeneration After Peripheral Nerve Injuries in Animal Models and Humans

Tessa Gordon[1]



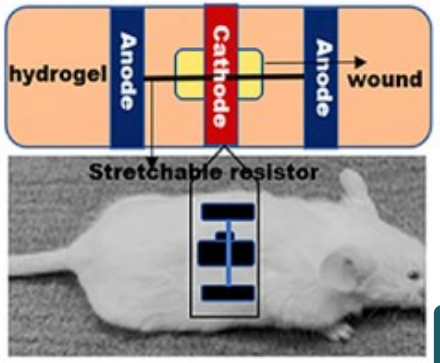


Tendons & ligaments



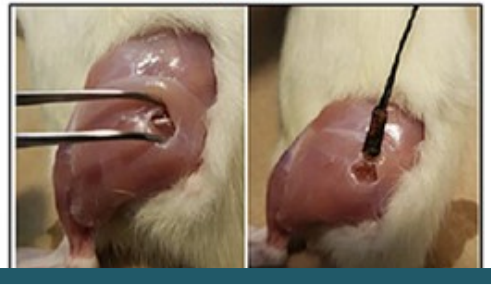
Ferrigno et al. Bio. Mat. 2020

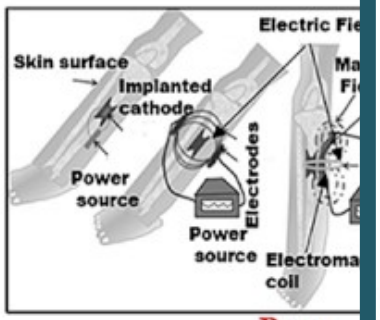
Wound Healing



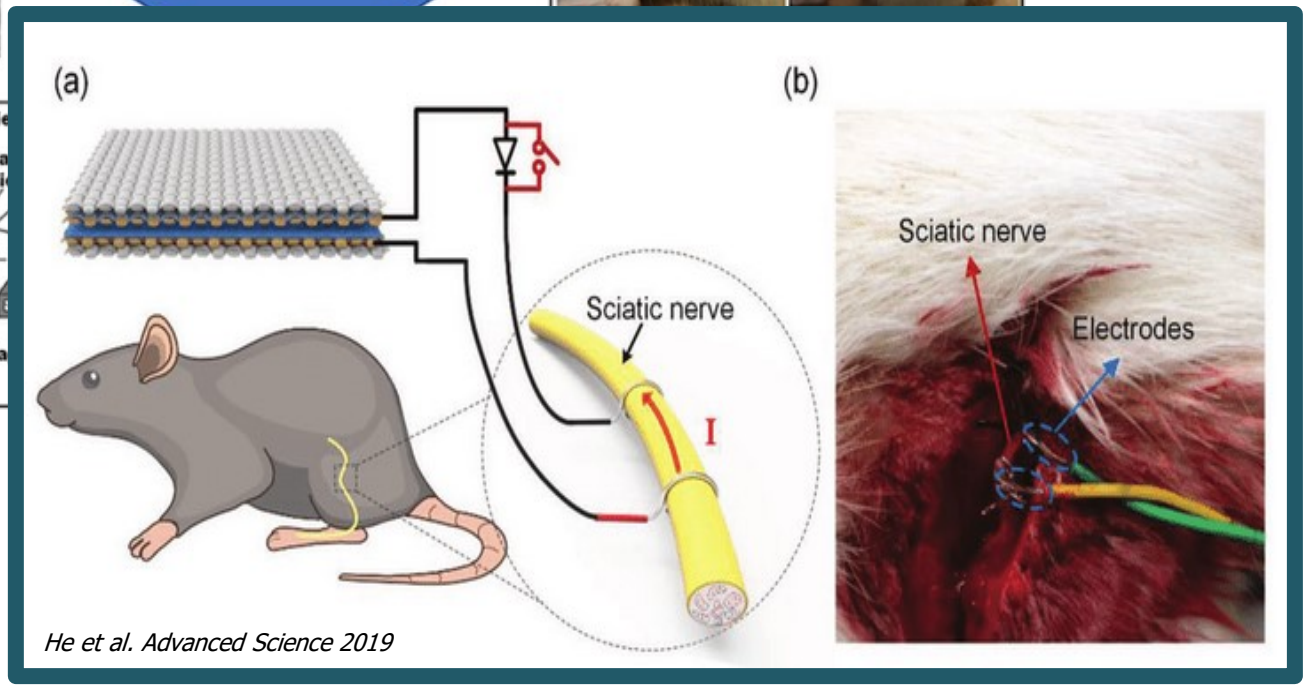
Electrical stimulation

Muscle



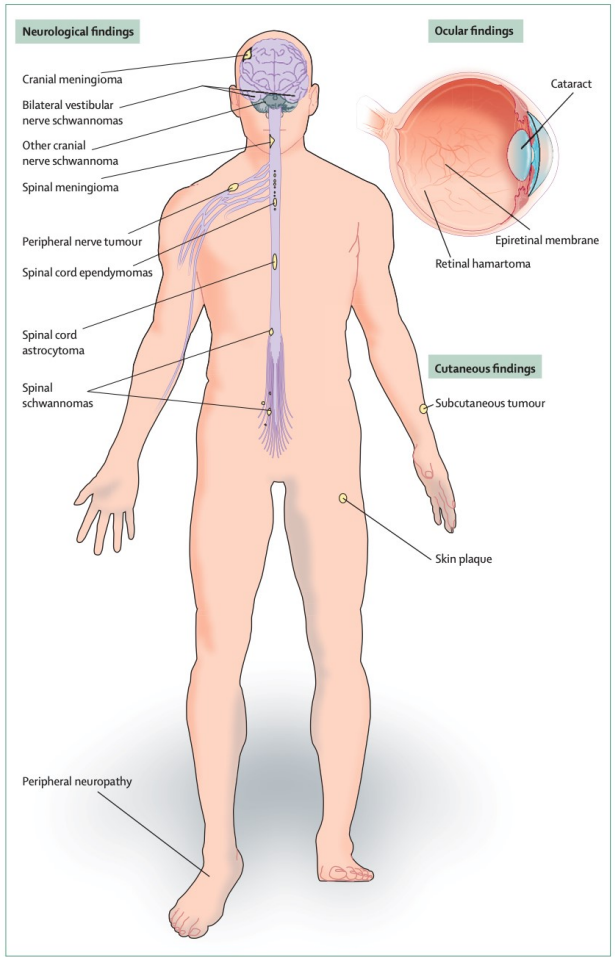


Bone



He et al. Advanced Science 2019

Neurofibromatosis Type 2 (NF2)

