SIMPOSIO AIRO-AIRB

MODELLI MOLECOLARI DI DANNO E RIPARO CELLULARE NELLE COMPLICANZE MIDOLLARI IN RADIOTERAPIA

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Spinal cord is one of the most important dose-limiting normal tissues in clinical radiotherapy

Pathogenesis of radiation myelopathy

Dual mechanisms for the pathogenesis of radiation myelopathy have been proposed depending on whether the major targets of irradiation are:

- glial cells, especially oligodendrocytes (**glial theory**)

- vascular endothelium (**vascular hypothesis**)

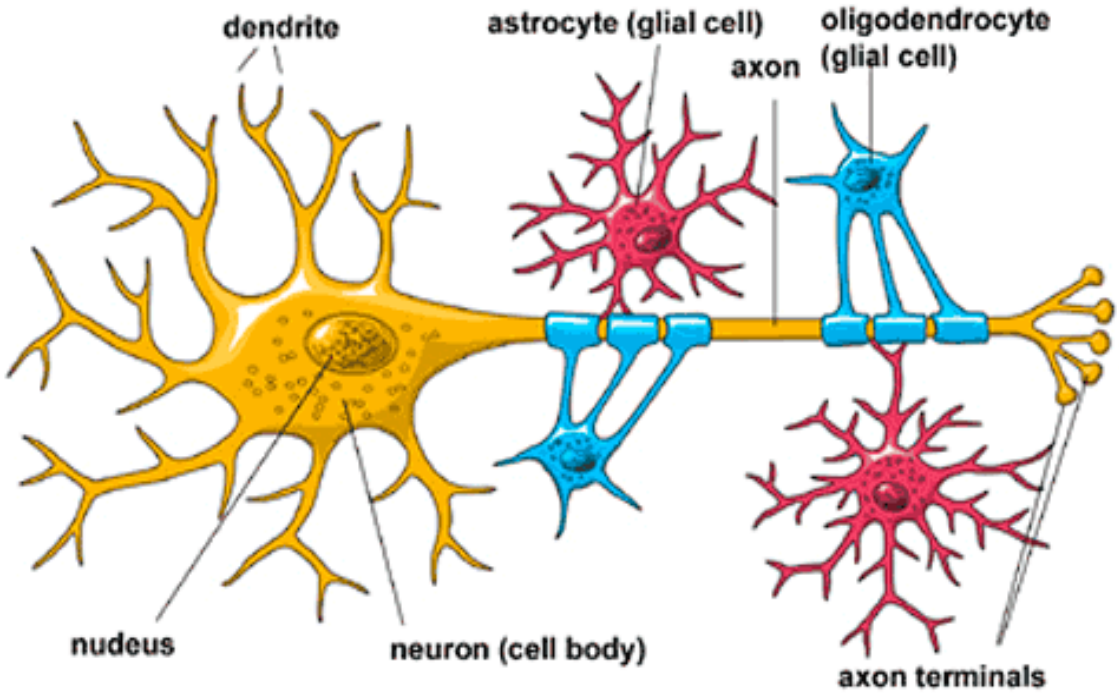
According to the vascular hypothesis, the primary changes are vascular lesions and parenchymal changes are induced secondarily.

A combination of both mechanisms is also proposed

Okada S., Okeda R. Neurophatology 2001

Glial theory

In the glial theory, **radiation induces DNA damage in oligodendrocytes**, resulting in cell death at mitosis (reproductive cell death), and a decrease in the number of oligodendrocytes beyond the capacity of progenitor cells to repopulate causes the destruction of the white matter.



Oligodendrocytes

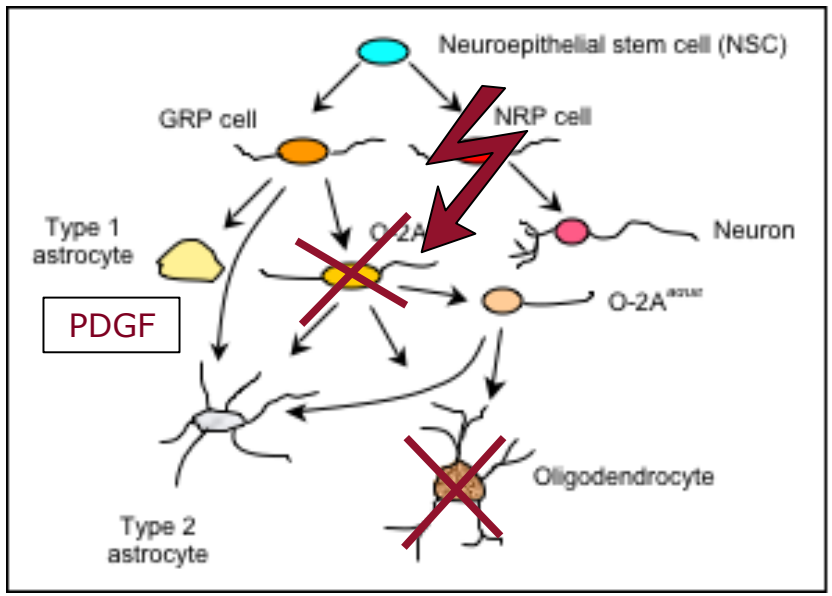
The mode of radiation-induced cell death is by apoptosis.

Irradiated oligodendrocytes have been shown to undergo apoptosis both *in vitro* and *in vivo*.

Oligodendrocytes are delivered from **oligodendrocyte- type 2 astrocyte (O-2 A)** progenitor cells in the presence of soluble mediators, such as platelet-derived growth factors (**PDGF**) released by type 1 astrocytes.

These O-2 A progenitor cells are therefore a possible target of radiation, and their damage may result in the depletion of oligodendrocytes, followed by myelin breakdown.

