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Update on Müller glia regenerative potential for retinal repair

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Abstract

Retinal regeneration efficiency from Müller glia varies tremendously among vertebrate species, being extremely limited in mammals. Efforts towards the identification of molecular mechanisms underlying Müller cell proliferative and neurogenic potential should help finding strategies to awake them and ensure regeneration in mammals. We provide here an update on the most recent and original progresses made in the field. These include remarkable discoveries regarding (i) unprecedented cross-species comparison of Müller cell transcriptome using single-cell technologies, (ii) the identification of new strategies to promote both the proliferative and the neurogenic potential of mammalian Müller cells, (iii) the role of the epigenome in regulating Müller glia plasticity, (iv) miRNA-based regulatory mechanisms of Müller cell response to injury, and (v) the influence of inflammatory signals on the regenerative process.

MAIN TEXT

The absence of retinal regeneration in mammals results in vision loss upon damage or degeneration. In contrast, some vertebrate species can regenerate their retina following injury thanks to the reprogramming of Müller glia into retinal stem cells. Müller cells are the main type of glial cells in the vertebrate retina which contribute to the maintenance of retinal homeostasis and visual function [1]. In case of retina damage, they undergo gliosis, a process that includes cell-cycle re-entry. This occurs very efficiently in zebrafish or *Xenopus*, and is accompanied by spontaneous neurogenesis and consequent regeneration of retinal neurons [2–4]. In post-hatched chicks, Müller cells also proliferate successfully in response to injury, but they possess a limited neurogenic competence, generating only inner retinal neurons [5]. In mammals, Müller glia have a very restricted proliferative capacity, leading to a negligible level of cell replacement in case of retinal degeneration [5,6]. Understanding why retinal self-repair varies tremendously across different species is essential to explore therapeutic strategies based on the stimulation of Müller cell regenerative capacity. This has been the subject of substantial investigations over the past decade. Our knowledge of the signalling network, and of the genetic or epigenetic events that either sustain or restrict Müller cell potential in different species, has recently increased spectacularly. In this review, we attempt to highlight the most recent and original progresses made in the field, opening new avenues for retinal repair.

Species-specific Müller cell response to retinal injury

Identifying the mechanisms underlying the variability of Müller cell regenerative behaviour in different species has been the subject of intense investigation. Among species-specific differences that have been identified is the expression of *Ascl1*. This proneural transcription factor, which is essential for retinal regeneration, is indeed upregulated in fish and bird Müller cells upon injury but not in mammalian ones [7]. Notch signalling impact on Müller glia proliferation also seems to differ between fish and mammals. Its inhibition was reported to potentialize the pro-proliferative effects of reprogramming factors such as *Ascl1* and *lin28a* in zebrafish, but not in mice [8]. In order to reach a more comprehensive and dynamic view of the intrinsic factors sustaining the regenerative ability of Müller cells across species, bulk and single-cell RNA sequencing (scRNA-seq) were recently applied [9]. RNA levels were profiled in zebrafish, chick and mouse, in undamaged retinas or at different time-points following neuronal cell death induction. This study reveals in an unprecedented manner, species-specific transcriptional responses of Müller cells to retinal injury. Among new molecular cues identified are transcription factors of the NFI family. These are expressed in resting Müller cells and down-regulated after retinal damage. While levels remain low in fish, an upregulation is observed at later stages in the mouse. NFI-deficient mouse Müller cells upregulate cell cycle regulators, along with the neurogenic factor *Ascl1*. This suggests that, upon acute retinal injury in mammals, NFI factors eventually repress proliferative and neurogenic competence, forcing reactive Müller glia to revert back to a resting state. Distinct regenerative capacities in animals may thus rely, at least in part, on the differential activation of regulatory networks that restore quiescence of activated Müller glia (Figure 1A,B). This large-scale and cross-species analysis clearly opens new avenues for the functional characterization of additional identified candidate genes.

The journey of a reactive Müller cell: reprogramming, proliferating and differentiating

What are the signals that trigger Müller cell response to injury? In the last decade, multiple extrinsic signalling pathways, including Wnt, BMP, TGF β , EGF, Notch, or Sonic Hedgehog (all known to be involved in retinal development), were shown to trigger Müller glia cell cycle re-entry or conversely to maintain their quiescent state [2,3,6,10]. Additional signalling pathways were recently recognized as key regulators of these processes (Figure 1A). First, mTOR and retinoic acid signalling were shown to promote the generation of proliferative Müller cell-derived progenitor cells (MGPCs) in the injured chick and/or fish retinas [11–13]. Second, *Fgf8a*, which was considered as an inhibitor of proliferation, surprisingly revealed more complex stage-dependent functions, with a mitogenic impact on young Müller cells and an anti-proliferative effect on older ones [14]. Finally, recent studies including ours,