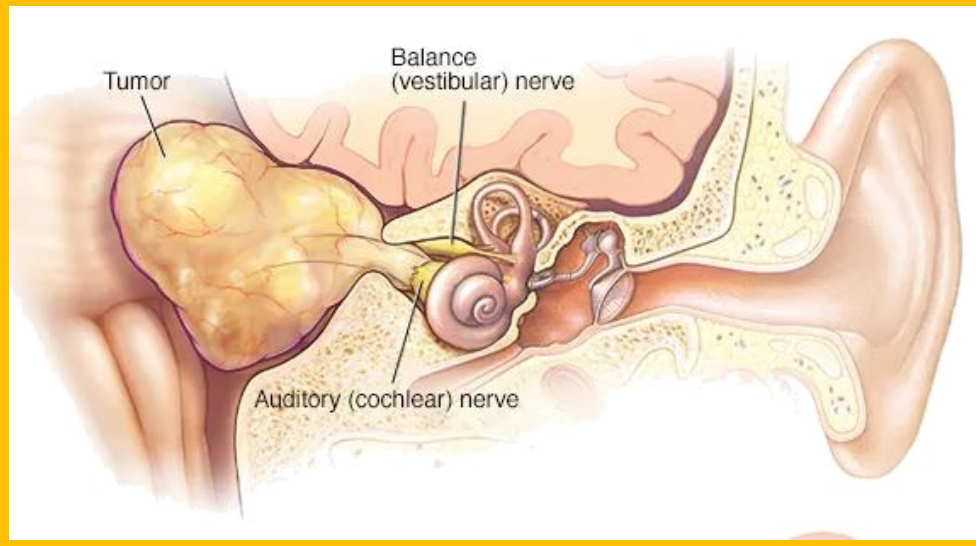


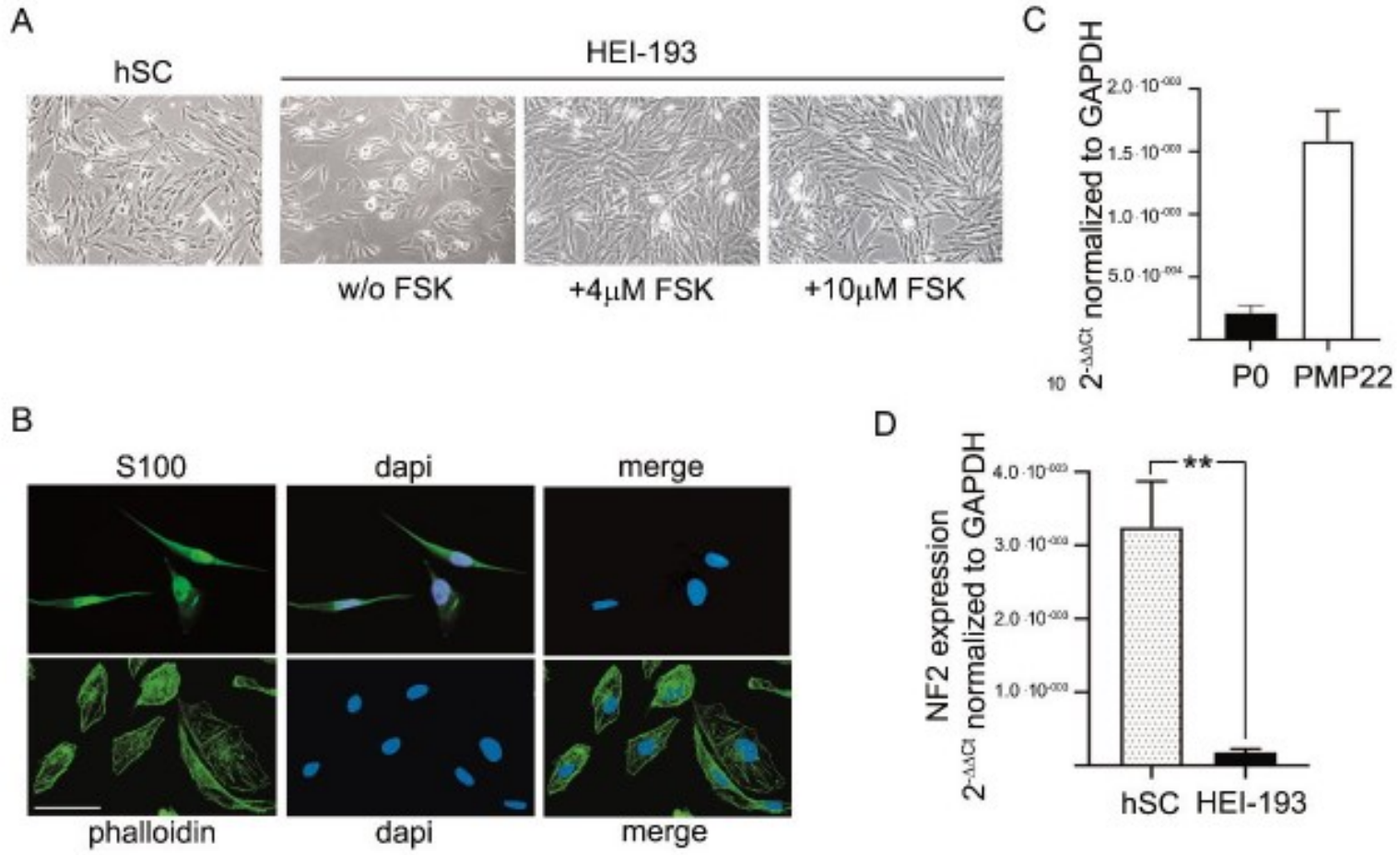
Clinical manifestations of neurofibromatosis type 2 (Asthagiri et al., 2009)

NF2 is characterized by the development of multiple schwannomas, meningiomas and spinal cord ependymomas.

Defects in the ***NF2 gene*** located on chromosome 22q12 and the consecutive loss of its protein **merlin.**

Hallmark of NF2 is bilateral VESTIBULAR SCHWANNOMA, present in almost all patients.




A
hSC
HEI-193
w/o FSK
+4μM FSK
+10μM FSK
B
S100
dapi
merge
phalloidin
dapi
merge
C
2-ΔΔCt normalized to GAPDH
P0
PMP22
D
NF2 expression
2-ΔΔCt normalized to GAPDH
**
hSC
HEI-193