GRP = glial restricted precursor cells



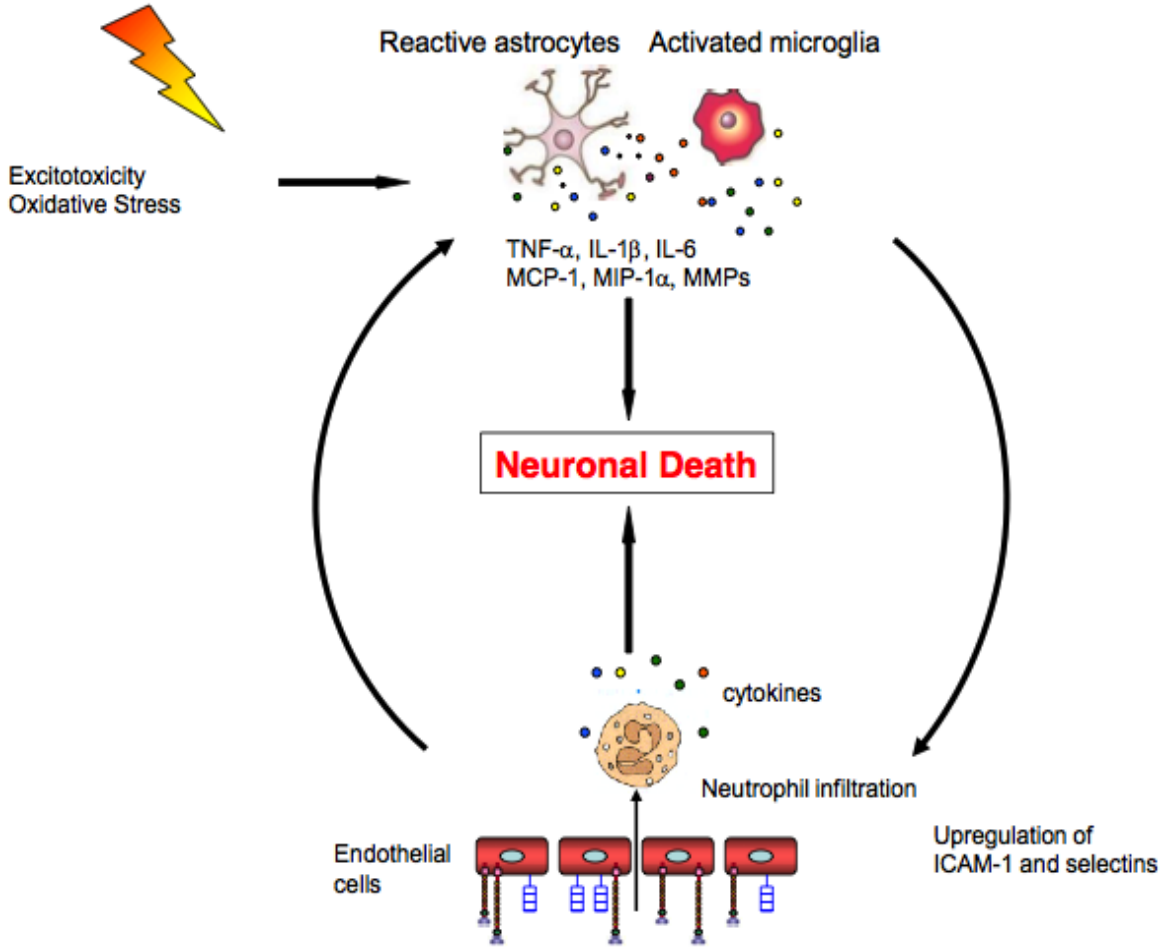
NRP = neuron restricted precursor cells

Noble M. et al. Dev. Biol. 2004

Astrocytes and microglia

Astrocytes and microglia release and respond to cytokines, which are important for the regulation of normal CNS functions or for responses to various pathological conditions.

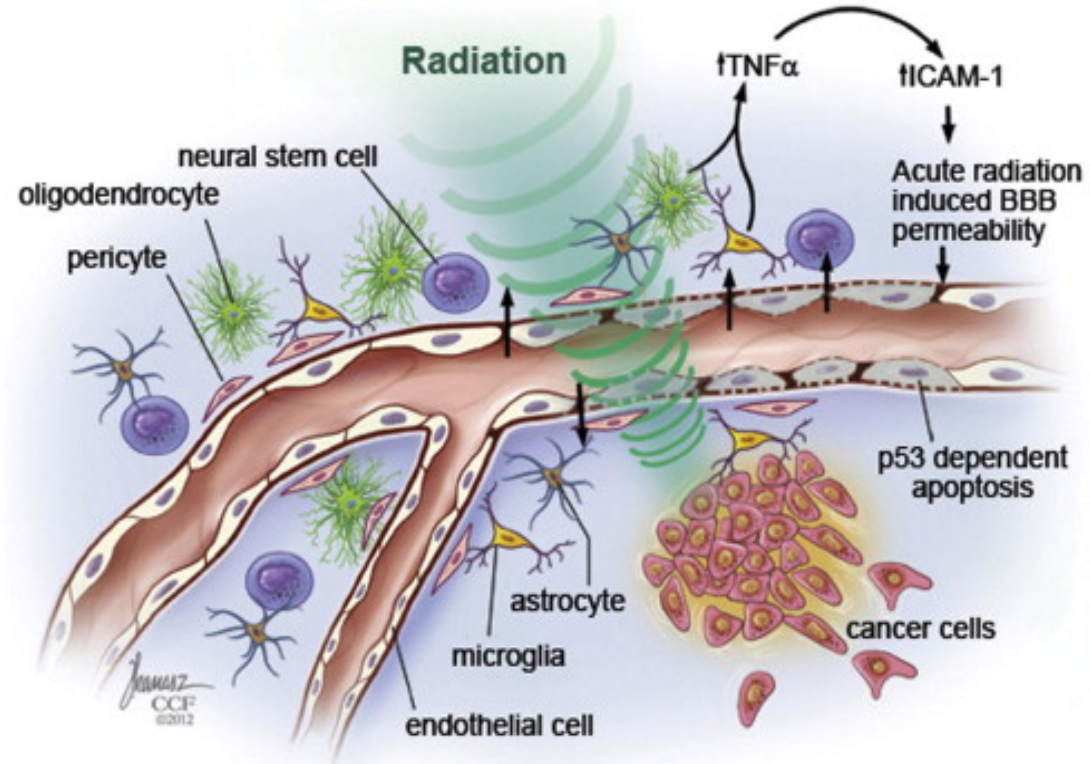
It is very likely that these cytokines influence oligodendrocytes and vascular endothelium, which are supposed to be the main target cells in radiation myelopathy.



