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Review

Nuclear receptors and microRNAs: Who regulates the regulators in neural stem cells?

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ABSTRACT

In this mini-review, we focus on regulatory loops between nuclear receptors and microRNAs, an emerging class of small RNA regulators of gene expression. Evidence supporting interactions between microRNAs and nuclear receptors in the regulation of gene expression networks is discussed in relation to its possible role in neural stem cell self renewal and differentiation. Furthermore, we discuss possible disturbances of the regulatory loops between microRNAs and nuclear receptors in human neurodegenerative disease. Finally, we discuss the possible use of nuclear receptors as pharmacological entry points to regulate neural stem cell self-renewal and differentiation.

1. Introduction

Nuclear receptors (NRs) are ligand-activated transcription factors that regulate the expression of target genes by binding to cis-acting sequences present in the DNA. NRs represent a large family of genes encoding receptors for various ligands, including thyroid hormones, retinoic acid, vitamin D and steroid hormones. In addition, based on sequence similarity to well-characterized NRs, numerous putative "orphan" NRs have been described, for which no ligand has yet been identified. Thus, the NRs comprise a superfamily of phylogenetically related proteins with diverse functions that are involved in regulation of development, differentiation, reproduction and homeostasis. By acting as ligand-activated transcription factors, NRs control the expression of groups of responsive genes. Members of the NR superfamily include well-known nuclear hormone receptors, such as the estrogen receptor (ER), the androgen receptor (AR), the progesterone receptor (PR) and the glucocorticoid receptor (GR) among others, the metabolic receptors such as the peroxisome proliferator-activated receptors (PPARs) alpha, beta/delta and gamma, and the liver X receptor (LXR) among others, as well as orphan receptors [1]. An example of the orphan receptors is the nuclear receptor homologue of the Drosophila tailless gene (TLX). TLX plays an important role in various vertebrate brain functions and regulates the timing of neurogenesis in neural stem cells (NSC) [2].

NRs, through their function as specialized ligand-induced transcription factors are key components of transcriptional regulatory networks in several tissues. Particularly, the brain is an important target of NR action and most of the family members are expressed in this tissue. 41 out of 49 NRs have been specifically detected in different brain areas, suggesting that NRs are centrally positioned within regulatory networks that control relevant brain functions [3].

Modulation by small non-coding RNAs represents a new level of control of gene expression. The recently discovered small non-coding RNAs are generally classified into endogenous small interfering RNAs (siRNAs), microRNAs (miRNAs) and piwi-interacting RNAs (piRNAs). In particular, miRNAs and piRNAs have been implicated in various aspects of animal development, such as neuronal, muscle and germline development [4]. miRNAs are endogenous, short, 21–24 nucleotide-long non-coding RNAs that are expressed in a tissue-specific and developmentally-regulated manner. They function as negative regulators of gene expression in a variety of eukaryotic organisms by specifically binding to mRNAs, which results in cleavage or translation inhibition of the target and thereby fine-tune protein expression. These small RNA regulators are involved in numerous cellular processes including development, proliferation, differentiation and cell fate decisions [5]. Moreover, miRNAs are key elements in controlling post-transcriptional gene

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regulation and are integral regulatory components of gene networks [6]. Interestingly, recent theoretical models have suggested that miRNAs confer redundancy to transcription factor networks. This reduces the repertoire of transcription factor target genes and places miRNAs in a good position to coordinate and influence gene expression network regulation [7].

In the following sections, evidence supporting an interaction between miRNAs and NRs in the regulation of gene expression networks will be presented and discussed in relation to its possible role in neural stem cell self renewal and differentiation and association with human neurodegenerative diseases.