Proliferation of HEI-193 cells exposed to acute and chronic EMF

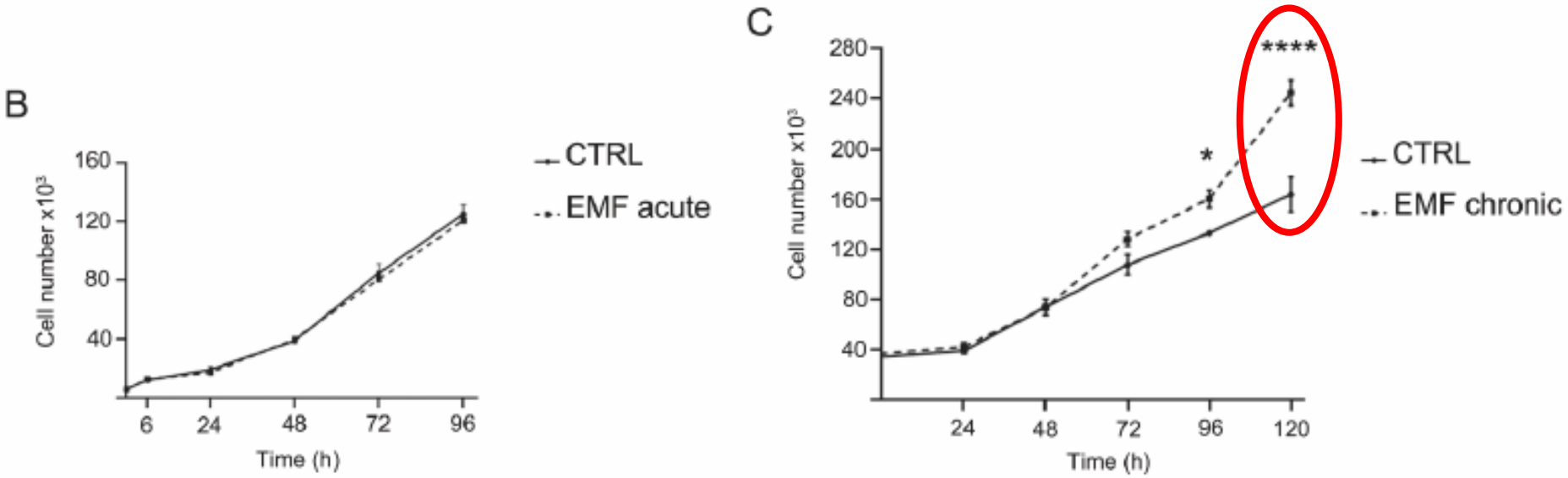


Figure 2. Proliferation effects on HEI-193 cells exposed to acute and chronic EMF. (A) Scheme of the experimental protocol applied. HEI-193 cells were exposed to EMF of 50 Hz, 0.1 T, for one 10-min single treatment (acute protocol) or for 10-min treatment/per day for five days (every 24 h at the same time; chronic protocol). Then, the cells were assayed for proliferation, migration, vitality, and NGS sequencing. (B) Proliferation was assessed at 6, 24, 48, 72, and 96 h, following a single acute EMF exposure. Experiments were repeated at least three times and data expressed as cell number ± SEM of the mean. (C) Proliferation was assessed at 24, 48, 72, 96, and 120 h, following a five day chronic EMF exposure. EMFs produced a significant increase in cell proliferation at 96 (* $p < 0.05$) and 120 (**** $p < 0.0001$) h. Experiments were repeated at least three times and data expressed as cell number ± SEM of the mean. Two-way ANOVA using Sidak's post-hoc test was used for statistical analysis.

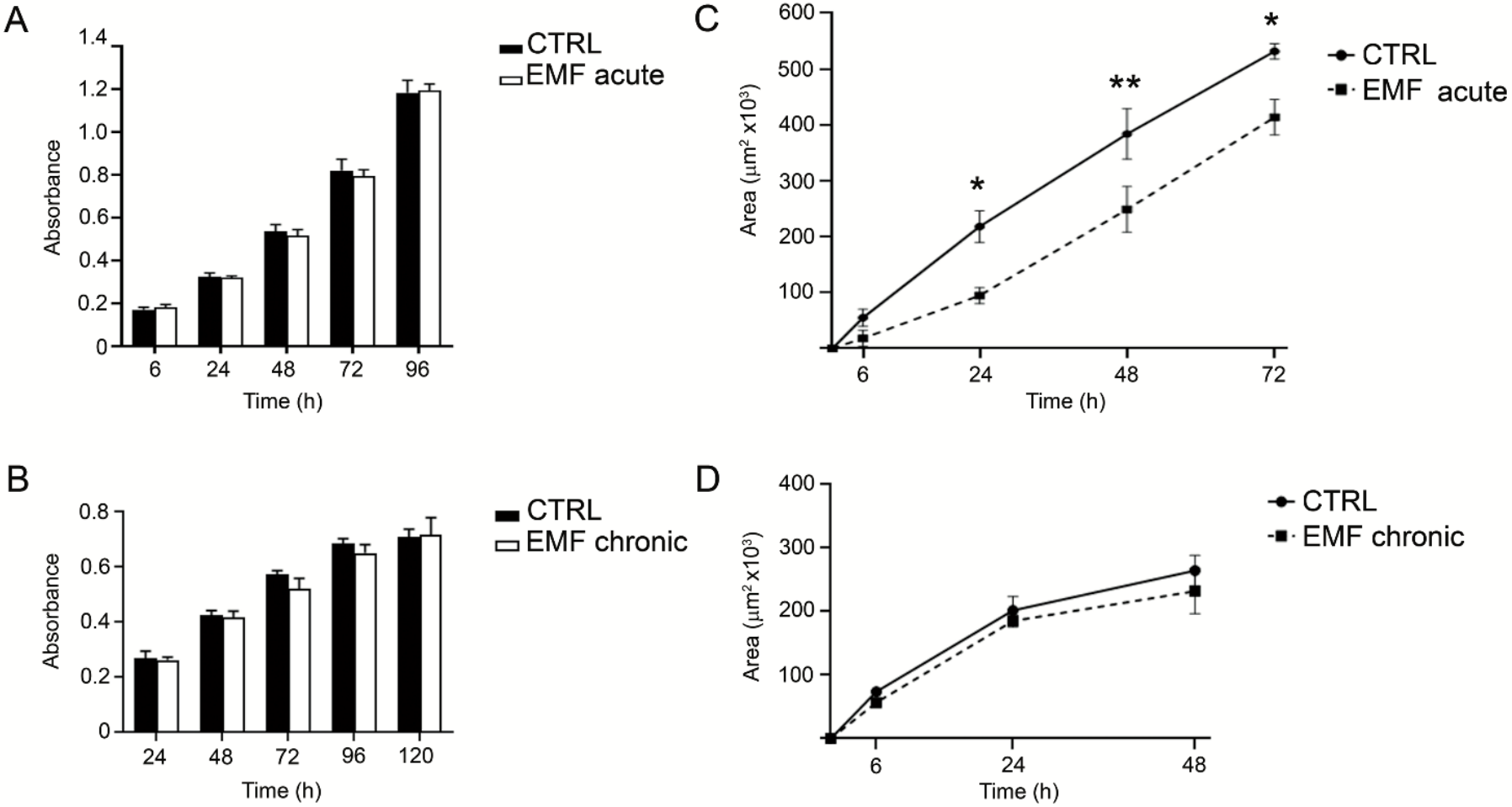


Figure 3. Migration and viability effects on HEI-193 cells exposed to acute and chronic EMF. (**A**) Cell viability was assessed by the MTT assay at 6, 24, 48, 72 and 96 h following a single acute EMF exposure. Each experimental point was in quadruplicate and experiments replicated at least three times; data were expressed as absorbance ± SEM of the mean. (**B**) Cell viability was assessed at 24, 48, 72, 96, and 120 h, following completion of a 5-day chronic EMF exposure. Each experimental point was in quadruplicate and experiments replicated at least three times; data were expressed as absorbance ± SEM of the mean. (**C**) Cell migration was assessed at 6, 24, 48, and 72 h, following a single acute EMF exposure. EMF treatment was associated with a significant decrease in cell migration at 24 (* $p < 0.05$), 48 (** $p < 0.01$), and 72 (* $p < 0.05$) h. Experiments were repeated at least three times. Each data point was calculated as the difference of the 2D scratched area (at time 0) minus the 2D remaining area at each specific time point, representing the 2D area covered by the cell migration. Data were expressed in μm^2 ± SEM of the mean. (**D**) Cell migration was assessed at 6, 24, and 48 following a chronic EMF exposure. Experiments were repeated at least three times. Each data point was calculated as the difference of the 2D scratched area (at time 0) minus the 2D remaining area at each specific time point, representing the 2D area covered by the cell migration. Data were expressed in μm^2 ± SEM of the mean. Two-way ANOVA using Sidaki's post-hoc test was used for statistical analysis.