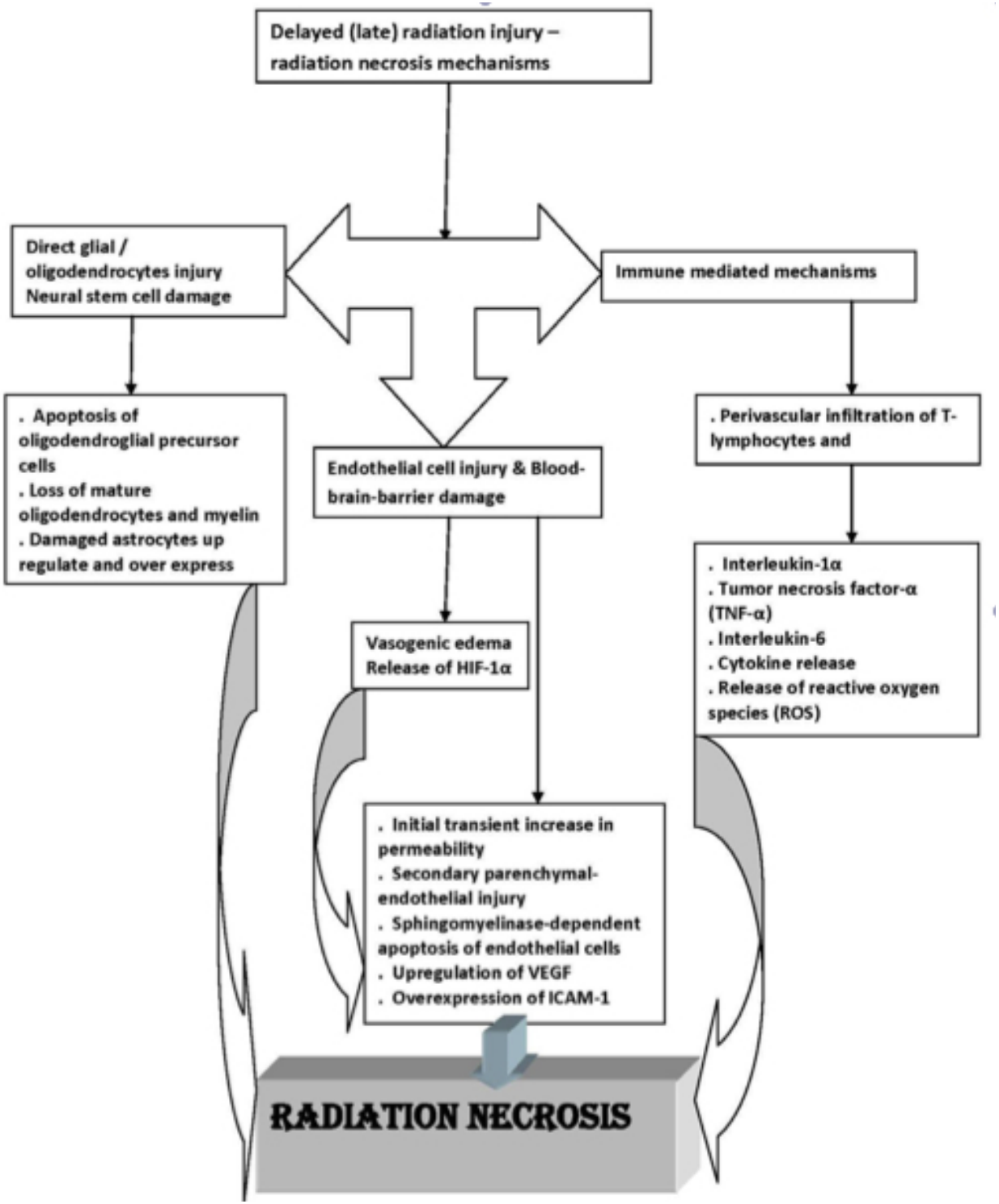
Vascular Hypothesis

Blood vessels are the main target of irradiation, and circulation disturbance following vascular injury secondarily induces white matter lesions.

Although the functional disturbance of vasomotor nerves resulting from stimulation or from obstructive endoarteritis by irradiation have been considered as the mechanisms, many investigators attached importance to **vascular hyperpermeability**, among various radiation-induced vascular lesions, as an **essential cause of radiation myelopathy**