2. Interactions between miRNAs and NRs in the regulation of gene-expression networks by reciprocal expression control

Beyond the phylogenetical relationships mentioned in the previous section, a functional convergence of NRs is also apparent in controlling morphogenesis and homeostasis by regulating gene-expression networks [1]. A recently emerging pattern within the NR family seems to be the ability to regulate, and in turn to be regulated by, miRNAs at different levels, in what has been defined as "regulatory loops" [8]. Regulatory feedforward and feedback loops involving miRNAs are common features of transcription-factor regulated gene-expression networks (see [7,8] and references therein). For the orphan NRs, where the complexity of ligand modulation is disregarded, it has been proposed that regulatory loops involving miRNAs may have central roles in controlling cell-intrinsic pathways involved in key cellular functions. In particular, miR-9 is expressed preferentially in neurogenic areas of the brain and has been implicated in neural stem cell self-renewal and differentiation [9]. The orphan NR TLX, forms a negative regulatory loop with miR-9, and thereby influences the balance between NSC proliferation and differentiation. In NSCs miR-9, among other functions, represses TLX expression, which results in a negative regulation of NSC proliferation and accelerated neural differentiation. Reconstitution of TLX function rescues miR-9–induced proliferation deficiency and inhibits precocious differentiation, underscoring the relevance of the regulatory loop involving TLX and miR-9 in orchestrating precise control of gene expression during NSC renewal and differentiation [10].

With respect to the liganded NR, regulatory loops involving miRNAs were recently demonstrated as well. Interestingly, many of these examples involve NRs for steroid hormones. This may be either related to a common theme in their regulatory mechanisms or to the mere fact that they have been more extensively studied. As we will discuss below, many of the studies exploring the interaction between miRNAs and liganded NRs have focused on the NRs for steroid hormones. As an extensive review of the relationships between NRs for steroid hormones and miRNAs was recently published [11], we will here concentrate on some well-characterized members of this NR family with known functions on NSCs, anticipating that in the future some of the observations and conclusions based on them will be extended also to other members of the NR family.

In *Drosophila melanogaster*, the steroid hormone ecdysone and its cognate receptor EcR regulate developmental progression [12]. This regulation is at least in part exerted via a positive autoregulatory loop involving EcR and miR-14 that controls steroid hormone signaling (Fig. 1). Ecdysone activates EcR, which stimulates EcR transcription. miR-14 modulates this loop by limiting expression of its target, i.e. the EcR. In turn, ecdysone-stimulated EcR downregulates miR-14, which alleviates miR-14 repression of EcR and hence amplifies the response [13].