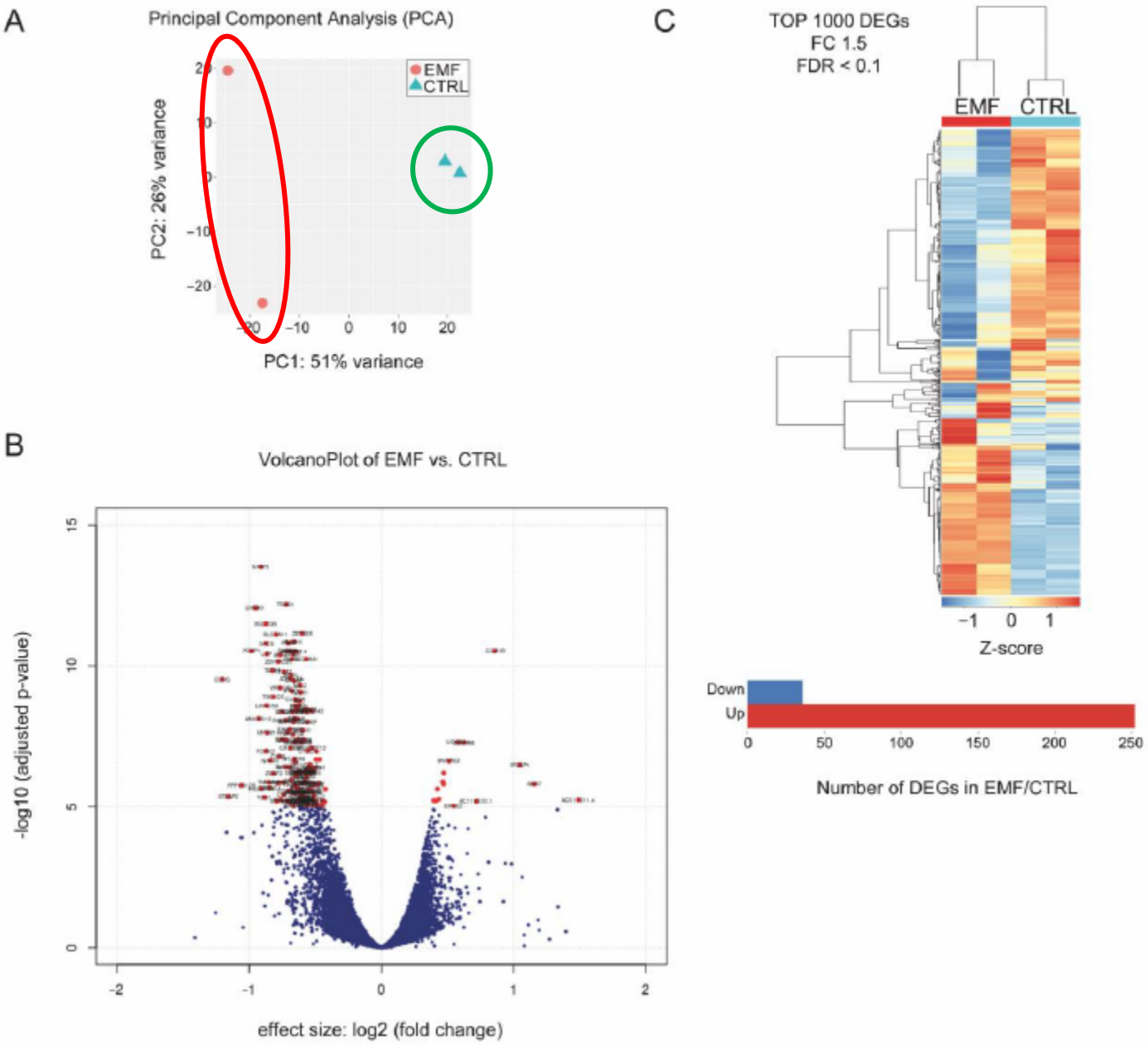
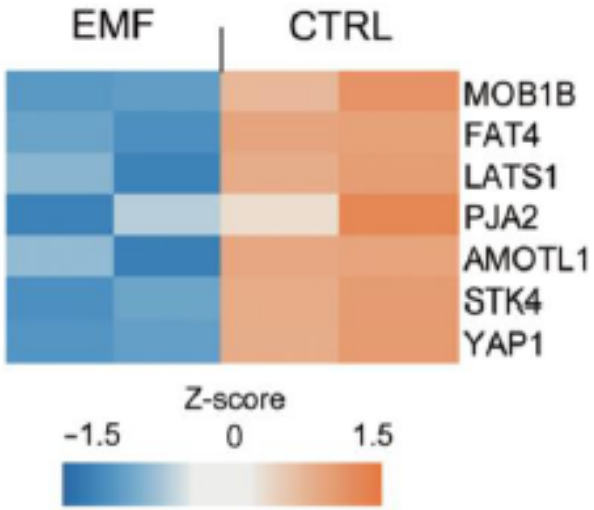

A
Principal Component Analysis (PCA)
EMF
CTRL
PC2: 26% variance
PC1: 51% variance
B
VolcanoPlot of EMF vs. CTRL
-log10 (adjusted p-value)
effect size: log2 (fold change)
C
TOP 1000 DEGs
FC 1.5
FDR < 0.1
EMF
CTRL
Z-score
Down
Up
Number of DEGs in EMF/CTRL

Table 1. Major signaling pathways upregulated in HEI-193 cells following chronic EMF exposure.