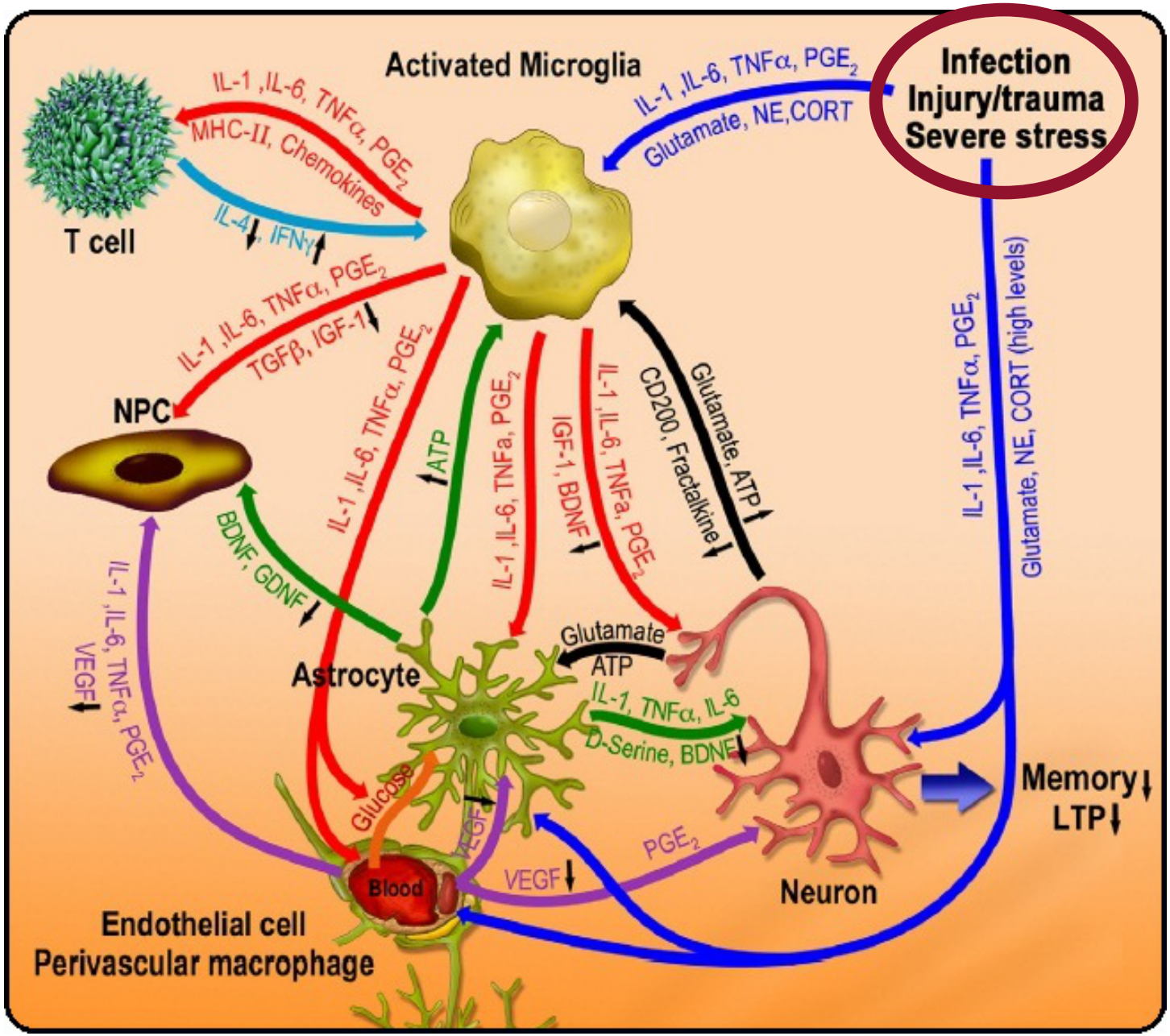


Rahmathulla G. et al. J.Clin.Neurosc. 2013



Rahmathulla G. et al. J.Clin.Neurosc. 2013

Cytokines


Activated Microglia
Infection
Injury/trauma
Severe stress
IL-1 ,IL-6, TNFα, PGE2
MHC-II, Chemokines
IL-4, IFNγ
T cell
IL-1, IL-6, TNFα, PGE2
Glutamate, NE,CORT
IL-1 ,IL-6, TNFα, PGE2
TGFβ, IGF-1
NPC
IL-1 ,IL-6, TNFα, PGE2
ATP
IL-1 ,IL-6, TNFa, PGE2
IGF-1, BDNF
IL-1 ,IL-6, TNFa, PGE2
CD200, Fractalkine
Glutamate, ATP
IL-1 ,IL-6, TNFα, PGE2
Glutamate, NE, CORT (high levels)
BDNF, GDNF
IL-1 ,IL-6, TNFα, PGE2
VEGF
Astrocyte
Glutamate
ATP
IL-1, TNFα, IL-6
D-Serine, BDNF
Glucose
VEGF
PGE2
VEGF
Blood
Endothelial cell
Perivascular macrophage
Neuron
Memory
LTP

Basic Fibroblast Growth Factor (bFGF)

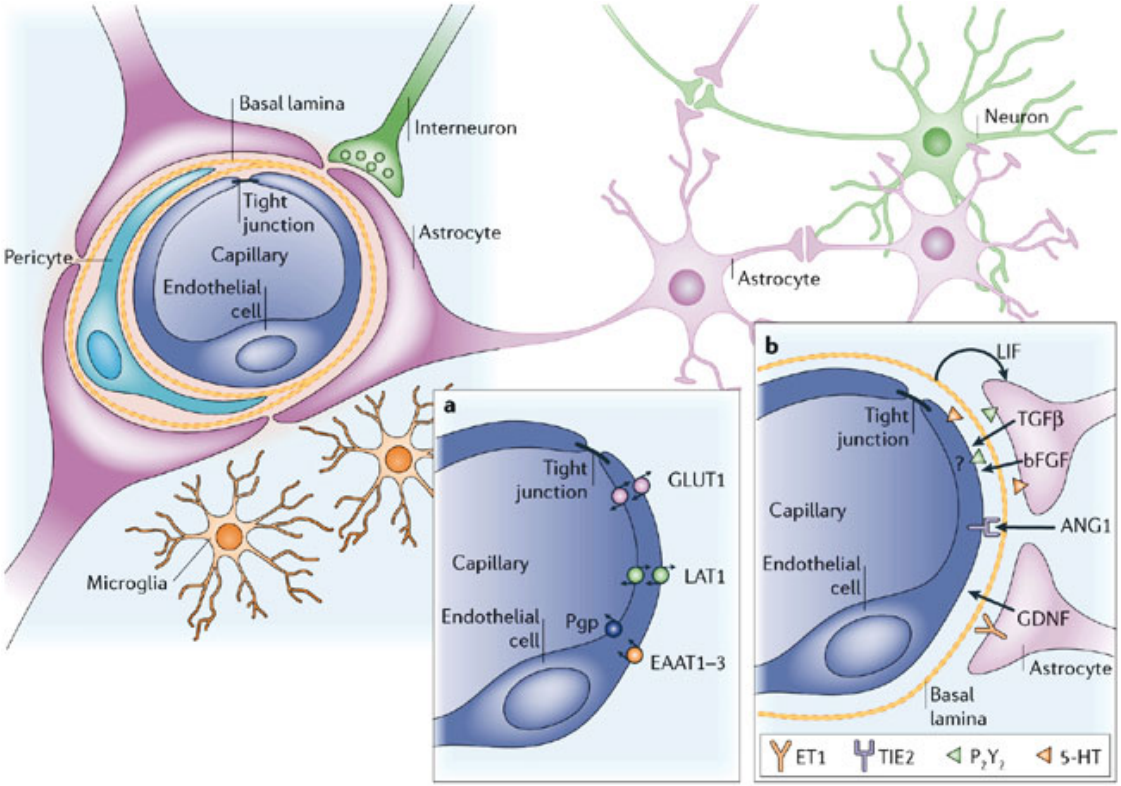
Basic FGF participates in the proliferation and differentiation of O-2A progenitor cells and has a mitogenic effect on immature oligodendrocytes.

bFGF is also known to possess angiogenic action.

Noel Fet al. **Radiat Res** 1997

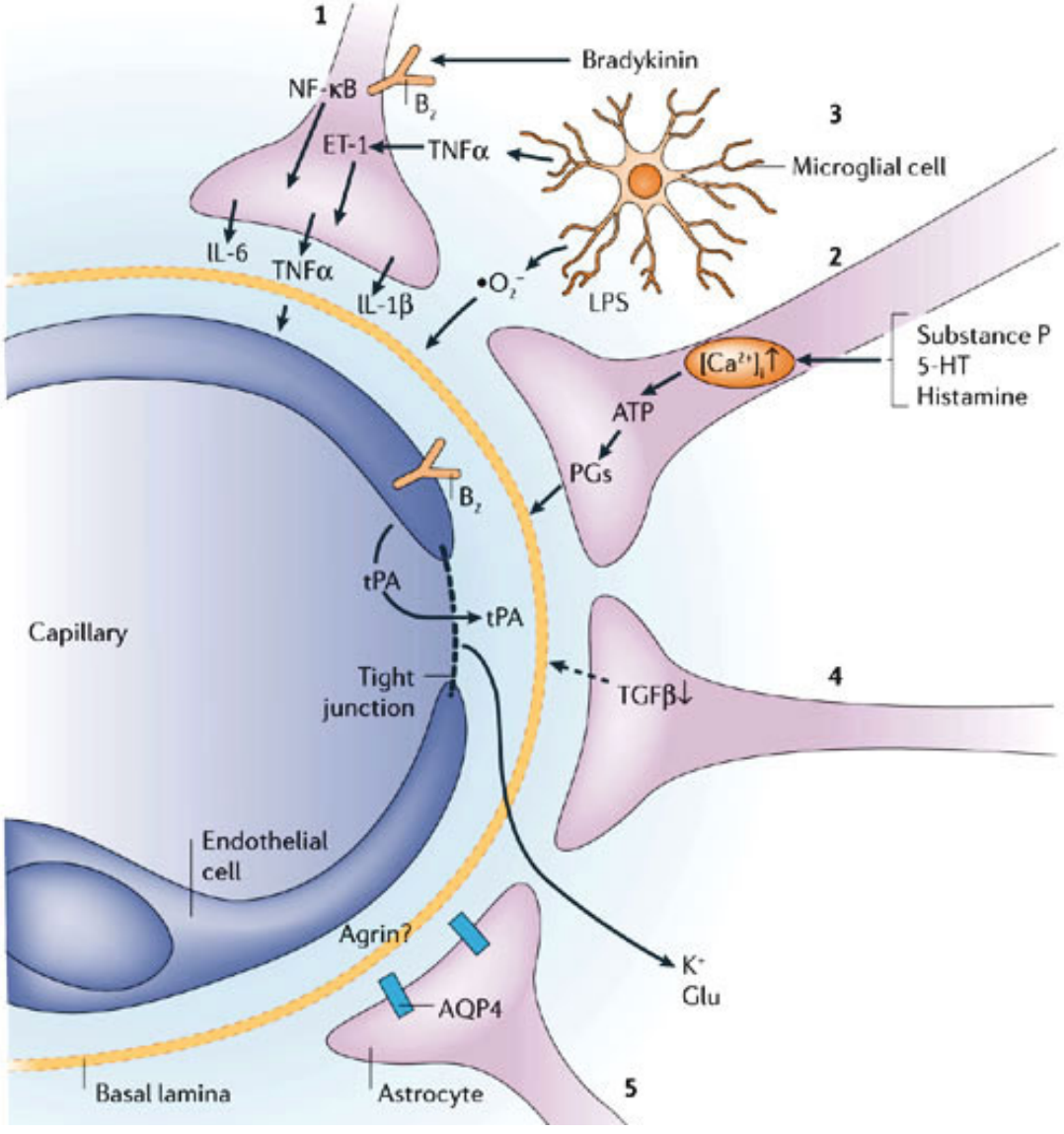
X-ray induced reduction of bFGF expression in primary astrocyte culture.

↳↓ bFGF may accelerate the depletion of O-2A progenitor cells and oligodendrocytes.

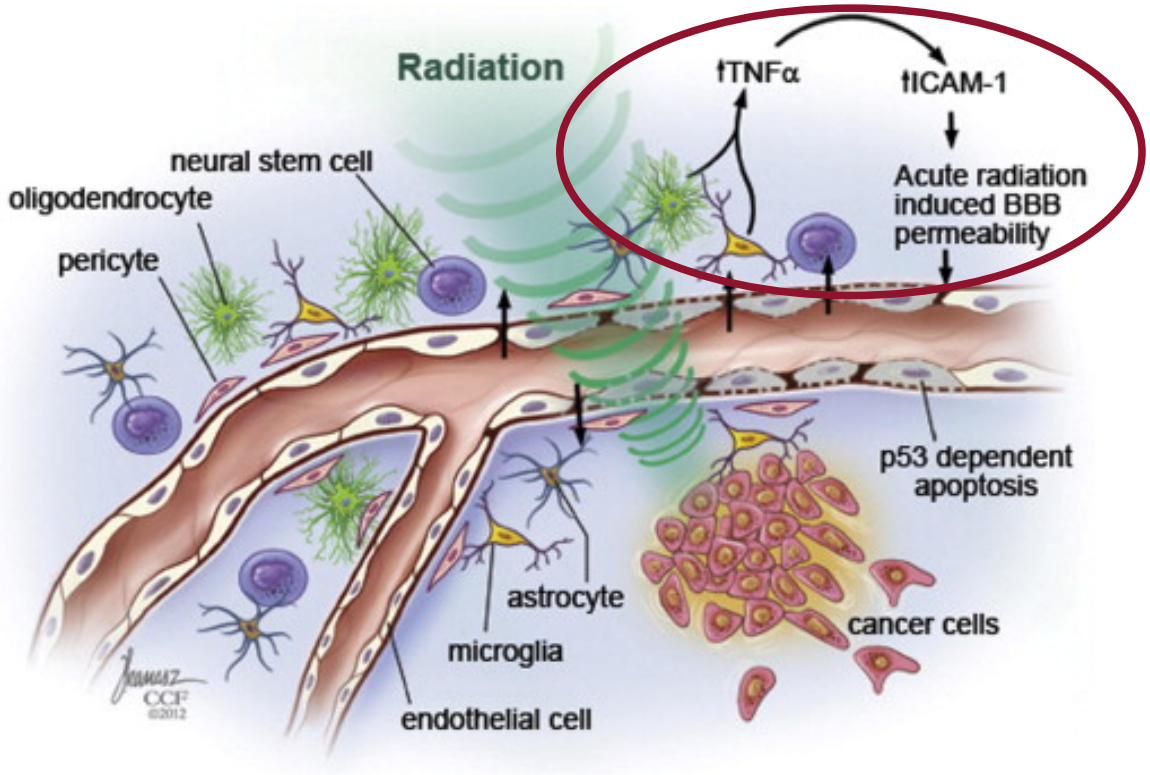


TNF-α and IL-6

TNF-α induces the mitosis of astrocytes directly or through the production of **IL-6** and is cytotoxic to oligodendrocytes.



Several features of radiation-induced CNS injury, such as astrocyte proliferation, myelin breakdown, and injury of oligodendrocytes and blood vessels, may be associated with elevated TNF production.