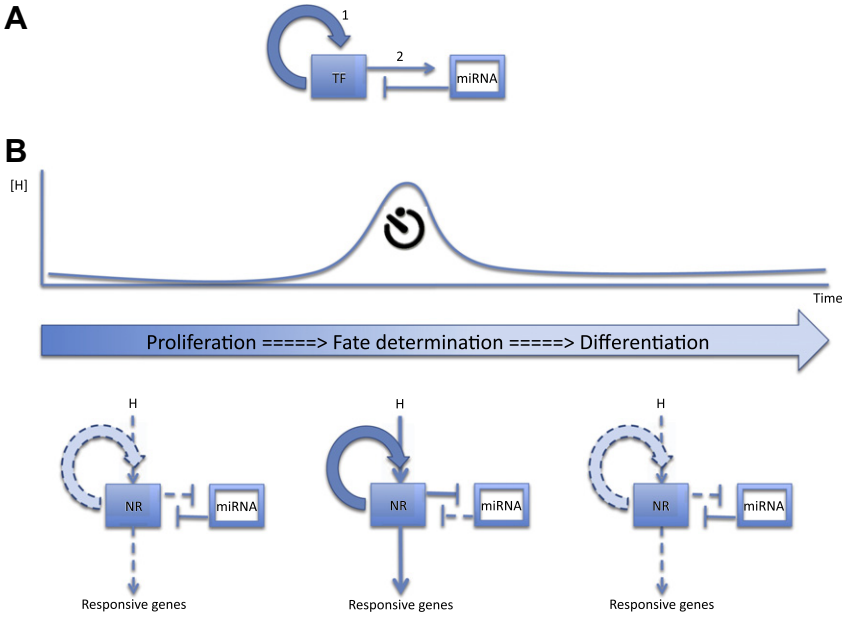

Fig. 1. NR as spatial and temporal orchestrators of miRNA expression during stem cell self-renewal and differentiation. (A) A theoretical model proposed to explain how miRNAs could act as controllers of regulatory loops involving transcription factors [49]. The scheme shows an example of a negative feedback loop reduced to two components, the protein component (representing the transcription factors (TF)) and the miRNAs component. Step 1 represents the TF positive action that may feedback positively on itself. The protein component in Step 1 is target of miRNA inhibition. Step 2 represents the TF-induced transcription of the miRNA component. (B) Extension of the model presented in A, to accommodate hormone-induced NR action. This extension is based on experimental data obtained with the steroid hormone receptor EcR [12,13] and proposes that NRs for steroid hormones may act as regulators of self-renewal, cell-fate determination and differentiation by modulating miRNA activity. In this extended model, a positive regulatory feedback loop involving NRs and miRNAs, is depicted. The *X*–*Y* axis graph represents a hypothetical cycle of hormone action. In basal conditions (left), low levels of NR activity under conditions of low hormone stimulation are present (dashed lines) and repression by miRNA dominates (full line). During the hormone peak (center), the effect of sustained hormonal activation (full lines) overcomes miRNA-mediated repression (dashed lines), allowing for a strong (auto)activation of the NR and thereby transcription of its responsive genes. Additionally, the decrease in miRNA expression induced by the hormone peak may affect other genes, which are not directly hormone-responsive. Once the hormone peak has receded, the system returns to its basal state (right), where repression by miRNA dominates. Nevertheless, this basal state is different from the one in the previous cycle, due to the expression of hormone-responsive genes during the previous peak.

In *Caenorhabditis elegans*, the nuclear receptor DAF-12 and its steroidal ligands, the dafachronic acids, control accurate progression of cell division and differentiation events during development. This control is exerted through a feedback loop between DAF-12 and the let-7-family miRNAs involving both the repression of DAF-12 by let-7-family miRNAs and transcriptional activation and repression of the let-7-family miRNAs by activated DAF-12. Thereby, during *C. elegans* development, microRNAs and NRs are components of a hormone-coupled molecular switch that shuts off earlier developmental programs to allow for later ones [14]. In mammalian cells, activation of the ER alpha induces expression of a characteristic miRNA profile, or ''microRNA signature'', that regulates ER alpha expression and its transcriptional response in a characteristic inhibitory feedback loop that may coordinate cellular responses to estrogens [15]. Also, recent observations demonstrate ER alpha to be involved in a positive feedback loop with miR-375, triggered by loss of epigenetic marks in human breast cancer cells [16].

Importantly, similar regulatory loops involving NRs and miRNAs have been intensively studied in cancer and metabolism. Therefore, extrapolation of some of the concepts learned from these systems could provide conceptual grounds to understand putative roles in other proliferative cells, such as NSCs. An overview of the vast literature describing the interplay between NRs (i.e. for steroid hormones) and miRNAs in various cancers is beyond the objective of this minireview and we refer to a recent review on this topic [17].

As discussed before, the mutual regulation between miRNAs (e.g., miR-375) and ER has been established in human breast cancer [16]. Moreover, the role of AR and other NRs in regulating microRNAs expression (e.g. mir-21 and mir-101) in prostate cancers (recently reviewed in [18]), is under intense investigation. Recent data suggest that regulatory interactions between the ER, AR, PR and GR and miRNAs may contribute to disease progression in hormone-responsive cancers [17]. As some of these NRs for steroid hormones and their regulatory miRNAs may be co-expressed in NSCs, the regulatory loops initially identified in cancer cells may become a useful guide to understand their possible roles in NSC regulation. Examples are presented in the following sections.

The NR Farnesoid X Receptor (FXR), is involved in the regulation of lipid homeostasis [1]. Recent evidence has shown the existence of an elaborate positive regulatory loop involving FXR, miR-34a and the NAD+-dependent deacetylase SIRT1. FXR inhibits transcription of the miR-34a gene, resulting in positive regulation of hepatic SIRT1 levels. In turn, SIRT1-mediated deacetylation of FXR increases binding of the FXR/RXR heterodimer to DNA, resulting in further repression of miR-34a expression [19]. Dysregulation of this feedforward loop due to elevated miR-34a levels may have serious implications for metabolic diseases [20]. Interestingly, in the adult hippocampus, miR-34a regulates glutamate metabotropic receptor 7 (mGluR7) levels while miR-34a may contribute to neurogenesis and neuronal structure remodeling [21]. This suggests that the feedforward loop involving FXR and mir-34a identified in liver may also have interesting implications in the brain, where gene expression studies have already identified the expression of some FXR isoforms [3].