identified the Hippo pathway as a key player for Müller glia cell cycle re-entry [15–17]. YAP, a downstream effector of the Hippo pathway, is expressed in *Xenopus* Müller cells and required for their division in response to injury [15]. YAP is also expressed in mouse Müller cells, upregulated upon photoreceptor degeneration and involved in cell cycle gene upregulation in reactive glial cells [15,16,18]. Clearly, this is however not sufficient to trigger mammalian Müller cell proliferation following injury. However, turning dormant Müller cells into actively proliferative cells can be achieved through a genetic bypass of Hippo signalling (leading to YAP activation), or by overexpression of a constitutively active YAP variant, and this even in uninjured retinas [15,16] (Figure 1C). It is thus likely that failure to activate YAP at a sufficient level in reactive Müller cells constitutes a key barrier for these cells to proliferate in mammals. Besides, successful regeneration will only be achieved if MGPCs differentiate appropriately into retinal neurons. With the genetic tools used so far, this is only the case for a very limited subset of YAP-overexpressing proliferative Müller cells [16], probably because the maintenance of a proliferative state counteracts the differentiation process. In addition, a two-step reprogramming approach, such as that recently developed by Chen and colleagues [19], may also be necessary to drive the process of regeneration until completion (Figure 1C). In this study, induction of mammalian Müller glia dedifferentiation and proliferation was first obtained by stimulating Wnt signalling. Activated Müller cells were then forced to differentiate into rod photoreceptors through a subsequent overexpression of transcription factors that are essential for rod cell fate specification, namely *Crx*, *Otx2* and *Nrl*. Importantly, these Müller glia-derived rods could restore some visual responses in a mouse model of congenital blindness. Although many questions obviously remain regarding the feasibility in human, this constitutes a first proof of concept that reprogramming endogenous Müller glia in mammals could restore some light sensitivity. Similar strategies may also be employed to direct the differentiation of proliferating Müller cells into other retinal cell types. NEUROG2 for instance was recently proved sufficient to convert postnatal Müller cells into neurons exhibiting features of retinal ganglion cells [20] and could thus be an interesting candidate.

Epigenetic basis of retinal regeneration

Müller cell-dependent regeneration involves a conversion of cellular identity, from a quiescent differentiated state to a multipotent retinal progenitor one. This is accompanied by significant changes in transcriptional programs which led researchers to investigate the remodelling of epigenetic marks, i.e. DNA methylation and histone modifications [21,22]. Analysis of DNA methylation landscape indeed revealed dynamic changes during retinal regeneration: demethylation predominates just after injury while *de novo* methylation occurs at later time-points [23] (Figure 2A). Contrasting with the situation observed during induced pluripotent stem cell formation, promoters of pluripotency- and regeneration-associated genes (such as *Ascl1a*, *Lin28*, *Sox2*, *Oct4*) were reported to be already hypomethylated in quiescent zebrafish Müller cells, likely contributing to their progenitor-like properties [23]. Surprisingly, a similar hypomethylated profile was found in mouse Müller glia as well. Based on these data, the authors proposed that DNA methylation of these genes may not be a barrier for these cells to reprogram [22–24]. This may however be more complex, as inferred from another study that examined *Oct4* methylation in the first exon, a region known to be important for its expression [25]. The authors here report that, in mouse, this *Oct4* region is demethylated shortly after injury, before returning back to a fully methylated state, similar to that observed in quiescent Müller cells. In terms of expression, this correlates with a rapid upregulation upon injury, followed by a subsequent silencing 24 hours later [25]. Importantly, *Oct4* was recently shown as essential for zebrafish Müller glia reprogramming through the regulation of several regeneration-associated factors such as *Ascl1a* and *Lin28a* [26]. Interfering with *Oct4* DNA methylation-mediated silencing may thus help enhancing mammalian Müller cell reprogramming. Another event of gene silencing has recently been identified in the injured medaka fish [27]. Medaka Müller cells, unlike their zebrafish counterparts, exhibit a restricted capacity to regenerate the retina and only give rise to photoreceptors. Lust and Wittbrodt found that *Sox2* expression is upregulated in the zebrafish damaged retina [27], where it is necessary and sufficient for Müller cell proliferation [28]. In contrast, it is downregulated in medaka in response to injury [27]. Remarkably, the regenerative capacity of