Rahmathulla G. et al. J.Clin.Neurosc. 2013

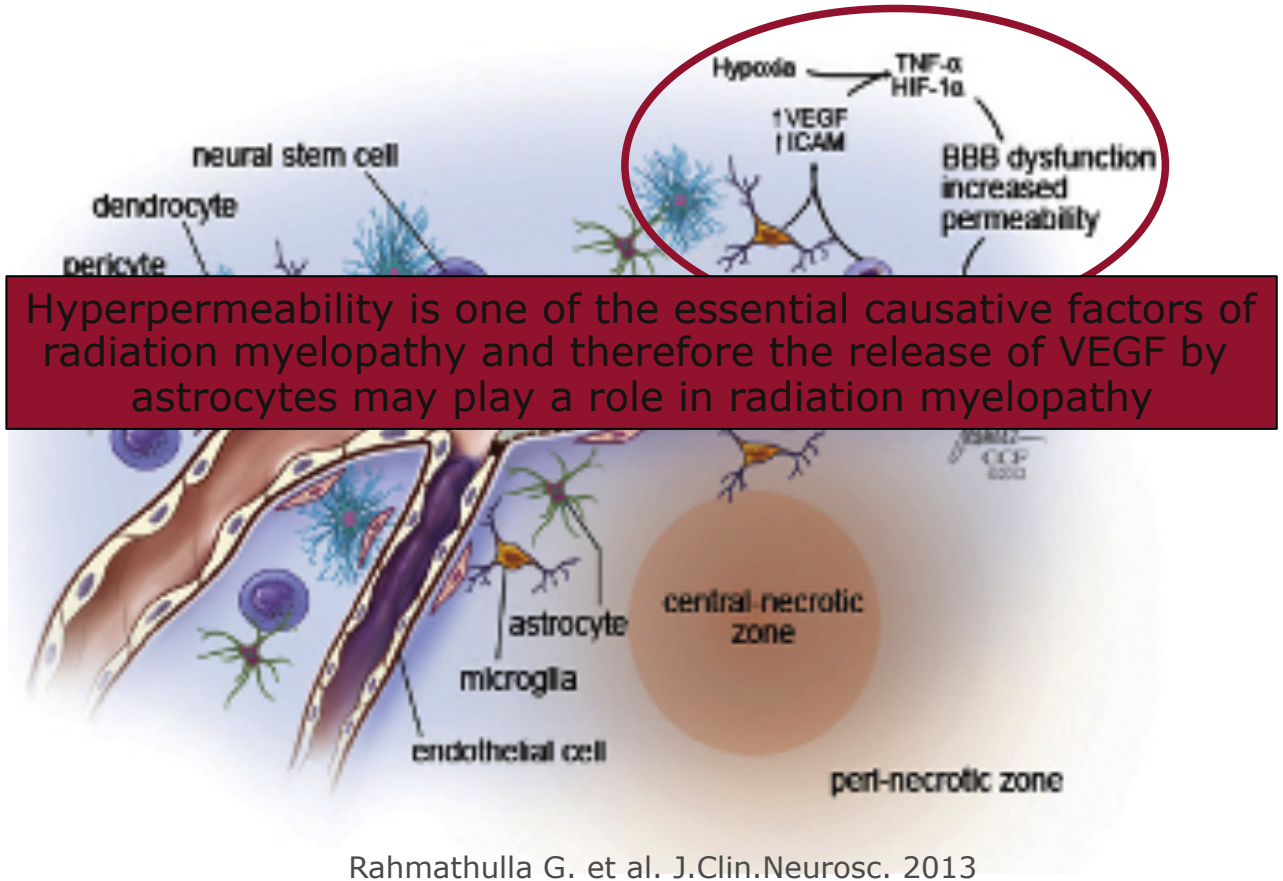
Le J et al. Lab Invest 1987
Robbins DS et al. J Immunol 1987
Selmaj KW et al.Anal Neurol 1988
Brosnan CF et al. J Neuroimmunol 1988
Lieberman A et al. Proc Natl Acad Sci USA 1989
Dickson DW et al. Lab Invest 1991
Selmaji KW et al. J Immunol 1990
Sawada M et al. Brain Res 1989

VEGF

Upregulation of VEGF in astrocytes of white matter is accompanying by disruption of the blood–spinal cord barrier. VEGF is produced in reactive astrocytes via upregulation of HIF-1a in the necrotic core and perilesional region.

VEGF acts on microvessel endothelium to induce hyperpermeability.

Nordal RA et al. Clin Cancer Res 2004



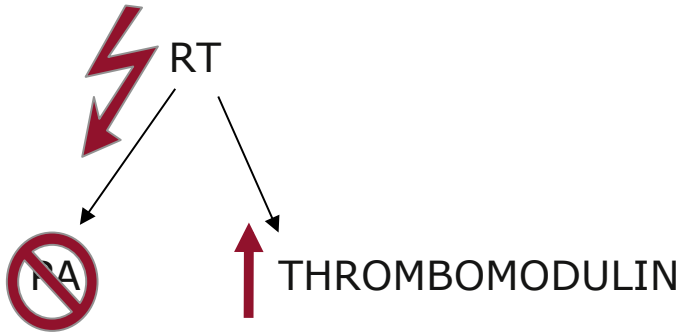
Hyperpermeability is one of the essential causative factors of radiation myelopathy and therefore the release of VEGF by astrocytes may play a role in radiation myelopathy

Rahmathulla G. et al. J.Clin.Neurosc. 2013

Plasmingen Activator (PA) and Thrombomodulin

Radiation also induces changes in the fibrinolytic and coagulation system.

Fibrinolytic activity is **significantly decreased** after radiotherapy in the endothelium



Radiation-induced defects in vascular fibrinolytic activity, together with radiation-induced hyperpermeability, results in the accumulation of extravasated fibrin and, finally, fibrosis develops.

Okada S., Okeda R. Neurophatology 2001

Pre-clinical studies

Reduction in the number of oligodendrocytes was observed as early as 24 hours after X-ray irradiation

Primary cultured adult neural stem cells, Schwann cells and olfactory ensheathing cells have been transplanted into the radiation-injured spinal cord.

Rezvani M et al. Radiat Res. 2001
Mothe AJ, Tator CH Exp Neurol. 2008
Chari DM et al. Exp Neurol. 2006
Lankford Kl et al. Glia 2008
Monje Ml et al. Nat Med.2002

JRRD Volume 45, Number 1, 2008
Pages 141–152
Journal of Rehabilitation Research & Development

Potential of olfactory ensheathing cells for cell-based therapy in spinal cord injury