One emerging pattern from the observations described above seems to be that regulatory loops comprising miRNAs and NRs control gene-expression networks involved in the spatio-temporal coordination of essential cell functions such as proliferation, fate determination and differentiation. In particular, for the NRs for steroid hormones this is highly reminiscent of the classical role proposed for hormonal action, which is to coordinate growth and development, tissue function, metabolism and other important systemic functions in multicellular organisms. On the other hand, miRNAs play an important role in repressing or promoting cell-fate regulators in a stage-specific manner [22]. In fact, the role for NRs in controlling the outcome of gene expression regulatory loops involving miRNAs that we propose here, is coherent with the accepted function of steroid hormones as coordinators of local cellular events with ''systemic needs'', through the activation of their cognate receptors [1].

Therefore, based on the published evidence discussed above, we propose that regulatory loops between NRs and miRNAs provide entry points for cell-extrinsic factors to impact on miRNAs, thereby orchestrating cell proliferation, fate determination and differentiation in time and space (Fig. 1). This hypothesis will be discussed in more extension in the following sections, with particular focus on NSCs.

3. Interactions between miRNAs and NRs in the regulation of gene-expression networks at other levels

The concerted action of protein co-regulators known as co-activators or co-repressors is required for accurate regulation of gene-expression networks by NRs. Interestingly, several miRNAs have been demonstrated to target various NR co-regulators as well (recently reviewed in [18]). These observations suggest that miRNAs may exert coordinating and redundancy-limiting actions on gene-expression networks controlled by NRs, not only by targeting the NRs directly but also indirectly by targeting key factors that control NRs action, i.e. NR co-regulators.

Another very interesting level of interaction between miRNAs and NRs is the regulation of miRNA biogenesis by NR. Two paradigmatic members of the steroid receptor family, i.e. ERa and the GR, have been shown to regulate miRNA biogenesis at different levels. ERa controls miRNA maturation by regulating the activity of Drosha, one of the key enzymes involved in the production of mature miRNAs from their precursors [23]. GR also modulates miRNA expression and processing by controlling the expression of several key miRNA processing enzymes; Dicer, Drosha and DGCR8/Pasha [24]. Although these observations are still restricted to some particular tissues or cell types, the emerging pattern seems to be that NRs for steroid hormones may be crucial in the post-transcriptional regulation of microRNA expression, favoring the functional expression of miRNA sets or ''signatures'' involved in the coordination of gene-expression networks [15].

4. miRNA-NR interactions in neural stem cells and possible implications for neurodegenerative diseases

Stem cells are unspecialized cells with the potential ability to become functionally specialized. They are defined by their ability to self-renew and their capacity to generate various types of differentiated progeny. Their functional differentiation is governed by a network of cell-intrinsic cues such as the transcription factor Sox2 (Sex determining region of Y chromosome-related high mobility group box 2) and the *Drosophila* membrane-associated protein Numb homologs and cell-extrinsic signals, such as vascular endothelial growth factor (VEGF), Eph/ephrin signaling molecules and epithelial- and brain derived-growth factors (EGF and BDNF) [25], just to mention some prominent examples of cell-intrinsic and extrinsic factors which impact NSC physiology.

Stem cell therapy is already applied in human patients through the transplantation of donor bone marrow stem cells or umbilical cord stem cells into the circulatory system of leukemia patients. Another therapeutic use of stem cells may come from their directed differentiation into other cell types, also known as transdifferentiation. In terms of pharmacological approaches to generate defined lineages from small populations of stem cells, members of the NR family seem very interesting candidates because of their

involvement in self-renewal and differentiation of various stem cell types and in their relatively well-known pharmacology [26]. Due to their ability to influence signaling pathways and gene transcription, NRs regulate key functions of stem cells. NRs play an important role in the maintenance of pluripotency (ERRbeta, SF-1, LRH-1, DAX-1) repression of the stem cell phenotype (RAR, RXR, GCNF) and differentiation of stem cells (LXR, PPARgamma) [27].

Remarkably, a central role for miRNAs in core regulatory networks underlying stem cell self-renewal, pluripotency and differentiation has started to emerge. Particularly, in NSCs a number of observations have suggested that self-renewal and differentiation involves the dynamic interaction between transcription factors, epigenetic control, miRNA regulators and cell-extrinsic signals ([28] and references therein). Therefore, we will now focus on NSC and discuss examples of regulatory loops involving miRNAs and NR that may control self-renewal and the differentiation of NSC.

