Redox Modulation of Cellular Function: Cellular and Mechanistic Analyses

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O-2A/OPCs

Oligodendrocytes

Type-2 astrocytes

Type-1 astrocytes

GRP cells

NEP cells

NRP cells

Neurons

Adult O-2A/OPCs
Myelination disorders: the largest category of neurological disorder

- thyroid hormone deficiency, iron deficiency, selenium deficiency, nutritional deficiency
  - fetal alcohol syndrome, fetal cocaine syndrome
  - traumatic injury, multiple sclerosis
  - stroke (lacunar infarcts)
  - leukomalacia in pre-term infants

PML - leukoencephalopathy in AIDS patients
Developmental maladies are diseases of precursor cells

- generation of specific precursor cell populations
- generation of differentiated cell types
- generation of sufficient numbers of cells
NEP

Type-1 astrocytes

GRP

Type-2 astrocytes

Oligodendrocytes

E10.5

TH, Fe

E13.5

O-2A

p1

TH, Fe

Type-1 astrocytes

Type-2 astrocytes
How do you control precursor cell fate?

Self-renewal  differentiation
Multiple signaling molecules modulate the balance between self-renewal and differentiation as in the O-2A lineage

• PDGF is sufficient to promote division and allow oligodendrocyte generation
• NT-3 and FGF enhance self-renewal
• Thyroid hormone and CNTF promote oligodendrocyte generation
• BMP-4 promotes differentiation into type-2 astrocytes
Physiology
What is redox state?

The balance between reducing and oxidizing equivalents.

Electron transfer = bioenergetics

Not all oxidation is oxidative stress
Cellular redox state modulates responsiveness to environmental signals

Being more reduced protects against cell death from cytotoxic agents and also enhances the response to cell survival signals

Critical point: The extent of redox change required to have large functional consequences is only ~15%.
Redox and cell function: Some general principles

1. Redox state controls precursor cell function.

2. Classical signaling molecules that enhance self-renewal or induce differentiation alter redox state as a necessary component of their mechanism.

3. The organism uses developmental (genetic) regulation of redox state to control precursor cell function.
Mitogens
Survival
Differentiation
Death

Reduced

Mitogens
Survival
Differentiation
Death

Oxidized
Many environmental toxicants are potent pro-oxidants
MeHg toxicity for precursor cells and oligodendrocytes is an order of magnitude lower than reported in the literature for other cells.

MTT+ Survival Curves
Environmentally relevant levels of toxicants (organic mercurials, lead, et al.) make cells more oxidized in precisely the range that alters the response to the environmental signals.

As a consequence:

- Cell division is suppressed
- Cells are made more vulnerable to inducers of cell death
Toxicant-mediated suppression of critical cell signaling functions are pathway specific - but are not toxicant-specific.
Small increases in oxidative status
(oxidized glutathione?)

EGFR
c-Met

PDGF

PDGFRα

Ras

PI3K

Raf

PDGF/PP1/PP2 Degradation

PI3K

NT-3

TrkC

Ras

PI3K

Akt

Mek 1/2

IKK

Erk 1/2

NF-κB

IkB/NF-κB

Elk 1

NF-κB

SRE

NF-κB response
Low-level MeHg exposure reduces RTK levels in vivo in a pathway-specific and region-specific manner.
Strain-specific vulnerability to toxicants may be redox-dependent
The CNS of SJL mice has lower levels of c-Cbl targeted RTKs than do CBA mice.
Some thoughts for consideration

- Reconciling the diverse data sets
- The importance of altered redox status
- The cerebellum as a target
- C-Met as a target of the redox/Fyn/c-Cbl pathway
- Effects of environmental toxicants on the developing CNS
- Organic mercurials vs. other toxicants or physiological stressors
- The relationship between susceptibility and outcome of exposure to physiological stressors (i.e., gene-environment interactions)
- Intervention strategies: Prevention, Repair, Re-configuring, Behavioral Adaptation
Precursor cells that are more reduced when isolated from the animal undergo more self-renewal in vitro.
Cell-extrinsic signaling molecules cause alterations in intracellular redox state.
Redox state modulation is a necessary component of the action of signaling molecules that alter the balance between self-renewal and differentiation.
Cortical O-2A/OPCs undergo more self-renewal and generate fewer oligodendrocytes than do optic nerve-derived O-2A/OPCs.
The redox state of freshly isolated O-2A/OPCs is in agreement with their self-renewal potential. In other words, redox modulation again appears to be part of in vivo regulation.
Signal A → **Redox State** → Altered Cell Behavior

Signal B → **Redox State**

Signal C → **Redox State**

Signal D → **Redox State**
Some relevant publications:


