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Review

Redox-regulated fate of neural stem progenitor cells ☆

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ABSTRACT

Background: Accumulated data indicate that self-renewal, multipotency, and differentiation of neural stem cells are under an intrinsic control mediated by alterations in the redox homeostasis. These dynamic redox changes not only reflect and support the ongoing metabolic and energetic processes, but also serve to coordinate redox-signaling cascades. Controlling particular redox couples seems to have a relevant impact on cell fate decision during development, adult neurogenesis and regeneration.
Scope of review: Our own research provided initial evidence for the importance of NAD^+-dependent enzymes in neural stem cell fate decision. In this review, we summarize recent knowledge on the active role of reactive oxygen species, redox couples and redox-signaling mechanisms on plasticity and function of neural stem and progenitor cells focusing on $NAD(P)^+$/NAD(P)H-mediated processes.
Major conclusions: The compartmentalized subcellular sources and availability of oxidizing/reducing molecules in particular microenvironment define the specificity of redox regulation in modulating the delicate balance between stemness and differentiation of neural progenitors. The generalization of "reactive oxygen species" as well as the ambiguity of their origin might explain the diametrically-opposed findings in the field of redox-dependent cell fate reflected by the literature.
General significance: Increasing knowledge of temporary and spatially defined redox regulation is of high relevance for the development of novel approaches in the field of cell-based regeneration of nervous tissue in various pathological states. This article is part of a special issue entitled Redox regulation of differentiation and de-differentiation.

1. Neural stem cells

Two specialized niches in the adult mammalian forebrain home stem cells that are primarily involved in generating neurons throughout life: the subgranular zone (SGZ) of the dentate gyrus in the hippocampus and the ventricular–subventricular zone (SVZ) in the lateral wall of the lateral ventricles [1–4] (Fig. 1). Although there are several structural differences, *e.g.* the unique "pinwheel" organization of SVZ stem niche [5], these two areas share a common architecture that allows close contact between neural stem cells (NSCs) with the extensive blood vessel network as well as the expansion of NSC processes into adjacent cell layers [6]. Both niches play a supportive role by assisting the essential functions of NSCs: multipotency and the ability to self-renew in response to mitotic stimuli. Furthermore, combination of various niche factors defines the neurogenic environment for differentiating progeny in order to support neuronal cell fate. Notably, NSCs transplanted into other areas of the brain predominantly differentiate into glial cells indicating the high degree of neural plasticity and the pro-neuronal role of stem niches [7].

1.1. SVZ niche

The SVZ is the largest neurogenic niche in the adult mammalian brain that maintains NSCs and progenitor cells, lying close to ependymal

Abbreviations: ARE, antioxidant response element; bHLH, basic helix-loop-helix; BMI1, B lymphoma Mo-MLV insertion region 1 homolog; CtBPs, C-terminal binding proteins; DLL4, delta-like protein 4; DVL, disheveled; DOUX, dual oxidases; ES, embryonic stem cells; EGFR, epidermal growth factor receptor; ERK1/2, extracellular-signal-regulated kinase 1/2; FGF2, fibroblast growth factor 2; FOXO, forkhead Box O; GFAP, glial fibrillary acidic protein; GCLC, glutamate cysteine ligase catalytic; GSH, glutathione; GSSG, glutathione disulfide; GPX1, glutathione peroxidase 1; GST, glutathione-S-transferase; GRX, glutaredoxin; GDPD, glycerophosphodiester phosphodiesterase domain; GSK-3β, glycogen synthase kinase-3 beta; HES1, hairy and enhancer of split homolog-1; HO-1, heme oxygenase-1; HGF, hepatocyte growth factor; HIF-1α, hypoxia inducible factor-1 alpha; FIP200, interacting Protein of 200 kDa; MAPK, mitogen-activated protein kinases; MASH1, mouse achaete-scute complex homolog 1; QR, NAD(P)H:quinone oxidoreductase; PARP-1, poly-(ADP-ribose) polymerase-1; NOX, NADPH oxidase; NSPCs, neural stem and progenitor cells; NSCs, neural stem cells; NEUROD1, neurogenic differentiation 1; NRF2, nuclear factor erythroid 2-related factor 2; NRX, nucleoredoxin; OCT4, octamer-binding transcription factor 4; PAX, paired box gene; PRX, peroxiredoxin; PI3K, Phosphoinositide-3-kinase; PDGFR, platelet-derived growth factor receptor; PcG, polycomb group; PRDM16, PR domain containing 16; RNS, reactive nitrogen species; ROS, reactive oxygen species; RMS, rostral migratory stream; SIRT, sirtuin; SOX2, sex determining region Y-box 2; SGZ, subgranular zone; SVZ, subventricular zone; SOD, superoxide dismutase; TBX3, T-box transcription factor; TRX, thioredoxin; TGFβ1, transforming growth factor beta 1; VCAM1, vascular cell adhesion molecule 1

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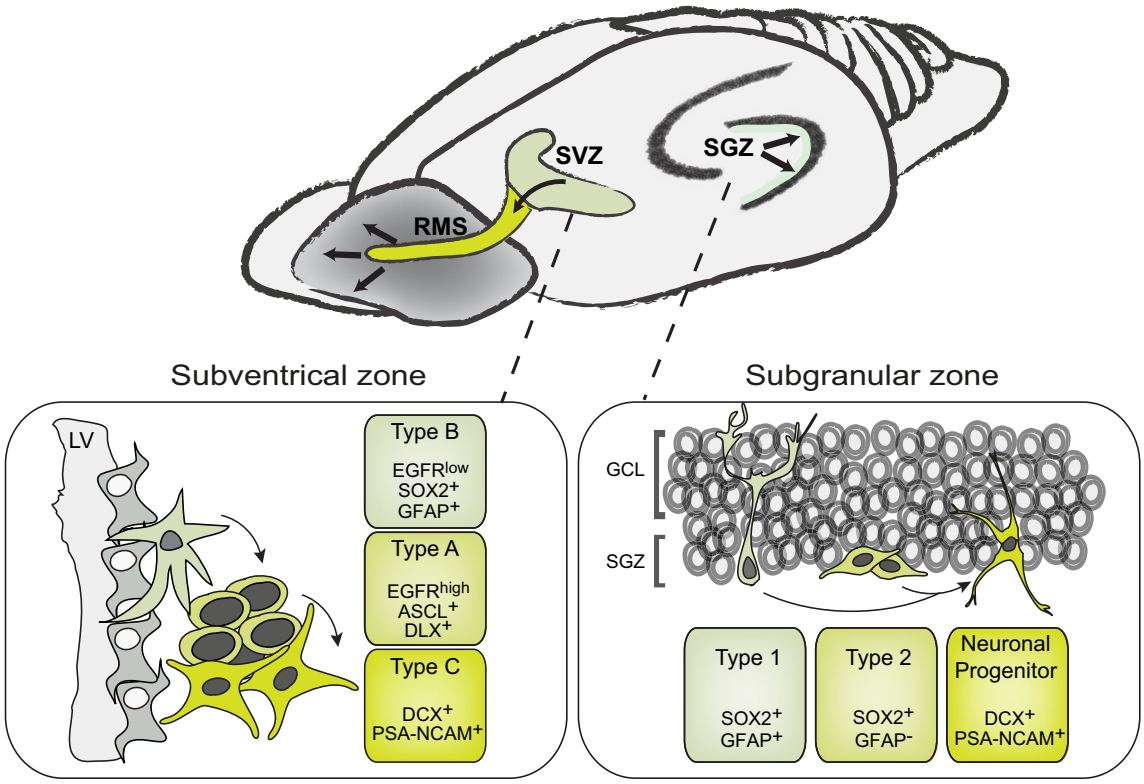

Fig. 1. Schematic representation of regional organization of NSC niches in the adult brain. The specific markers of NSCs and their progeny are shown for the ventricular–subventricular zone (SVZ) of the lateral ventricles (LV) and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus. Immature neurons born in the SVZ migrate along the rostral migratory stream (RMS) into the olfactory bulb. Immature neurons derived from the SGZ of the hippocampus migrate a short distance into the granular cell layer (GCL).

cells of the ventricle. NSCs (Type B cells) are long-lived [8], slowly proliferating [9] and resistant to anti-mitotic agents [10]. These cells express glial fibrillary acidic protein (GFAP) and are characterized by the lack of a surface receptor for epidermal growth factor (EGF) [9]. When isolated from the SVZ and cultured *in vitro*, cells with characteristics of Type B cells are not able to form colonies under commonly used culture conditions and remain in a relatively quiescent state [11,12]. Upon activation, Type B cells up-regulate EGFR and generate rapidly dividing, short-lived, multipotent Type C cells [12,13] that retain high mitotic activity *in vitro* [11]. This finding is high relevant as the majority of *in vivo* and *in vitro* experiments directed to analyze the proliferation capacity do not consider the role of NSCs (Type B), but rather reflect the mitotic property of their activated progeny. For this reason, we will use the definition of neural stem and progenitor cells (NSPCs) to describe the population of uncharacterized cells possessing both self-renewal and multipotent capacities. The Type C cells give rise primarily to immature neurons (Type A cells or neuroblasts) that migrate anteriorly over a long distance along the rostral migratory stream (RMS) to the olfactory bulb and generate interneurons [14]. These cells express immature neuronal markers, *e.g.* doublecortin (DCX) and polysialylated neural cell adhesion molecule (PSA-NCAM). In addition to neuronal fate, NSCs of the SVZ generate astrocytes in the olfactory bulb and oligodendrocytes in the cortex and the corpus callosum [15,16].

1.2. SGZ niche

Two putative types of NSCs are located in the SGZ and generate neurons in the dentate gyrus [17]. Type 1 cells divide slowly, have a radial structure and expand their processes into the adjacent granular cell layer. These cells express the stem cell marker sex determining region Y-box 2 (SOX2) and the glial protein GFAP. Type 2 progenitors are GFAP-negative, have short processes and proliferate more extensively as compared to Type 1. Both populations generate DCX-positive immature neurons which migrate and integrate into the adjacent granular cell layer [18,19]. Stem cells of the SGZ are also able to generate astrocytes [18].

2. Redox state of NSPCs

The redox state within cells is defined by dynamic changes in the ratio of the interconvertible oxidized and reduced form of specific redox couples such as the nicotinamide adenine dinucleotide (NAD^+/NADH), NAD phosphate ($NADP^+$/NADPH), glutathione (GSSG/2GSH), thioredoxin (TrxSS/Trx$(SH)_2$), superoxide ($O_2^{-}\bullet$)/oxygen, hydrogen peroxide (H_2O_2)/water, and many other redox pairs. Accumulation of oxidizing molecules such as reactive oxygen (ROS) and nitrogen species (RNS), due to their increased production or inefficient clearance, shifts the intracellular redox environment to a more oxidized state and promotes oxidation reactions. The subcellular origin of endogenous ROS has become more increasingly considered as the response of NSPCs to different oxidants and their amount can vary [20–26]. It became obvious that dynamic in the activity of endogenous sources of ROS are essential for both sustained self-renewal capacity [27,28] and differentiation of NSPCs [29]. Further data indicated that modulation of ROS may impact cell fate commitment towards glial or neuronal lineages [27,30]. This review aims to summarize and evaluate the existing data on the specificity in ROS signaling in the context of NSPC biology focusing on i) tempo-spatial generation of ROS, ii) specific redox-regulated signaling pathways, and iii) involvement of $NAD(P)^+$/NAD(P)H redox couples.

2.1. Hypoxic microenvironment of stem cell niches

The oxygen tension in the adult brain among different mammalian species is estimated in the range of 0.1–5.3% [31,32] and low levels of O_2 of around 1.3% have been observed in the regions with high cellular

density such as the hippocampal dentate gyrus [33]. Based on *in vitro* culture conditions in which atmospheric oxygen levels are traditionally maintained at 20%, it has been accepted to consider O_2 levels below 5% as hypoxic. The propagation of embryonic stem (ES) cells and NSPC cultures under lowered oxygen concentrations confirmed a crucial homeostatic role of "physiological hypoxia" for survival and self-renewal of stem cells [34–38].

The hypoxic microenvironment of neurogenic niches may exert effects on NSC function in part by differential regulation of endogenous ROS levels, particularly in sub-cellular compartments. Thus, hypoxia promotes stemness by supporting the generation of ROS *via* up-regulation of membrane-bond NADPH oxidases (NOX, discussed below) [27]. On the other hand, oxygen availability may also be a major factor in regulation of mitochondrial activity and therefore mitochondrial ROS production in stem cells [39–42]. As depicted below, in striking contrast to NOX system, mitochondria-derived ROS serves as a signal to inhibit proliferation of NSPCs.

Mitotic activity of ES cells is supported by glycolytic flux and low mitochondrial oxygen consumption [43]. With respect to this, inhibition of mitochondrial respiration enhances the pluripotency of ES cells [44]. Moreover, reprogramming of somatic cells towards pluripotent stem cells is associated with the acquirement of an "anaerobic" metabolic profile and mitochondrial properties reminiscent to an ES cell-like phenotype (in regard to morphology, distribution, low ROS and low ATP production) [45]. Collectively, these data indicate that low oxygen tension in stem cell niches maintains the proliferating undifferentiated state of stem cells by differentially regulating the activity of different sources of ROS and compartmentalization of redox signaling.

2.2. Mitochondria-derived ROS

Mitochondrial oxidative phosphorylation (OXPHOs) produces high amounts of ATP and endogenous ROS, which are mainly generated by complex I (NADH:ubiquinone oxidoreductase) and complex III (ubiquinol:cytochrome c oxidoreductase) of the electron transport chain [46,47].

Recent studies, in which the mitochondrial ROS sensitive probe mt-cpYFP was claimed to detect superoxide production, allowed characterization of the mitochondrial input in oxidative state of proliferating [48] and differentiating NSPCs [29]. It has been shown, despite the weak basal superoxide signal, cultured proliferating cortical NSPCs exhibit spontaneous burst-like generation of mitochondrial superoxide anions (superoxide flashes) without global changes in intracellular ROS levels [48]. The supposed superoxide oscillation requires the opening of the mitochondrial permeability transition pore (mPTP) and activity of the electron transport chain. The frequency of this oscillation responds to environmental changes in oxygen concentration and Ca^{2+} fluxes. In parallel, these mitochondrial flashes negatively regulate NSPC proliferation *via* inhibition of the mitogen-activated protein (MAP) kinases ERK1 and ERK2 (extracellular-signal-regulated kinases 1 and 2) [48]. However, these data are under debate since cpYFP probe may rather reflect the alterations in pH than being an exclusive superoxide sensor [49]. Nevertheless, the mitochondrial flashes are linked to redox changes in the mitochondria [50], while the molecular explanation for this interesting physiological phenomenon remains unclear. According to the *in vitro* experiments, embryonic brains of superoxide dismutase 2 (SOD2)-deficient mice display increased superoxide levels and are characterized by reduced neurogenesis in the ventricular zone, related to diminished proliferating capacity of NSPCs [48]. Interestingly, deficiency in superoxide metabolism in SOD1 and SOD2 knockout mice has an impact on cell lineage decision favoring the glial fate of SGZ NSPCs [51]. These results are consistent with our own findings showing that depletion of intracellular GSH favors the glial lineage specification of NSPCs in expense of the neuronal fate [30].

The shift from anaerobic glycolysis to OXPHOs is an essential requirement to support the energy demand of differentiating cells. Therefore, treatment of NSPC cultures with the mitochondrial complex IV inhibitor antimycin predominantly affects the survival of immature differentiating neuronal progenitors with less impact on dividing cells [52]. Additionally to ATP supply, it was shown that metabolic oxidation favors the differentiation of ES cells [53]. Early steps of neuronal differentiation, which can be synchronized by growth factor withdrawal, are associated with progressively increased mitochondrial biogenesis, mitochondrial mass, ATP production and concomitant rise in ROS formation [39,54–56]. The experiments involving the modulation of mitochondrial activity have revealed the key role of "superoxide" flashes, as depicted by application of mt-cpYFP probe, in neuronal differentiation. Pharmacological inhibition of superoxide anions has been shown to favor the maintenance of immature state of progenitors [29]. In line with this, elevated ROS levels are mostly found in newly generated neurons *in vivo* [57,58]. Obviously, redox changes in the mitochondria are of great importance for differentiation processes, although their molecular mechanisms and therein associated targets still remain largely unknown.

The proper control of mitochondrial ROS generation is essential for NSPC fate decision. Several stem niche factors have been implicated in the control of mitochondrial ROS production. B lymphoma Mo-MLV insertion region 1 homolog (BMI1), a member of the polycomb group (PcG) of transcriptional repressors, is a key factor for the maintenance of both hematopoietic stem cells and NSCs [59–61]. *Bmi1*$^{-/-}$ mice are characterized by reduced proliferation and neurogenesis in the SVZ [59,62,63]. Importantly, treatment with antioxidant N-acetyl-cysteine rescues some developmental defects in *Bmi1*$^{-/-}$ mice such as the thymus size and the overall number of thymocytes [64]. This can argue that in addition to well-known function in the repression of the cell cycle inhibitor INK4a/ARF locus, BMI1 plays a role in oxidative metabolism. BMI1-deficient cells exhibit elevated mitochondrial ROS levels and impaired mitochondrial function [64]. In neurons, BMI1 represses pro-oxidant activity of tumor suppressor p53 [65]. Thus, it is likely that BMI1 may support the stemness of NSPCs at least in part through the control of ROS production.

Hepatocyte growth factor (HGF) [66] reduces ROS levels in various cell types including NSPCs [67]. Expression of HFG and its tyrosine kinase receptor c-MET has been found in NSPCs of the SVZ [68]. *In vitro* and *in vivo* experiments with exogenous HGF demonstrated the positive effect on proliferation and self-renewal of NSPCs [67,68]. Moreover, mice deficient for the transcription factor PR domain containing 16 (PRDM16), an activator of HGF expression, display elevated levels of ROS [67]. The abnormal ROS levels as well as decreased proliferation of *Prdm16*$^{-/-}$ NSPCs can be reversed by treatment with exogenous HGF or N-acetyl-cysteine [67]. The molecular mechanism by which HGF controls ROS is still elusive. In epithelial Mv1Lu cell line HGF prevents the disruption of the mitochondrial respiratory function and ameliorates antimitotic effect of mitochondrial ROS overproduction induced upon prolonged treatment with transforming growth factor β1 (TGFβ1) [69]. Thus, it will be important to determine whether HGF-mediated control of mitochondrial activity is involved to support the self-renewal state of NSPCs.

More recently, it has been shown that mitophagy, the autophagosomal removal of severely damaged mitochondria, is another mechanism to protect NSPCs from aberrant ROS production [70]. Conditional deletion of focal adhesion kinase (FAK)-family interacting protein of 200 kDa (FIP200), a protein essential for induction of autophagy [71], leads to p53-dependent apoptotic response and cell cycle arrest with subsequent depletion of the NSPC pool in both germinative zones, the SVZ and the SGZ of the postnatal brain [70]. Disturbed mitophagy was associated with increased mitochondrial number and aberrant ROS production as a result of mitochondrial damage. Treatment with N-acetyl-cysteine rescued the abnormalities in self-renewal of FIP200-deficient NSPCs, indicating the detrimental role of mitochondrial ROS overproduction. In addition, the decreased neurogenesis observed in *Fip200*$^{-/-}$ mice is paralleled with enhanced generation of astrocytes. This shift towards astrogenesis was

blocked by N-acetyl-cysteine, demonstrating that a more oxidative state of NSPCs in the adult brain defines the glial lineage commitment [70]. This findings extend our own observations for the instructive role of redox state in the commitment of embryonic NSPCs [30]. In summary, the long-term maintenance of NSPC functions such as multipotency and self-renewal require a rigid control mechanism for mitochondrial metabolism.

2.3. Non-mitochondrial sources of ROS

Apart from the mitochondrial electron transport chain, other sources of ROS formation localized in distinct subcellular compartments were implicated in NSPC biology (*e.g.* cyclooxygenases [53,72,73], lipoxygenases [53,74,75], nitric oxide synthases [76–79], and cytochrome P450 enzymes [80,81]). Among these, the family of membrane-associated NAD(P)H oxidases (NOX) is the best-characterized for its role in NSPCs.

The NOX proteins generate ROS (superoxide as a primary product) from NADPH to molecular oxygen through electron transport across membranes [82–84]. These evolutionary conserved oxidases can be considered as "professional" ROS producers for various cellular functions related to the host defense mechanism against pathogens (innate immunity), signal transduction, and modification of the extracellular matrix [85,86]. The NOX family consists of seven homologues as follows: NOX1, NOX2 ($gp91^{phox}$), NOX3, NOX4, NOX5 and dual oxidases (DOUX) 1 and 2. Enzymatic activity of NOX1-3 is regulated by complex formation with the membrane-bound $p22^{phox}$ and the cytosolic regulatory subunits, such as $p40^{phox}$, $p47^{phox}$, $p67^{phox}$, and the small GTPase RAC. DUOX's activity is regulated by the maturation factors DUOXa1 and DUOXa2 [87–89]. The interaction of NOXs with various targeting proteins defines their specific subcellular localization (*e.g.* lamellipodial leading edge, focal adhesions, lipid rafts, the endosomes, the endoplasmic reticulum, or the nucleus) [86,87,90,91]. Therefore, in diverse cellular context, NOXs are responsible for localized ROS production and compartmentalization of redox signaling in response to growth factors, cytokines, and G-protein coupled receptor activators [90].

Expression of NOX2 is enriched in the SVZ of adult mice as compared to adjacent cortical tissue [27]. In striking contrast to mitochondria-derived superoxide (see above), several studies suggest the crucial physiological role of NOX2-generated superoxide in support of self-renewal and multipotency of NSPCs of both niches, the SVZ [27] and the SGZ [92]. Consistent with results observed in NOX2-deficient mice [27,92], administration of apocynin, a pharmacological inhibitor of NOX, lowers the levels of superoxide and diminishes the self-renewal of SVZ NSPCs *in vivo* [27] and in cultured embryonic hippocampal progenitors [93]. Interestingly, NOX-deficiency affects the multipotency and favors the glial fate of SVZ-derived NSPCs [27], highlighting the role of NOXs in neuronal commitment.

The beneficial effect of NOX-derived ROS on NSPC homeostasis can be explained by its spatially confined, compartment-specific production and immediate coupling into signaling cascades. Supporting this hypothesis, it was shown that downstream signaling involves ROS-dependent inactivation of phosphatase and tensin homolog (PTEN) [94], the negative regulator of NSC proliferation [95–98], and the subsequent activation of phosphoinositide-3-kinase (Pi3K)/AKT pathway [27,99]. Regulation of PTEN and AKT activity occurs upon their recruitment to the plasma membrane and mediated by the reversible oxidation of active site cysteines [100,101]. Thus, it is likely, that co-locolization of NOX, PTEN and AKT on the plasma membrane is required for proper signal transduction.

Activation of NOXs is involved in signaling cascades initiated by several niche factors known to be essential for ability of NSPC to self-renew. For example, fibroblast growth factor 2 (FGF2), a potent mitogen for NSPCs, requires the activation of NOX2 and generation of H_2O_2 in cultured adult hippocampal progenitors [92]. Silencing of NOX2 abrogates FGF2-induced AKT phosphorylation and inhibits proliferation [92]. Inhibition of NOX or treatment with N-acetyl-cysteine abrogates the brain-derived neurotrophic factor (BDNF)-induced mitotic activity of NSPCs [27]. Similar to non-neural cells, it is likely that other receptors present on the surface of NSPCs may involve NOX activity for signal transduction (*e.g.* epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR) [102]).

NOX2-generated ROS have been identified as the important mediators of vascular cell adhesion molecule 1 (VCAM1)-dependent maintenance of Type B NSCs in the SVZ niche [103]. VCAM1 and NOX2 are co-expressed on the end feet of Type B cells. Inhibition of VCAM1 by intra-ventricular administration of blocking antibodies leads to premature differentiation and subsequent loss of NSC pool. VCAM1 may support the response of NSCs to various niche factors *via* induced expression of NOX proteins. Consistent with this, silencing of VCAM1 by shRNA decreases the level of NOX2 transcripts [28]. Similarly, the positive effect of Angiotensin II on proliferation of the neural stem cell line C17.2 is linked to the induction of NOX4 and generation of superoxide [104]. NSPCs express Angiotensin II type-1 and type-2 receptors [105]. The latter is involved in Angiotensin II-induced proliferation of embryonic hippocampal NSPCs *via* activation of MAPK signaling [105], known target of NOX4 activity [106].

The plasma membrane-targeted DUOXs may also be involved in regulation of the NSPC fate. DUOX maturation factor, DUOXa1 (also known as a Numb-interacting protein 1) was described as an intrinsic regulator of neuronal fate in stem cell differentiation [107]. DUOXa1 is highly expressed in undifferentiated NSPCs and plays a role in DUOX1-dependent superoxide and H_2O_2 generation. Ectopic expression of DUOXa1 in the pluripotent embryonic carcinoma cell line P9 is associated with increased ROS levels and transient up-regulation of pro-neuronal genes Neurogenin1 and 2 followed by neuronal differentiation [107]. Accordingly, silencing of DUOXa1 diminishes ROS and partially inhibits retinoic acid-induced neuronal differentiation in this cell line [107].

In summary, hypoxic conditions in stem cell niches are likely required to up-regulate NOX proteins [27] in order to promote signaling cascades downstream from distinct niche signals. Of note, generation of NAD^+ upon NOX activation may support glycolysis [108,109], the main cellular energy source in hypoxic microenvironment. In this regard, the bioavailability and the ratio of $NAD(P)^+$/NAD(P)H redox couple is an important prerequisite for the maintenance of stem cell homeostasis.

3. Redox sensitive pathways in NSPCs

The homeostatic self-renewal, lineage commitment and differentiation of NSCs are coordinated by several signaling pathways such as WNT/β-catenin [110] and NOTCH [111]. A growing area of interest has arisen in redox-dependent modulation of these pathways. Accumulated evidence suggests the crucial role of NOX-derived ROS, reducing NADPH-dependent thioredoxin systems and redox-sensitive molecules such as NRF2 and NAD^+/NADH-dependent enzymes in spatiotemporal regulation of these signaling cascades for appropriate NSPC fate decision.

3.1. NRF2 signaling

One of the emerging targets to counteract ROS and to increase intracellular oxidative defense is nuclear factor erythroid 2-related factor 2 (NRF2), a basic leucine zipper transcription factor featuring a cap 'n' collar structure [112]. Under basal conditions, NRF2 is retained in the cytoplasm by interaction with Kelch-like ECH-associated protein 1 (KEAP1), a cysteine rich protein, which can also serve as an adaptor protein for ubiquitin ligase E3 complex [113]. Oxidative modifications of reactive cysteine residues of KEAP1 in response to ROS lead to dissociation of the KEAP1/NRF2 complex and translocation of NRF2 into the nucleus [114]. NRF2 contains the multiple redox-sensitive nuclear export and localization signal (NES/NLS) motifs, indicating that in addition to interaction with KEAP1, the cellular distribution of NRF2

may be *per se* regulated by the intracellular redox environment [115]. Nuclear heterodimerization of NRF2 with the small Maf proteins initiates transcription of a battery of cytoprotective genes harboring the antioxidant response element (ARE) in their promoter region [116,117]. Intriguingly, among the genes associated with antioxidant defense, NRF2 up-regulates transcription of genes involved in redox signaling (*e.g.* thioredoxin 1 [118]) and genes encoding for the key proteins of NOTCH pathway (NOTCH1 [119]; Jagged 1 [120]). The functional role of NRF2-mediated NOTCH signaling was demonstrated in a model of liver regeneration [119] and reconstitution of hematopoietic stem cell niche following myelo-suppressive irradiation [120]. Activation of NRF2 by low levels of ROS is required for NOTCH-mediated self-renewal of airway basal stem cells [121]. Notably, NRF2 expression itself is regulated by active NOTCH signaling [122], indicating a more complex interaction between these two pathways. Taken together, these results provide evidence that ROS-sensing ability of NRF2 is integrated in NOTCH functioning in the distinct stem cell niches.

Similar to other organs, NRF2 supports the stem cell-based regeneration of the neural tissue. In this regard, it was shown that NRF2 is essential for ischemia-induced neurogenesis in the SGZ niche [123]. *In vitro*, ectopic expression of NRF2 or treatment with a NRF2 activating compound, pyrrolidine dithiocarbamate, increases NSPCs self-renewal under proliferating conditions and supports neuronal differentiation upon mitogen withdrawal [123]. This indicates that beside its role in antioxidant defense NRF2 may be involved in the mechanisms coordinating the stem cell-fate decision. Particularly, it will be interesting to elucidate whether NRF2-dependent regulation of NOTCH contributes to NSPC homeostasis.

3.2. ($NADP^+$)/(NADPH)-dependent signaling

NADPH is generated by the pentose phosphate pathway and provides the reducing equivalents for regeneration of a variety of redox-regulating enzymes, especially members of the thioredoxin family. Oxidoreductases of this protein family are the key players in redox-dependent signaling. These proteins possess the ability to reverse oxidative modifications of protein thiols and to detoxify H_2O_2 [124], an important second messenger in diverse cellular processes [125]. Oxidative modifications, *e.g.* formation of disulphides and sulfenic acids, S-glutathionylation, or S-nitrosylation, occur at specific cysteine residues and modulate activities of an emerging number of proteins involved in signal transduction pathways. Reduction of oxidative thiol modifications is catalyzed by oxidoreductases in the expense of NADPH.

3.2.1. Thioredoxin system

The thioredoxin system (thioredoxin (TRX), thioredoxin reductase and NADPH) reduces protein disulfides and S-nitrosylated thiols. Several lines of evidence suggest a role of TRXs in proliferating cells. Consistent with early stage lethality of $Trx^{-/-}$ embryos, ES cells isolated from TRX-deficient blastocysts fail to proliferate [126]. TRX enhances transcriptional activity of the key factor for ES cell totipotency, octamer-binding transcription factor 4 (OCT4), by increasing its DNA-binding capacity *via* reduction of oxidized cysteines in the DNA binding POU domain [127]. Treatment of ischemic mice with recombinant human TRX1 promotes neurogenesis *via* increasing NSPC proliferation in the SGZ [128,129]. Although, the precise mechanism underlying the capacity of TRX to support proliferation of NSPCs is unknown, it might be linked to its facilitating role in PTEN/PI3K/AKT signaling. Thus, TRX1 binds to PTEN in a redox-dependent manner and inhibits its lipid phosphatase activity resulting in activation of AKT [130], the well-known mediator of NSPC survival and proliferation [98,131]. Consistent with the role of TRX, mice with specific deletion of cytosolic TRX reductase 1 in the nervous system develop cerebellar dysfunction associated with impaired proliferation of cerebellar progenitors in the external granular layer [132].

3.2.2. Glutaredoxin system

In addition to the reduction of protein disulfides, glutaredoxins (GRXs) has the capacity to reduce glutathionylated thiols [133]. Oxidized GRXs are re-reduced by GSH, glutathione reductase, and NADPH. GRXs 1 and 2 were shown to de-glutathionylate SIRT1, the crucial regulator of NSPC fate (see 3.3.3). However, the precise role of these molecules in NSPC biology is remained to be elucidated. Using the zebrafish model and retinoic acid-induced differentiation of SH-SY5Y neuroblastoma cell line, we demonstrated that Grx2 promotes neuronal differentiation, in part by enhancing axonal outgrowth and survival [134].

3.2.3. Peroxiredoxin system

Peroxiredoxins (PRXs) constitute a family of enzymes (PRX1-6 in mammals) that catalyze the reduction of H_2O_2 with the use of reducing equivalents provided by the thiol-containing proteins such as TRX [124]. Notably, PRXs can be reversibly inactivated by H_2O_2 and their slow-rate reduction is catalyzed by sulfiredoxin or sestrin proteins. The sensitivity of PRXs to oxidation may be considered as an important "switch-off" mechanism to insure the availability of H_2O_2 for redox signaling [135,136]. Furthermore, the activity of cytosolic PRX1 is tightly regulated by the cyclin-dependent kinase Cdc2 during cell-cycle progression [137]. PRXs have been implicated in the maintenance of stemness in cultured cells *via* lowering of the intracellular levels of H_2O_2. $Prx1^{-/-}$ and $Prx2^{-/-}$ ES cells exhibit aberrant ROS levels and rapid loss of stemness associated with premature differentiation, a phenotype which could be rescued by N-acetyl-cysteine administration [138]. Enhancement of PRX activity by overexpression of Sestrin 3 reduces the elevated ROS levels and enhances the self-renewal capacity of FOXO-deficient NSPCs [96]. $Prx1^{-/-}$ embryos are characterized by deficit in post-mitotic motor neurons in the ventral spinal cord. However, this failure is not associated with either survival of motor neuron progenitors or altered neuronal commitment, but rather related to impaired capacity of proliferating $Prx1^{-/-}$ progenitors to exit the cell cycle [139]. This finding is consistent with the notion that active form of PRX1 is sustained in G_1 [137], the critical phase for the cell cycle exit decision and differentiation. The mechanism, by which PRX1 promotes the differentiation of motor neurons relies on its ability to reduce disulphide bonds in the cytosolic part of pro-neurogenic factor GDE2 [139,140]. Whether GDE2-dependent timing of cortical neuronal differentiation [141] may similarly require the PRX activity is remained to be elucidated. The lack of the phenotype in developing spinal cord of $Prx1^{-}/^{-}$ mice related to diminished self-renewal capacity [139], as it would be expected from *in vitro* studies [96,138], may rely on the differences in the compensatory mechanisms to detoxify H_2O_2. Further studies are needed to dissect the neural role of particular PRXs in ROS detoxification and in modulation of specific redox signaling.

3.2.4. Nucleoredoxin system

Nucleoredoxin (NRX) is composed of three TRX-like modules and possess oxidoreductase activity [142]. In several publications, Funato et al. demonstrated the crucial role of nucleoredoxin (NRX) in regulating the activity of the WNT/β-catenin pathway [143–145]. Binding of WNT ligands to their cognate receptors activates disheveled (DVL) protein leading to inhibition of β-catenin phosphorylation by GSK-3β. Non-phosphorylated active β-catenin translocates into the nucleus and serves as a cofactor for the TCF/LEF family of transcription factors. Interaction of NRX with DVL protects the protein pool of DVL from proteasome-dependent degradation [145], but on the other hand suppresses the WNT/β-catenin signaling [143]. This interaction is primarily dependent on the redox-catalytic motif (WCPPC) of NRX and abrogated by elevated hydrogen peroxide levels [143,144]. Therefore, it is reasonable to assume, that WNT signal transduction may primarily depends on the permissive oxidative environment. Using an immortalized neural progenitor cell line ReNcell VM197, Rharass et al. demonstrated that dissociation of the NRX/DVL2 complex correlates

with increased mitochondrial generation of ROS and activation of the WNT signaling axis in initial steps of differentiation [55]. Additionally to its role in neuronal differentiation [146], the WNT/β-catenin pathway supports self-renewal capacity of NSPCs [110,147,148]. Does the activity of WNT pathway in undifferentiated cells depend on ROS? Yoneyama et al. showed that treatment of embryonic hippocampal NSPCs with the selective superoxide scavenger, TEMPOL, reduces the level of nuclear β-catenin [93], indicating that regulation of the signaling cascade may involve endogenous sources of ROS. Accordingly, it was shown that NOX1-mediated superoxide generation is required for dissociation of the NRX/DVL complex and subsequent activation of signaling in colon epithelial cells [149,150]. In contrast to endogenous superoxide, treatment with exogenously applied H_2O_2 negatively regulates the WNT pathway by promoting de-phosphorylation of GSK-3β at Ser9 and therefore diminishing the pool of active β-catenin [151,152]. This difference may rely on the specific type of ROS and/or dependency on oxidative status at a particular site for signal transduction rather than overall cellular oxidation. Taken together, these data indicate that redox-dependent activity of non-nuclear NRX seems to be an important mechanism involved in spatiotemporal regulation of the WNT signaling in NSPCs.

3.3. (NAD^+)/(NADH)-dependent signaling

The (NAD^+)/(NADH) ratio is one of the most important redox pairs due to the strong reducing capacity of NADH [153]. This ratio is mainly defined by the activity of complex I of the mitochondrial respiratory chain, making NAD^+ a signal of mitochondrial OXPHOs [154]. Additionally to its function as electron carrier, this pyridine nucleotide has emerged as a critical cofactor in the signaling pathways providing a link between redox state and gene expression. Hydrolysis of NAD^+ by several glycohydrolases is associated with post-translational protein modifications, such as ADP-ribosylation or deacetylation, and generation of messenger molecules (ADP-ribose, cyclic ADP-ribose or O-acetyl-ADP ribose). Several NAD^+-consuming enzymes connected to signaling networks are involved in regulation of fundamental biological processes in NSPCs. Depletion of NAD^+ in the adult murine brain is associated with loss of proliferating NSPCs [155]. Consistently, pharmacological inhibition or ablation of nicotinamide monophosphoribosyltransferase (NAMPT), the rate-limiting enzyme in NAD^+ biosynthesis, affects G_1/S cell cycle transition, self-renewal capacity and maintenance of the NSPC pool. Moreover, NAMPT plays a role in lineage commitment and differentiation of NSPCs into oligodendrocytes *via* activities of NAD^+-dependent enzymes SIRT1 and SIRT2.

3.3.1. C-terminal binding proteins

Mammalian C-terminal binding proteins (CtBP1 and CtBP2) were initially described as evolutionary conserved transcriptional co-repressors [156]. Although, CtBPs share sequence homology with NAD^+-dependent 2-hydroxy acid dehydrogenases [157], it is currently unclear whether this intrinsic enzymatic activity is involved in their repressor function [158]. In fact, CtBPs display high sensitivity to free nuclear NADH and alterations in the nuclear (NAD^+)/(NADH) ratio modulate their binding to a large number of transcriptional repressors containing the specific PxDLS consensus motif [159,160]. Furthermore, NADH is required for dimerization of CtBP2, comprising the unique nuclear localization signal, with other CtBPs and therefore guiding their nuclear localization [161]. Consistent with the (NAD^+)/(NADH)-dependency it is not unexpected that CtBP-mediated gene silencing is tightly regulated by oxygen availability and cellular metabolism [159,162,163]. Two recent studies demonstrate how the spatially and temporary defined differences in the oxygen levels may direct distinct NSPC fates by involving fundamental CtBP repressor activity [163,164]. Developing chick's neural tube exhibits a region-specific pattern in the oxygen gradients with highest oxygen level in the dorsal roof plate and decreasing in a graded manner towards the intermediate regions. High oxygen concentrations in the non-neurogenic roof plate inhibit neuronal fate *via* establishing the CtBP/hairy and enhancer of split homolog 1 (HES1) repressor complex binding to the promoter region of pro-neuronal factor mouse atonal homolog 1 (MATH1) [163]. For comparison, in other parts of the dorsal neural tube, neurogenesis is permitted by more hypoxic environment [163]. In these regions CtBP promotes cell-cycle exit and neuronal differentiation through repression of transcriptional activities of Wnt-target genes by forming a repressor complex with β-catenin/T cell factor [164]. Interestingly, lowering (NAD^+)/(NADH) ratio in cultured NSPCs by decreasing oxygen tension enhances CtBP-mediated transcriptional repression of HES1 [165]. Taken together, these data suggest that CtBP act as a master regulator of oxygen-dependent switch in activity of signaling pathways during stem cell fate decision. Consistent with this notion, CtBP2-deficient mouse embryos exhibit severe developmental defects related to changes in embryonic patterning [166]. It is reasonable to hypothesize that redox/metabolic state will determine the mode of CtBP action in particular cellular system. Therefore, differences in metabolic processes could explain the either promoting [167–169] or inhibiting [169,170] effects of CtBP on the WNT signaling axis reported in literature.

3.3.2. Poly(ADP-ribose) polymerase

NAD^+-dependent poly(ADP-ribose) polymerase 1 (PARP1) is another example of redox sensing enzymes that modulate activity of the signaling pathways and define the gene transcription profile. Initially identified as a DNA single-strand break repairing enzyme [171,172], PARP1 has been further characterized as a co-transcriptional regulator localized at the promoters of actively transcribed genes [173]. The capacity of PARP1 to modulate chromatin structures and the activity of transcription factors is dependent on the amount of NAD^+ and its poly-ADP-ribosylation activity [173–176]. PARP1 contributes to the maintenance of transcriptional activity of a wide range of genes in ES cells [177]. Upon differentiation of ES cells, PARP1 enhances FGF4 transcription by poly-ADP-ribosylating SOX2 at the FGF4 promoter region [178]. In NSPCs, PARP1 enzymatic activity is required for dissociation of groucho/TLE co-repressor complex from the promoter of pro-neuronal mouse achaete-scute complex homolog 1 (MASH1) gene [175]. In the postnatal SVZ, deficiency of PARP1 directs cells towards glial fate, further supporting the pro-neuronal role of PARP1 [179]. Therefore, NAD^+-dependent PARP1 activity may serve as a mechanism to promote the differentiating program by regulating repressor/co-repressor dissociation from the promoters of specific genes [175].

3.3.3. Sirtuins

SIRT1, the mammalian ortholog of yeast silent information regulator 2 (SIR2), belongs to an evolutionary conserved family of proteins (sirtuins; 7 members in mammals) with NAD^+-dependent de-acetylating and mono-ribosyltransferase activity [180]. SIR2 was first identified as a histone deacetylase that suppresses genome-wide transcription and extends replicative lifespan [181]. Since then, numerous target genes and non-histone substrates of SIRT1 de-acetylating activity have been identified. SIRT1 expression and activity is tightly regulated by changes in the (NAD^+)/(NADH) redox state [182,183]. Thus, the availability of the metabolic cofactor NAD^+ determines the catalytic activity of SIRT1 and other sirtuins [184–187]. SIRT1 transcription is controlled by the redox-sensing ability of the transcriptional co-repressor CtBP [188]. Increase in the (NAD^+)/(NADH) ratio affects the binding of the CtBP/hypermethylated in cancer 1 (HIC1) complex to the SIRT1 promoter and leads to de-repression of SIRT1 transcription. This regulation seems to be involved in low oxygen-mediated SIRT1 suppression [188], since hypoxic conditions lead to a drastic increase in the levels of NADH and activation of the repressor function of CtBP [159]. Depletion of NADH levels by 2-deoxyglucose, an inhibitor of glycolysis, or by treatment with pyruvate restores SIRT1 expression under hypoxic conditions [188]. In addition, the activity and expression of SIRT1 are modulated by the GSH/GSSG redox couple in cell context-dependent manner. Although

increasing evidence suggests that redox regulation *via* GSH is enzyme-dependent, the ratio between reduced GSH and the oxidized glutathione disulfide (GSSG) is still considered as an important regulator of cellular redox events [189]. Depletion of GSH in NSPCs sustains the transcriptional and translational level of SIRT1 upon differentiating conditions [30]. Regulation of SIRT1's enzymatic activity is connected to reversible oxidative thiol modifications. SIRT1 activity is inhibited following GAPDH-dependent S-nitrosylation [190] or S-glutathionylation of critical cysteinyl groups [134,186,191,192]. Reduction of S-glutathionylated cysteines by GRXs re-activates SIRT1 [134,186,192]. Irreversible oxidative modifications, *i.e.* carbonylation, mark SIRT1 for proteasomal degradation [186].

Sirtuins are associated with a variety of cellular functions connected to redox regulation (for recent reviews see [193,194]). High levels of sirtuins are associated with more oxidized state of cells [195,196], suggesting their role in cellular anti-oxidative defense mechanisms. Sirtuins 1, 2, and 3 reduce cellular ROS damage by FOXO3-mediated activation of both, SOD2 and catalase [195–198]. The expression of SOD2 and other antioxidant proteins upon activation of NRF2 is enhanced *via* SIRT1-dependent deacetylation of p53 [199,200]. SIRT1 knockout mice are smaller at birth, exhibit several developmental defects, and show elevated postnatal lethality [201,202]. Consistent with an early expression of SIRT1 during CNS development [203], three independently generated *Sirt1*$^{-/-}$ mouse strains exhibit frequent CNS abnormalities characterized by neural tube closure defects (exencephaly) and disturbed neuroretinal morphogenesis [201,202,204]. These animals display cognitive deficits associated with reduced synaptic plasticity and altered activity of hippocampal genes encoding for proteins involved in synaptic function, lipid metabolism and myelination [205]. Similar to CtBP, SIRT1-mediated transcriptional regulation is implicated in the self-renewal as well as in differentiation processes of NSPCs. The ability of SIRT1 to modulate distinct NSPC fates is at least in part dependent on its interaction with specific transcription factors at particular differentiation state of the cell. For example, Ichi et al. showed that SIRT1 supports NSPC maintenance in the developing brain by deacetylating the transcription factor paired-box 3 (PAX3) and subsequent induction of the basic helix-loop-helix (bHLH) transcriptional factor HES1 [206]. In addition, SIRT1-mediated interaction of PAX3 with another bHLH transcription factor, the pro-neuronal factor Neurogenin 2, impairs its activity to initiate differentiation [206]. Consistent with these findings, down-regulation of SIRT1 in human and mouse ES cells is required for transcriptional de-repression of a set of pro-neuronal genes and the establishment of the neuroectodermal lineage differentiation program [207]. Further, upon pro-oxidative challenge (such as GSH depletion), sustained expression of SIRT1 in NSPCs inhibits neuronal fate by promoting HES1-mediated repression of the pro-neuronal gene MASH1 [30]. However, in differentiating NSPCs SIRT1 functions in opposite way to suppress the promoter activity of specific stemness genes [208,209]. This is consistent with its predicted role in cell differentiation as a component of the polycomb repressive complex 4 (PRC4) [210]. Thus, upon neuronal differentiation SIRT1 transiently translocates to the nucleus [208] to form a complex with nuclear receptor co-repressor (N-coR) and B-cell lymphoma 6 (BCL6) thereby suppressing HES1 [208] and HES5 [209] genes, respectively. The roles of SIRT1 in promoting neuronal differentiation under normal conditions [208,209] and inhibition of neuronal commitment upon oxidative challenge [30] coincide with a data showing that oxidative conditions cause a relocation of chromatin-associated SIRT1 across the genome leading to changes in the expression of individual genes [211]. Altogether these findings support the key role of SIRT1 in redox/metabolism-dependent coordination of NSPC fate. Such broad spectrum of SIRT1 functions in proliferating and differentiating cells requires tight control of SIRT1 activity to ensure proper NSPC differentiation. In this regard, identification of factors that regulate SIRT1 nuclear-cytoplasmic shuttling [212] and defining the subcellular alterations in the NAD^+/NADH ratio might lead to a better understanding of specific SIRT1-driven mechanisms.