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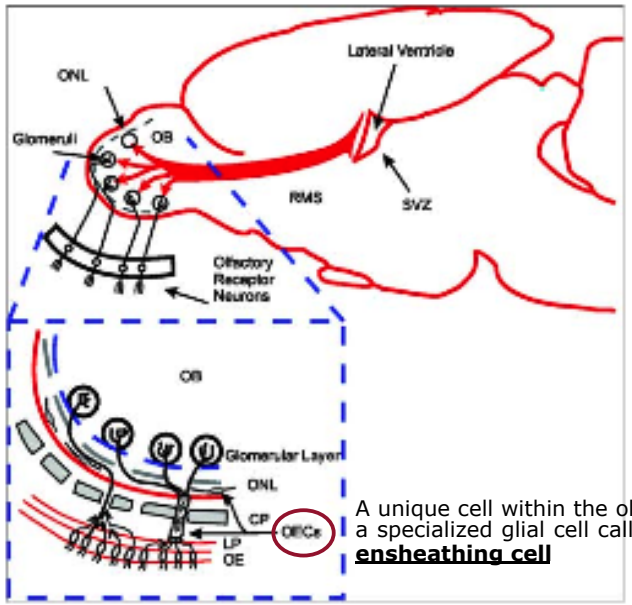
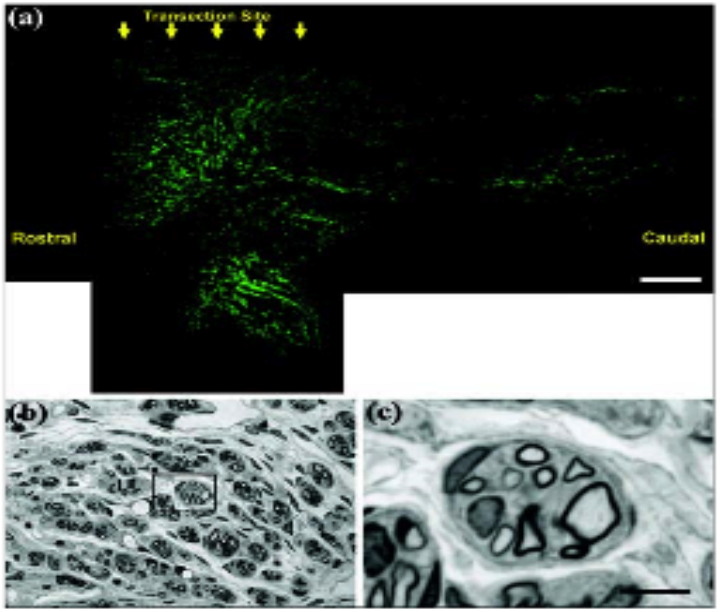
[1]Neuroscience Research Center, Department of Veterans Affairs Connecticut Healthcare System, West Haven, CT; [2]Department of Neurology and Center for Neuroscience and Regeneration Research, Yale University School of Medicine, New Haven, CT; [3]Department of Plastic, Hand, and Reconstructive Surgery, Hannover Medical School, Hannover, Germany



A unique cell within the olfactory system is a specialized glial cell called the **olfactory ensheathing cell**

OECs' unique property of bridging the peripheral nervous system and CNS and providing a channel for peripheral axonal growth into the CNS led to the suggestion that these cells may be therapeutic if transplanted into transected spinal cord tracts.



In experimental SCI models transplantation of OECs within a week after injury can improve functional recovery. Some functional improvement was reported when OECs were transplanted several months after injury. While the precise mechanisms for the therapeutic effects of OECs are not fully understood, several studies indicate that facilitation of axonal regrowth, remyelination, and neuroprotection may contribute.

Adult neural stem cells, Schwann cells and olfactory ensheathing cells

have limited capacity in producing oligodendrocytes,
the primary cell type that is damaged in radiation injury

Oligodendrocyte precursor cells (OPCs), which can be isolated from brain tissues, offer an alternative source. Nevertheless, they need to be derived from brain tissues.

Zhang SC et al. J Neurocytol 1998
Avellana-Adalid V et al. J Neurosci Res 1996

Embryonic stem cells (ESCs)

may become a suitable candidate because they are genetically normal, pluripotent, and capable of indefinite replication, and they can be differentiated to all the cell types in the body, including OPCs.