	Pathway	Direction	NES	*P* adj
	Cotranslational protein targeting to membrane	Up	7.859	5.30×10^{-10}
	Protein targeting to ER	Up	7.807	5.30×10^{-10}
	SRP dependent cotranslational protein targeting to membrane	Up	7.797	5.30×10^{-10}
	Establishment of protein localization to endoplasmic reticulum	Up	7.585	5.30×10^{-10}
	Mitochondrial translational elongation	Up	6.081	6.10×10^{-6}
	Mitochondrial translational termination	Up	6.022	6.70×10^{-6}
	Translational termination	Up	5.668	1.50×10^{-5}
	Mitochondrial respiratory chain complex assembly	Up	4.546	9.00×10^{-4}
	Mitochondrial ATP synthesis coupled electron transport	Up	4.404	1.20×10^{-3}
	Cytoplasmic translation	Up	4.360	1.50×10^{-3}
	ATP synthesis coupled electron transport	Up	4.234	1.90×10^{-3}
	NADH dehydrogenase complex assembly	Up	3.955	6.60×10^{-3}
	Mitochondrial respiratory chain complex I assembly	Up	3.955	6.60×10^{-3}
	Ribosomal large subunit biogenesis	Up	3.920	6.60×10^{-3}
	Respiratory electron transport chain	Up	3.858	6.60×10^{-3}
	Ribosome assembly	Up	3.414	3.10×10^{-2}

Clustering of Hippo path



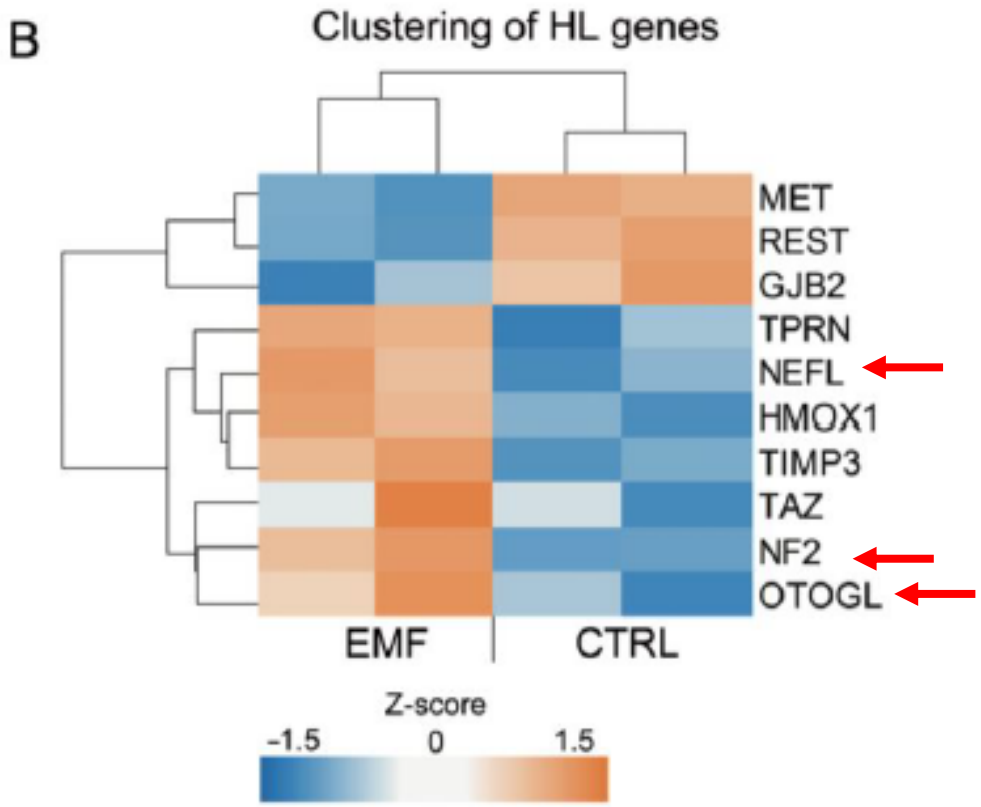


Figure 5. Identification of Hippo and HL-related DEGs in HEI-193 cells following chronic EMF. (A) Clustering of the Hippo-related genes that are deregulated in VS cells from control (CTRL) versus EMF exposed. (B) Clustering of the HL-related genes that are deregulated in VS cells from CTRL versus EMF exposed.

Summary

- **Chronic EMF exposure modify rat SCs proliferation, in parallel with intracellular signaling**
- **Some metabolic pathways changes, mostly related to translation and mitochondrial activities**
- **Expression of HL-related genes (e.g. NEFL, TPRN, OTOGL, GJB2, and REST) deregulated in chronic EMF exposure.**

cells

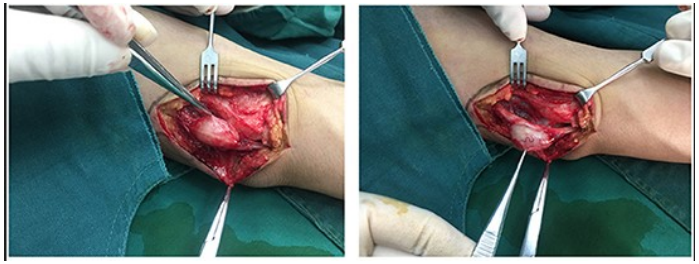
MDPI

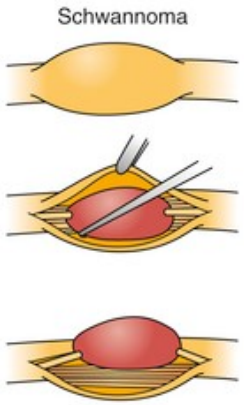
Article

Transcriptomic Profile Reveals Deregulation of Hearing-Loss Related Genes in Vestibular Schwannoma Cells Following Electromagnetic Field Exposure

Alessandra Colciago [1], Matteo Audano [1], Veronica Bonalume [1], Valentina Melfi [1], Tasnim Mohamed [1], Adam J. Reid [2,3], Alessandro Faroni [2], Peter A. Greer [4], Nico Mitro [1] and Valerio Magnaghi [1,*]

Schwannomatosis



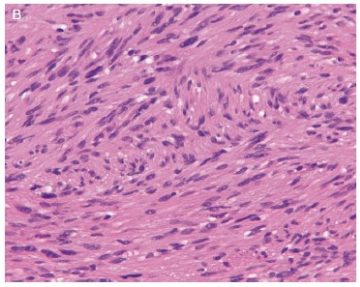


SWN is a tumor predisposition syndromes, that predispose to the development of multiple intracranial (~8%), spinal (~75%) and peripheral schwannomas (~90%)

Schwannomas might change into MPNST or induce other anaplastic tumor such as craniopharyngioma or meningioma

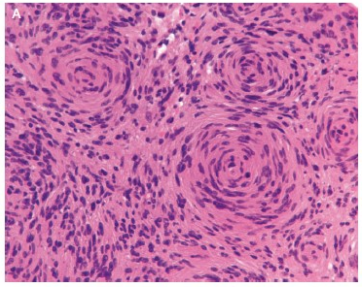
SWN is a rare disorder, estimated incidence of 1/40,000 to 1/60,000

Schwannomas are composed almost exclusively of Schwann cells



classic Antoni A cellular tissue and whorl formation

(*Brain Pathology 24 (2014) 205–220*)