4. Concluding remarks

The intracellular redox state is emerging as an intrinsic regulatory mechanism for the long-term maintenance of the stem cell pool and directing the differentiation of essential cell lineages for regeneration and neural tissue homeostasis (Fig. 2). As demonstrated in this review, considerable attention needs to be paid to the source of ROS and the

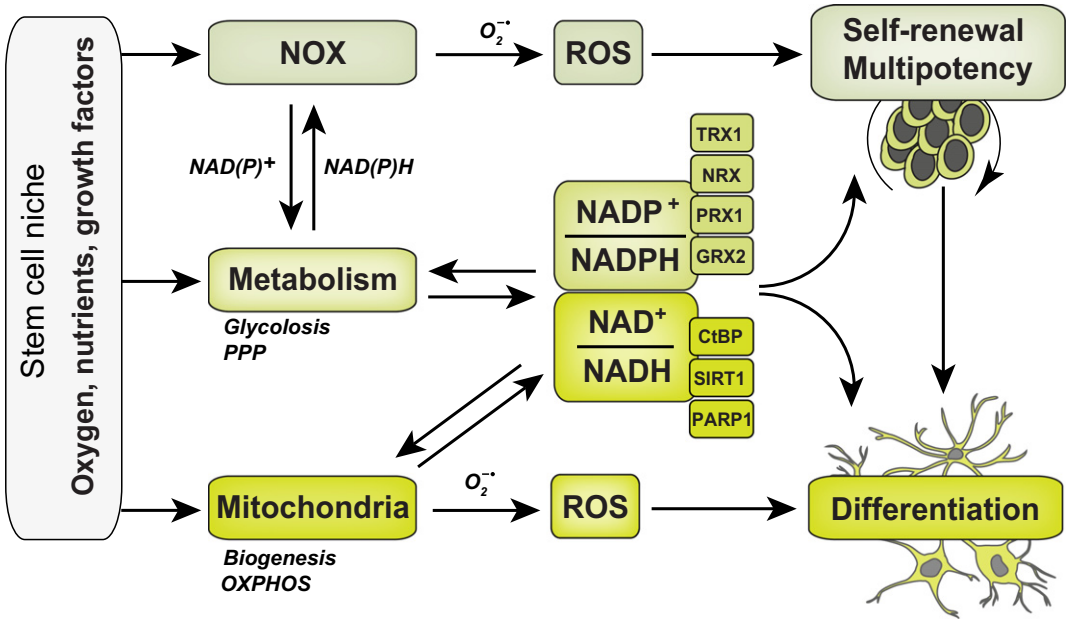

Fig. 2. Schematic summary of the main neural stem cell (NSC) functions and their dependency on ROS and redox couples. Anion superoxide ($O_2^{-\bullet}$) is the principal form of ROS produced by membrane-bound NAD(P)H oxidase (NOX) complex or mitochondria electron-transport chain. During the activation of NSCs NOX enzymes shift redox homeostasis towards more oxidized state and trigger self-renewal. In contrast, mitochondria-derived ROS are implicated in NSPC differentiation. To maintain redox signaling, the living cells engage NADPH-dependent oxidoreductases (TRX1, NRX, PRX1, GRX2) to reduce oxidative thiol modifications in redox-sensitive cysteine residues. NAD^+/NADH-dependent transcriptional co-repressors (CtBP, SIRT1, PARP1) further modulate the specific functions of signaling pathways to promote stemness or differentiation of NSPCs.

compartmentalization of redox signaling for NSC fate determination. Notably, experimental approaches based on the analysis of exogenous application of ROS, such as treatment with H_2O_2, generates conflicting results, particularly regarding the ability of NSPCs to self-renew. Therefore, these types of experimental data were not included within the review. Obviously, modulation of ROS levels in defined cellular compartment by using specific pharmacological agents or genetic modifications represents a far more reliable method.

In this review, we mainly used the term "NSPCs" to describe the uncharacterized populations of multipotent stem cells with the capacity to self-renew. In fact, these cells encompass the population of quiescent NSCs (qNSCs) retaining non-proliferating state in typical culture conditions (10 and 11) and their mitotically-active progenies. Due to technical challenge, the most approaches are used to characterize the actively dividing progenitors and do not address the role of redox state in the biology and plasticity of qNSCs, the major population of NSCs in the adult mammalian brain. Thus, the development of new strategies (*e.g.* recently described in [11,12]) that allow to distinguish between these two population is of great importance for NSC research and may advance our knowledge about redox-dependent mechanisms in the long-term maintenance of endogenous stem cell pool.

Therapeutic interventions altering the redox/metabolic state of CNS tissue may have a profound impact on the vital NSC functions and has to be considered with caution. On the other hand, the increasing knowledge of redox-dependent mechanisms will help to establish novel approaches to elicit NSCs-based regenerative capacity of CNS tissue in various pathological states and normal aging.

Authors' contributions

TP, RS, CB, and OA wrote the manuscript. HPH provided critical input. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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