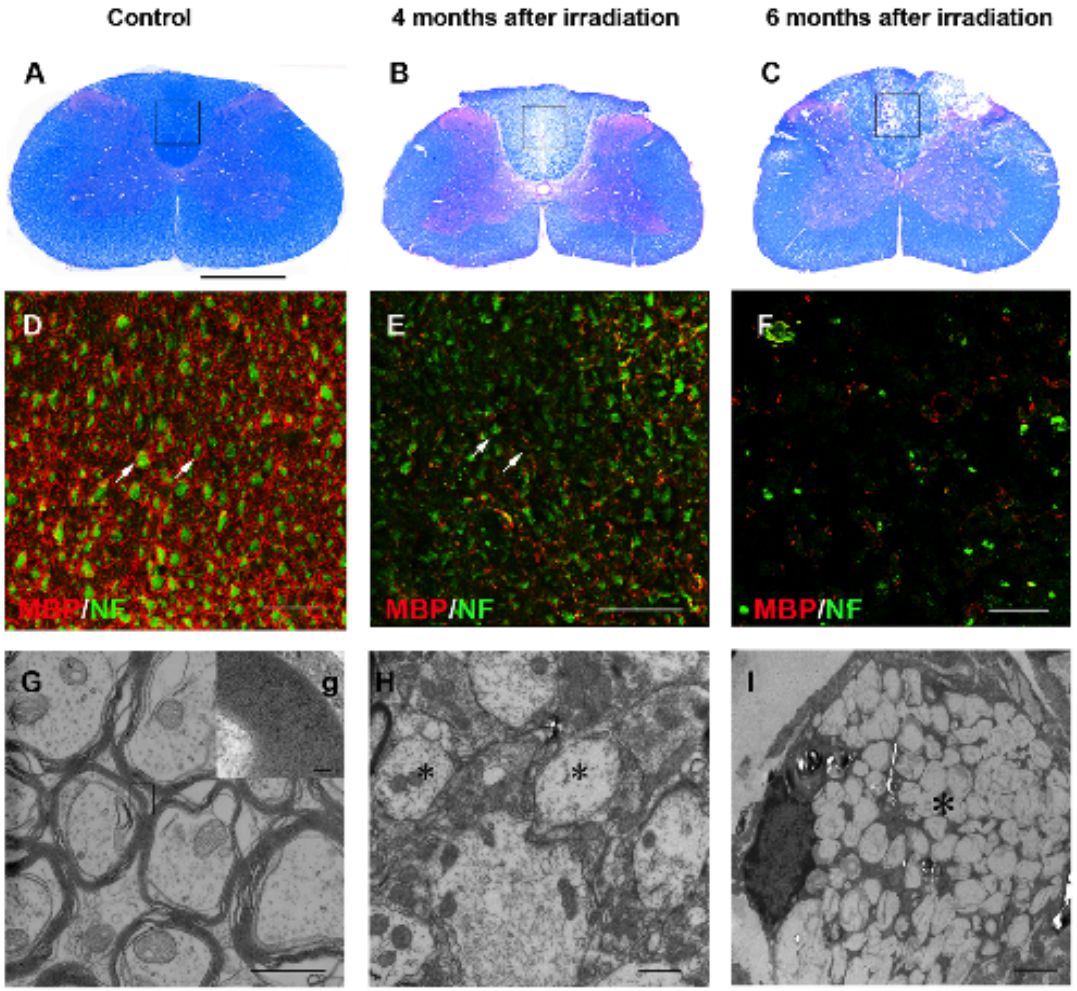
OPEN ACCESS Freely available online

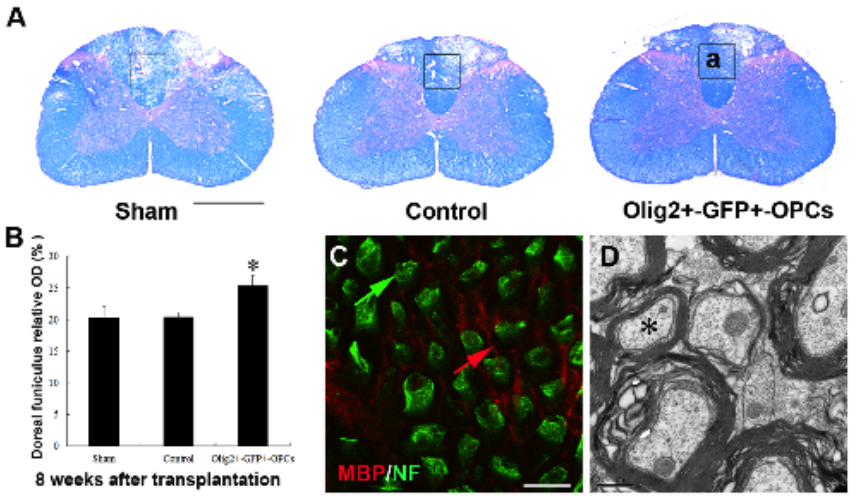
PLOS ONE

Transplantation of Oligodendrocyte Precursor Cells Improves Locomotion Deficits in Rats with Spinal Cord Irradiation Injury

Yan Sun[1☯], Chong-Chong Xu[1☯], Jin Li[2], Xi-Yin Guan[3], Lu Gao[1], Li-Xiang Ma[1], Rui-Xi Li[1], Yu-Wen Peng[1*], Guo-Pei Zhu[3*]

Female Wisteria adult rats' cervical spinal cords were irradiated (22 Gy)





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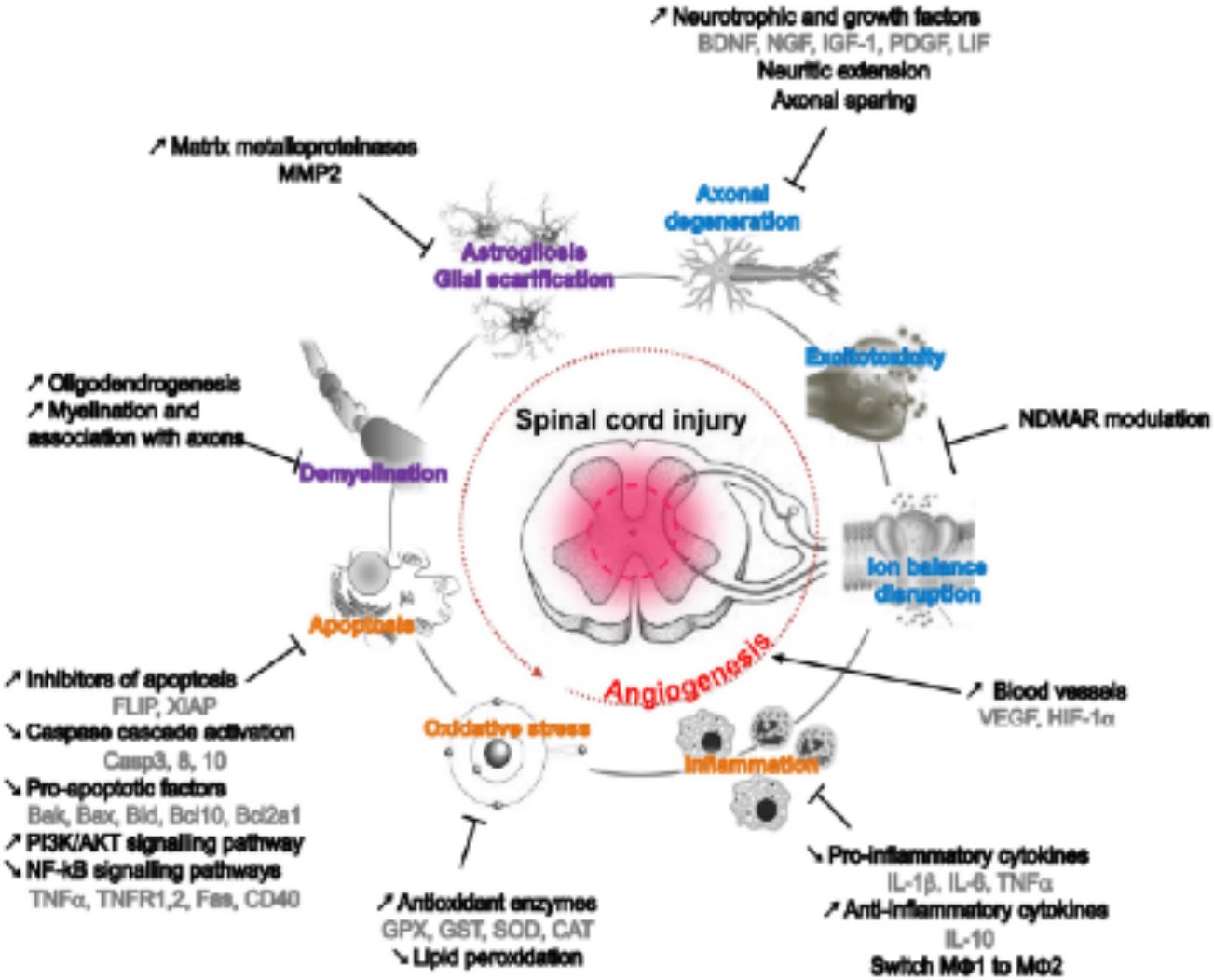
Spinal Cord Injuries – How Could Adult Mesenchymal and Neural Crest Stem Cells Take Up the Challenge?

Virginie Neirinckx[1], Dorothée Cantinieaux[1], Cécile Coste[1], Bernard Rogister[1,2,3], Rachelle Franzen[1], and Sabine Wislet-Gendebien[1].



Adult MSCs/NCSCs properties and the different ways they can contribute to functional recovery after spinal cord injury.

Conclusions

Currently, there is no clinically established strategy for prevention of Radiation Myelophaty, the endpoint of complex tissue alterations developing during a long latent period.

It has been hypothesized that therapeutic intervention in the asymptomatic phase might inhibit the pathologic cascade.

With increasing emphasis on accelerating SCI translational research, the issue thus becomes one of striking a balance between ideal versus optimized preclinical progressions and timely bench-to-bedside translations.