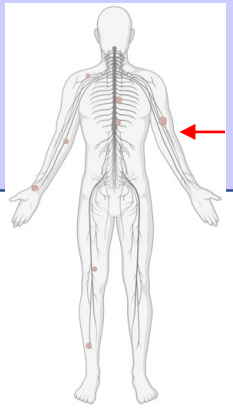
Neurology®

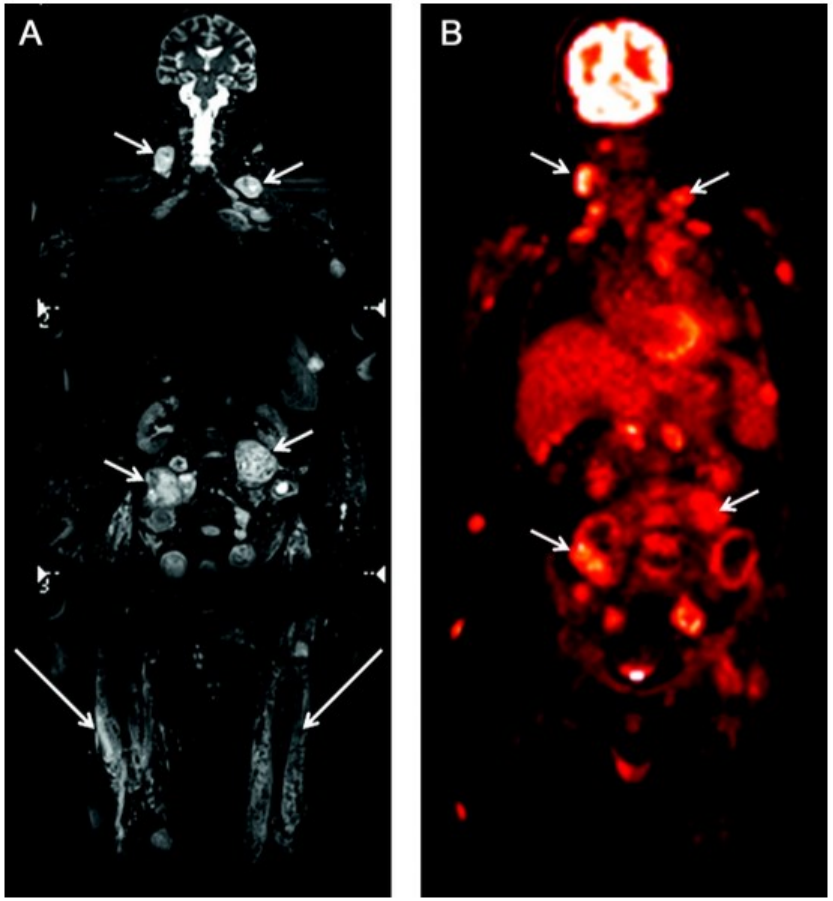
Whole-body imaging in schwannomatosis

Avneesh Chhabra, MD, and Jaishri Blakely, MD | AUTHORS INFO & AFFILIATIONS

June 7, 2011 issue • 76 (23) 2035 • https://doi.org/10.1212/WNL.0b013e31821e55b0

The **most common symptom** reported by SWN patients is pain, either local or diffuse





Coronal whole-body MRI (A) showing numerous mass lesions (short arrows) in a patient with schwannomatosis. FDG-PET (B) also shows the lesions, but MRI better depicts anatomy and displays lesions of any etiology regardless of FDG avidity. Muscle denervation (large arrows) is seen as edema-like T2 hyperintensity without perifascial edema on MRI.

Genetics in Medicine (2022) 24, 1967–1977

ELSEVIER

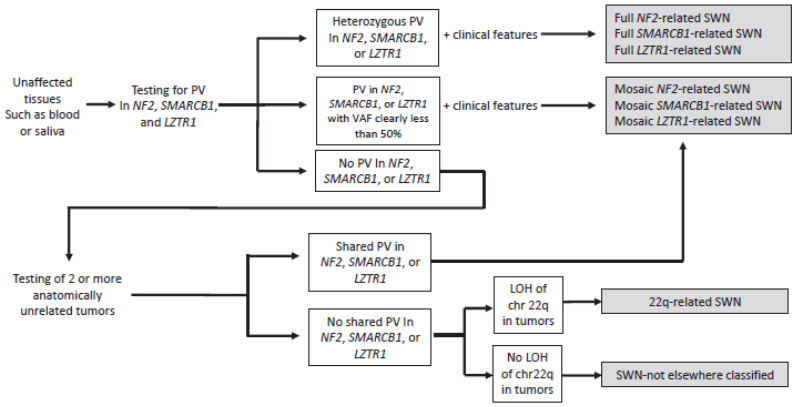
Genetics in Medicine

www.journals.elsevier.com/genetics-in-medicine

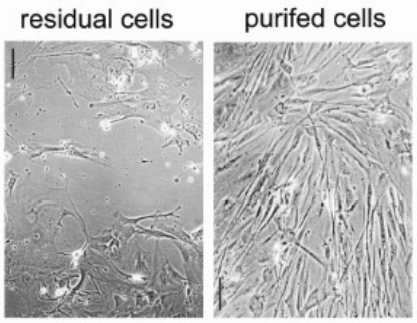
ARTICLE

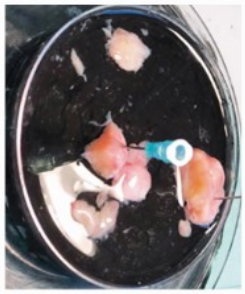
Updated diagnostic criteria and nomenclature for neurofibromatosis type 2 and schwannomatosis: An international consensus recommendation

Scott R. Plotkin[1,*], Ludwine Messiaen[2], Eric Legius[3], Patrice Pancza[4], Robert A. Avery[5], Jaishri O. Blakeley[6], Dusica Babovic-Vuksanovic[7], Rosalie Ferner[8], Michael J. Fisher[9], Jan M. Friedman[10], Marco Giovannini[11], David H. Gutmann[12], Clemens Oliver Hanemann[13], Michel Kalamarides[14], Hildegard Kehrer-Sawatzki[15], Bruce R. Korf[2], Victor-Felix Mautner[16], Mia MacCollin[17], Laura Papi[18], Katherine A. Rauen[19], Vincent Riccardi[20], Elizabeth Schorry[21], Miriam J. Smith[22], Anat Stemmer-Rachamimov[23], David A. Stevenson[24], Nicole J. Ullrich[25], David Viskochil[26], Katharina Wimmer[27], Kaleb Yohay[28], International Consensus Group on Neurofibromatosis Diagnostic Criteria (I-NF-DC), Susan M. Huson[29], Pierre Wolkenstein[30], D. Gareth Evans[22]

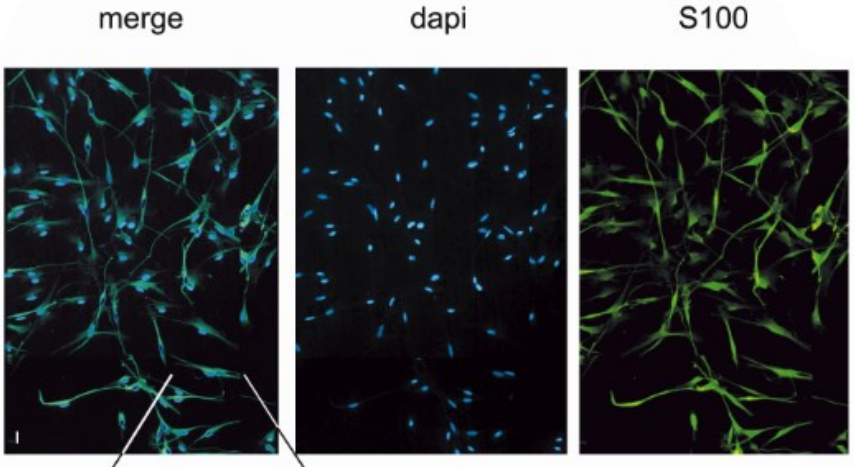


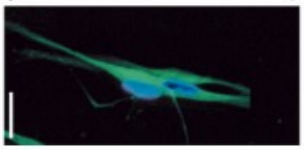
- NF2-related schwannomatosis (first NF2 or SWN type II)
- SMARCB1-related schwannomatosis (first SWN type III)
- LZTR1-related schwannomatosis (first SWN type III)
- 22q-related schwannomatosis (NO germline mutation)