Recently, NSC-based approaches have received much attention as potential treatment for neurodegenerative disorders. Transplantation of stem cells in animal models of neurodegenerative diseases can, under specific conditions, improve function by replacing the lost neurons and glial cells and by mediating remyelination, trophic factor actions and modulation of inflammation. Endogenous NSCs are also potential therapeutic targets, because they produce neurons and glial cells in response to injury and could be affected by the degenerative process. Therefore, restoration of damaged neural tissue through the use of exogenous or endogenous NSCs would be an exciting therapeutic option, if one could control their proliferation, migration and differentiation according to specific tissue repair demands [29].

The generation of neurons during mammalian embryonic brain development involves a switch of NSCs from proliferation to differentiation. Ablation of Dicer, a key enzyme for miRNA biogenesis in mammals, during embryonic brain development has demonstrated that miRNAs are essential for survival and differentiation of newborn neurons [30]. Moreover, embryonic and adult NSCs frequently undergo asymmetric cell divisions, generating a variety of neuronal and glia lineages necessary for building functional neural tissue. Cell identity is acquired in different brain structures according to a stereotyped timing schedule where miRNAs seem to play an important role by repressing transcription factors involved in cell-fate and proliferation-rate regulation [31].

Several individual miRNAs, including miR-124 and miR-9 among others, have been associated with regulation of neurogenesis from NSCs (recently reviewed in [32]). As mentioned before, miR-9 is expressed preferentially in neurogenic areas of the brain and is engaged in a regulatory loop with TLX, mutually controlling their expression levels in NSCs and regulating self-renewal and differentiation. MiR-124, one of the most abundant miRNAs in the adult brain, is an important regulator of the temporal progression of adult neurogenesis, particularly from NSCs present in the subventricular zone. Knockdown of endogenous miR-124 expression maintains NSCs as dividing precursors, whereas ectopic expression leads to precocious and increased neuronal differentiation, i.e. by antagonizing the anti-neural REST/SCP1 pathway [33,34].

As discussed in previous sections, the existence of regulatory feedback loops linking miRNAs to transcription factors expression and vice-versa, has been extensively documented in several systems including cancer, metabolic diseases and stem cell biology and some of these regulatory loops involve NRs. These miRNA-mediated positive and negative feedback loops could be of physiological relevance in NSCs [8]. MiRNA regulatory feedback loops may further have consequences for neurodegenerative diseases such as Huntington's disease; the levels of several miRNAs responsive to the REST transcription factor (specifically miR-9 and 9∗) were e.g. decreased in HD patients brain relative to healthy controls. In turn, miR9/9∗ control the expression of components of the REST complex, conforming a mutual regulatory feedback loop [35,36]. This may suggest that TLX, due to its ability to regulate miR-9 expression in the mutual regulatory loop previously discussed, could be involved in the decrease in miR-9 expression observed in Huntington patient's brain.

Interestingly, microRNA feedback loops have been linked to other neurodegenerative diseases, such as Parkinson's. Here, miRNA133b controls the transcription factor Pitx3 in an intrinsic regulatory feedback loop [37]. In *C. elegans*, the expression of the Alzheimer's amyloid precursor protein-like gene is regulated by regulatory loops involving let-7 and its targets, the transcription factors hbl-1 and lin-42, involved in developmental timing [38]. Moreover, recent observations have demonstrated that besides expression regulation, miRNAs may be involved in the regulation of alternative splicing of the amyloid precursor protein (APP) mRNA, which affects β-amyloid peptide production. Interestingly, a lack of miRNAs induced by ablation of Dicer in post-mitotic neurons *in vivo* is associated with APP exons 7 and 8 inclusion, while ectopic expression of miR-124 reversed these effects [39].

With respect to the mutual regulatory loop involving FXR and miR-34a discussed in previous sections that may have significant effects on lipid and glucose metabolism [20], it is interesting to note that the lipid profile of the CNS is of considerable interest with respect to neurodegenerative diseases. High levels of cholesterol are present in the CNS (with cerebral cholesterol homeostasis being altered in Alzheimer's diease). Since some cholesterol metabolites can act as ligands for nuclear receptors, this has raised interest in their role in neurodegenerative disease, e.g. into the role of LXR in Alzheimer's disease [40]. Since miR-34a is known to modulate differentiation of stem cells, the identification of the FXR/miR-34a loop in NSCs could provide new avenues to control NSC self-renewal and differentiation. Then, as a general remark, NR ligands may provide attractive pharmacological entry points to replace stem cell genetic reprogramming factors. Thus, NRs could become important for drug discovery and cell replacement therapies for neurodegenerative diseases.