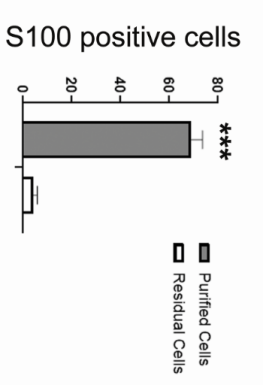

residual cells
purifed cells

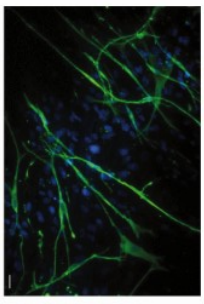


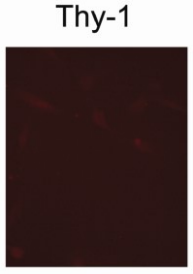
1wk

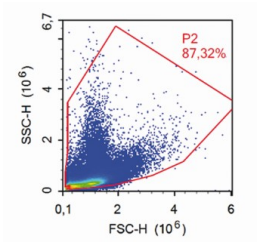

merge
dapi
S100



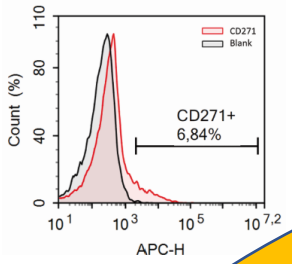

S100 positive cells
0
20
40
60
80
***
Purified Cells
Residual Cells


primary naive hSCs
S100
dapi


Thy-1

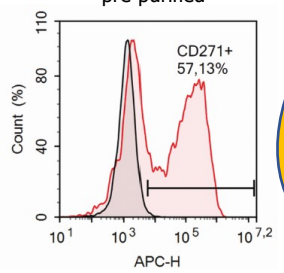


post-digestion

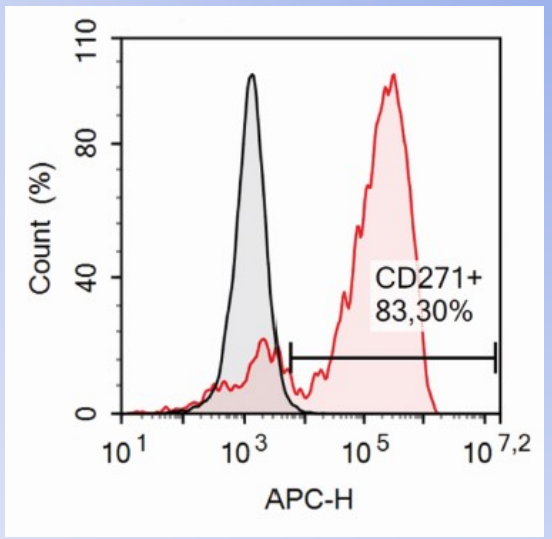


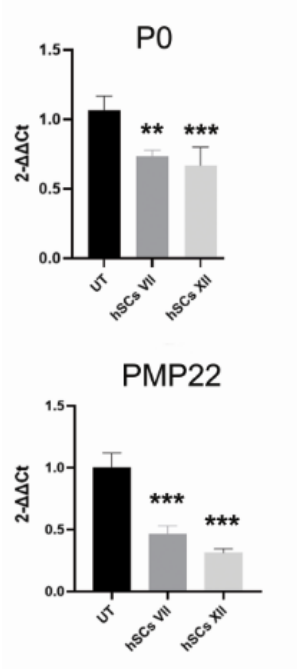
1wk

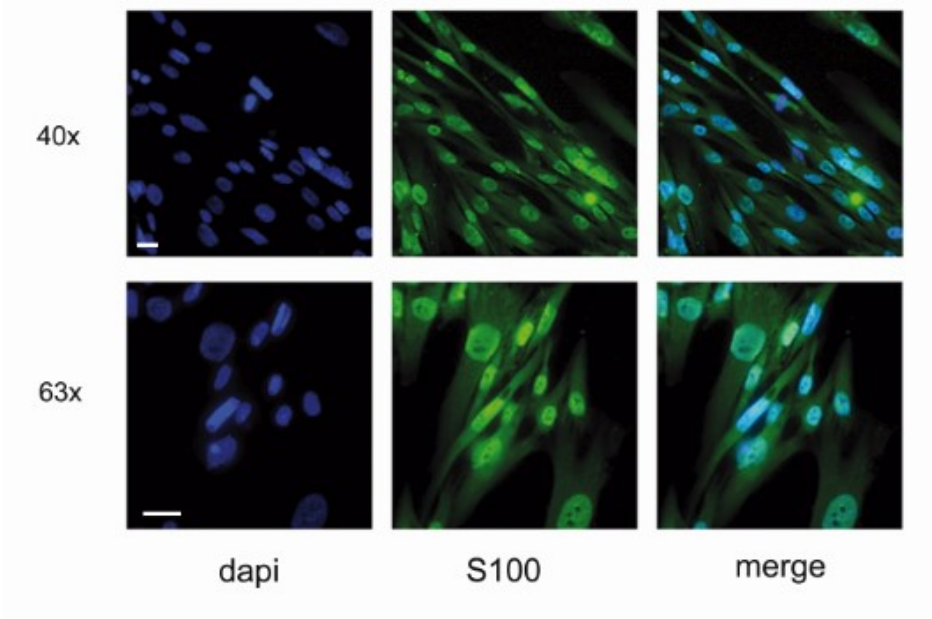
pre-purified



purified hSCs

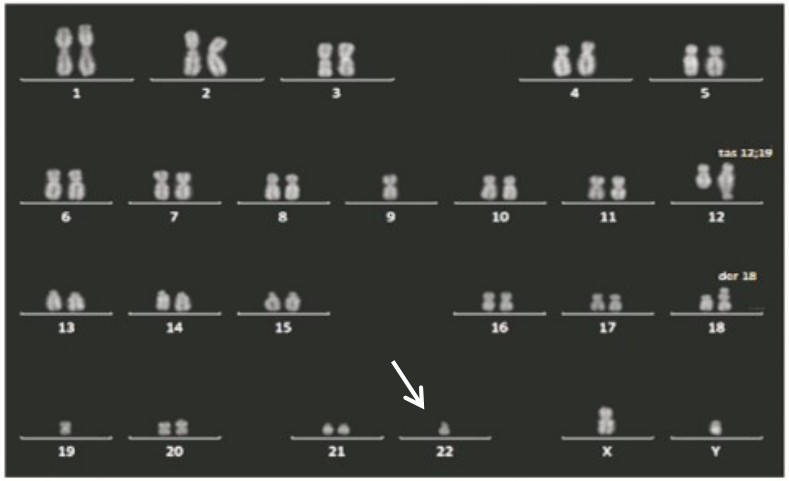


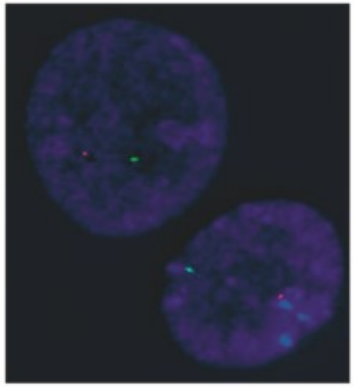

P0
2-ΔΔCt
1.5
1.0
0.5
0.0
**
***
UT
hSCs VII
hSCs XII
PMP22
2-ΔΔCt
1.5
1.0
0.5
0.0
***
***
UT
hSCs VII
hSCs XII


40x
63x
dapi
S100
merge

*Copy Variation Numb*er….22q loss !!!

	Variant	Effect on protein	VAF variant allele frequency	ACMG criteria	Reported
LZTR1	NM_006767.4:c.27dup Exon 1	p.(Gln10Alafs*24) LoF	64%	Class 5 pathogenic (PVS1vs, PM2sup, PP5s)	ClinVar 24362817 32623905
NF2	NM_000268.4:c.448-21_452del Exon 5	p.(?) LoF	32%	Class 4 likely pathogenic (PVS1s, PM2sup	-





Two cell sub-lines: one hypodiploid 45,XY,-22
one hypotetraploid 80-82 chrs

Summary