The concept we highlight here is to some extent inspired by observations done with the steroid hormone receptor EcR, that incorporates nuclear receptors into miRNA regulatory feedback loops (Fig. 1B). This allows for a cell-extrinsic coordination of the regulatory feedback loops in vivo by endocrine/paracrine/autocrine active molecules. This implies that important cell-intrinsic factors controlling stem cell self-renewal, fate and differentiation, such as miRNAs, could be influenced, modulated and coordinated in space and time by the extracellular environment through activation of NRs. In the developing CNS, subtypes of neurons and glial cells are generated according to a schedule that is defined by cell-intrinsic and extrinsic mechanisms that function at the progenitor-cell level [41]. Interestingly, during CNS development, the NRs Coup-tfI and Coup-tfII, also known as Nr2f1 and Nr2f2, are required for the temporal specification of neural stem/progenitor cells [42]. This could provide a relevant system for validation of the general relevance of regulatory loops involving NRs and miRNAs in NSC self-renewal and differentiation to neurons and other neural cell types.

Regulatory loops between miRNAs and NR, explicitly demonstrated in NSC, involve members of the orphan NR group, i.e TLX. This has suggested that TLX may be involved in orchestrating members of the miRNA signature (i.e. mir-9) [10] to control NSC differentiation through precise transitions between neural progenitors and differentiated cells. Although specific regulatory feedback loops involving NR for steroid hormones and miRNAs have not been demonstrated unequivocally in NSC yet, mounting evidence suggests that they may exist. Both GR and ER expression are regulated by several miRNAs ([43] [44], and extensively reviewed

in [18]). In addition, both receptors regulate the expression of multiple miRNAs [15,45].

Many steroid hormone receptors are expressed in adult NSC, including GR and ER [46,47]. Although NSC self renewal and differentiation are thought to be essentially cell-intrinsic processes, steroid hormones and their cognate receptors may influence neural NSC through the regulation of transcriptional and posttranscriptional process in a cell-extrinsic fashion. Estrogens, via ER, affect the proliferation and differentiation of NSC cells, probably acting in conjunction with other extrinsic factors governing NSC development [46]. In this respect, it could be very interesting to see if the feedforward loop involving ER and miR-375 recently described in human cancer cells [16], is expressed in NSCs and if so, which effect it could have on their proliferation/differentiation. On the other hand, adrenal "stress" steroids (i.e glucocorticoids) are strong inhibitors of adult neurogenesis, acting through the GR [48]. MiR-124, a key regulator of adult neurogenesis [33], negatively regulates the expression of genes involved in NSC differentiation, among which are components of the REST/SCP1 pathway and the GR [34,43]. If effects of the GR on miR-124 expression in NSC could be experimentally demonstrated, they would provide evidence for the existence of new regulatory feedback loops involving miRNAs and steroid receptors, with potential mechanistic and therapeutic importance for NSCs and neurodegenerative diseases.

5. Concluding remarks

In this article we have briefly discussed the existence of regulatory feedback loops involving various miRNAs and NRs that could have central physiological relevance, particularly in neural stem cells. Recent evidence reviewed in this article suggests that these loops could be more common than previously anticipated. Obviously, this concept together with its mechanistic and physiological implications, await further experimental demonstration.

Initial attempts to apply stem cells to CNS tissue engineering relied on intrinsic cellular properties of NSC. However, it is now appreciated that the environment surrounding the cells plays an indispensible role in regulating stem cell behavior. Therefore, NRs could provide a therapeutic entry point to exploit regulatory feedback loops with miRNAs involved in stem cell self-renewal and determination. In this way, using known NRs ligands or small molecules designed to mimic them, one could be able to instruct endogenous or transplanted neural stem cells to respond or ignore signals from the surrounding environment consequently benefiting specific tissue repair demands.

Thus, modulation of NR activity by pharmacological agents could be applied in the future to reprogram stem cells, particularly NSC, with strong implications for the future treatment of neurodegenerative disease.

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