- The **hSC line obtained is an excellent *in vitro* tool of SWN**, for further studies: e.g. wide genome screening, genomic editing, etc.
- The hSC line obtained is unique, bearing rare NF2/LTZR1 mutations
- The characterization of hSCs from patients with different genotype-phenotype allows the identification of other molecular pathw and/or genes of SWN
- The method is replicable and may be relevant for precision medicine and patient-tailored therapies

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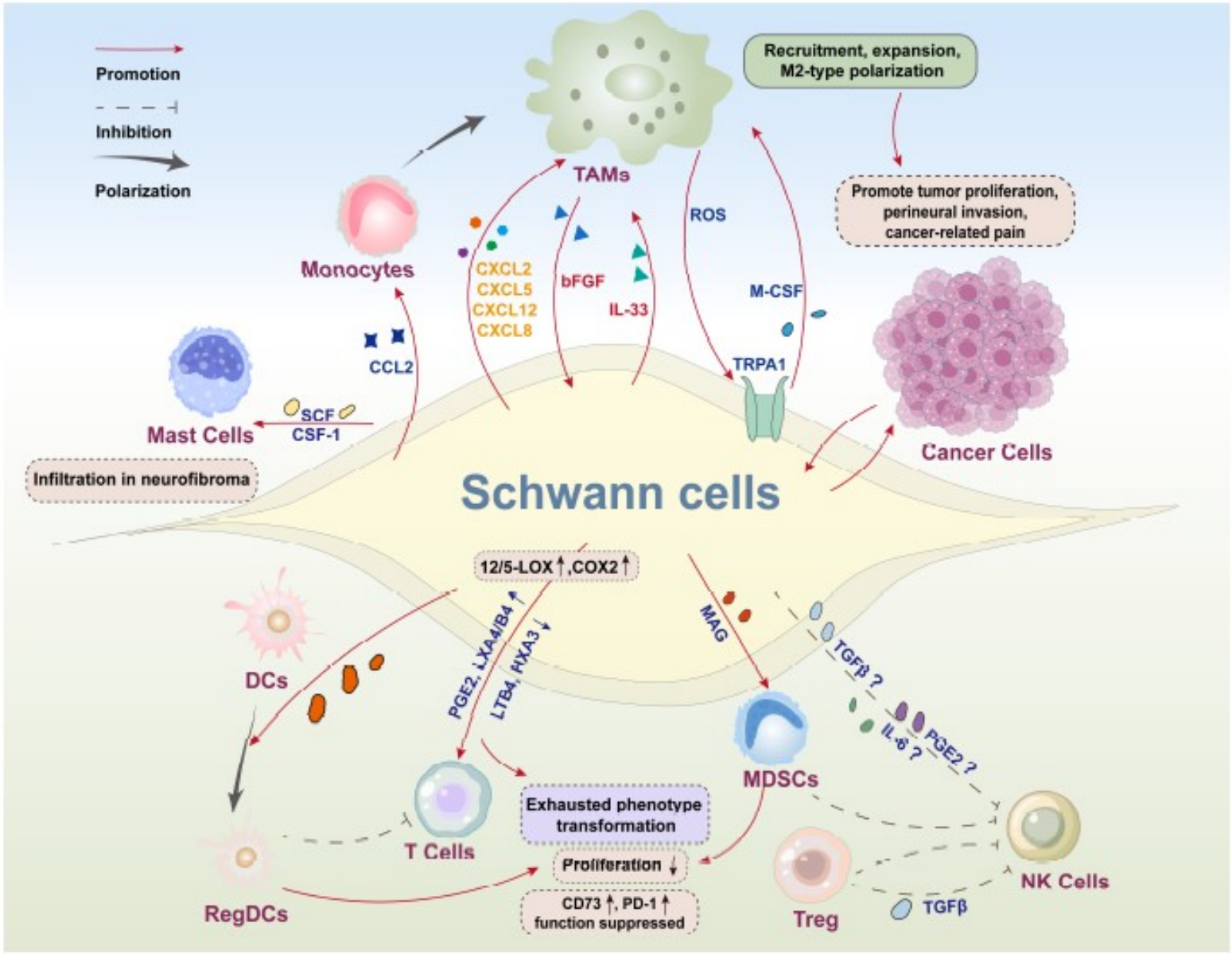
Research article

Typical NF2 and LTZR1 mutations are retained in an immortalized human schwann cell model of schwannomatosis

Valentina Melfi [a,1], Tasnim Mohamed [a,1], Alessandra Colciago [a], Alessandra Fasciani [b], Raffaele De Francesco [a,c], Daniela Bettio [d], Cristina Cerqua [d], Francesca Boaretto [d], Elisabetta Basso [e], Stefano Ferraresi [e], Marco Montini [f], Marica Eoli [g], Laura Papi [f], Eva Trevisson [d,**], Valerio Magnaghi [a,*]

role of SCs in tumor-immune microenvironment



The Emerging Role of Schwann Cells in the Tumor Immune Microenvironment and Its Potential Clinical Application

Shan Zhang [1,†], Jing Chen [1,†], Fanjun Cheng [1,*] and Fang Zheng [2,*]

Int. J. Mol. Sci. **2024**, *25*, 13722. https://doi.org/10.3390/ijms252413722