medaka Müller glia could be upgraded at a level comparable to that of zebrafish when *Sox2* expression was restored. This suggests that differential regulation of a single factor is responsible for the divergent regenerative capabilities of these two teleost species [27]. Besides, silencing of differentiation genes may also represent a barrier for efficient regeneration of fully functional neurons or for the production of specific cell types. In line with this, highly methylated DNA was found in promoter regions of several key mouse genes required for early-born retinal neuron specification or phototransduction [22]. In addition to DNA methylation, histone modifications are epigenetic mechanisms that also have profound effects on gene regulation. Therefore, not surprisingly, chromatin modifying enzymes are emerging as regulators of retinal regeneration in zebrafish. For instance, both the histone methyltransferase *Dot1l* and the histone deacetylase *HDAC1* were recently shown to be necessary for Müller cell-dependent regeneration [29–31]. While *Dot1l* drives their dedifferentiation and cell cycle re-entry through canonical Wnt signalling activation [30], *HDAC1* seems to dynamically regulate MGPC formation through its action on the *Her4.1/Lin28a/let-7* miRNA axis [29]. Of note, whether histone acetylation-independent effects of *HDAC1* are involved remains to be determined. In the mouse, the limited capacity of adult Müller cells to reprogram correlates with reduced chromatin accessibility. Along this line, the use of *HDAC* inhibitors in conjunction with *Ascl1* overexpression was shown to promote chromatin accessibility at key gene loci and thereby improve Müller cell regenerative potential [32]. Thus, simultaneous manipulation of mitogenic/neurogenic factors and epigenetic modifiers could be envisaged to efficiently reprogram Müller cells and regenerate neurons in diseased retina.

microRNA-driven mechanisms of gene regulation during retinal regeneration

In recent years, several microRNAs (miRNAs) proved to play important roles during retinal regeneration [33]. Highlighting this fact is the finding that suppression of *Dicer*, a critical regulator of miRNA biogenesis, impairs zebrafish Müller glia cell cycle re-entry in response to injury [34]. High-throughput sequencing allowed identifying miRNA that exhibit differential expression in intact *versus* regenerating retinas. Some of them, *miR-142b*, *146a*, *7a*, *27c*, and *31* turned out to be required for the proliferation of MGPCs [34] (Figure 2B). Conversely, others miRNAs are downregulated following injury, and are therefore potentially involved in the maintenance of Müller cell quiescence and/or in the inhibition of their reprogramming. A well-known example is *let-7* miRNA, which needs to be inhibited to allow derepression of crucial dedifferentiation genes. Blockade of its maturation occurs through the action of the RNA binding protein *Lin28*, which is activated downstream *Ascl1* [35], Wnt signalling [36] or *Shh* signalling [37]. Of note, *let-7* miRNA in turn regulates *Shh* pathway components, thereby participating to a complex regulatory loop [37]. *miR-203* and *miR-216a* are also repressed following injury, which contributes to Müller cell dedifferentiation through derepression of the transcription factor *Pax6* and the histone methyltransferase *Dot1l* [30,38]. Together, this raised the question as to whether the manipulation of miRNA could promote retinal regeneration in mammals. Interestingly, overexpression of *miR-124*, *miR-9* and *miR-9** (alone or in combination with *Ascl1*) proved effective in stimulating the conversion of cultured murine Müller cells into MGPCs [40] (Figure 2B). To provide a more comprehensive view of miRNAs that differ between progenitors, neurons and glial cells in the mouse, miRNA expression profiling was performed, which revealed a Müller glia-specific miRNA signature, named mGliomiR [39,41,42]. Functional assays revealed that antagonizing *let-7* while overexpressing *miR-25* and *miR-124* was sufficient to increase *Ascl1* expression and consequently to reprogram mouse Müller glia into neural progenitors *in vitro* [42]. Subsequent single cell RNA-seq analysis of reprogrammed Müller glia allowed to identify potential targets of these miRNA [42]. For instance, the top target of *miR-25* was the Wnt inhibitor *Dkk3*, which may partly explain its effect in stimulating Müller cell proliferation following overexpression. Thus, microRNAs are emerging as additional key targets for enhancing retinal regeneration.

The influence of inflammatory signalling pathways on retinal regeneration

There has been a recent surge of interest in investigating the relationship between the immune system and the regenerative potential of neural tissue [43]. In the nervous system, microglia are the resident

immune cells that can sense the microenvironment and rapidly respond to various insults by producing molecular mediators, in particular cytokines [44]. Compelling evidence points to the implication of microglia in shaping the responsiveness of Müller cells to injury (Figure 2C). Indeed, the ablation of microglia, either in the chick or fish retina, suppresses Müller cell proliferation, supporting a positive influence of inflammation on retinal regeneration [45–47]. However, microglia likely have multifaceted effects, being either beneficial or detrimental for neural tissue repair depending on the duration of their activation and on their polarization phenotypes (pro- or anti-inflammatory) [48]. Along this line, White and coll. found that immune suppression performed before injuring the retina delays regeneration, while it accelerates it when performed after [46]. The inflammatory response in zebrafish is thus necessary for Müller cell activation but becomes a brake to the regeneration process if resolution is delayed [46,47]. This likely implies that immune-targeted therapeutic strategies should aim at adjusting the balance between microglia polarization states. In addition to resident microglia, infiltrating immune cells also appear to participate to the inflammatory response triggered by retinal injury [49]. The precise contribution of each immune cell types to the regeneration process remains to be investigated. Besides, cytokines/chemokines mediating the dialog between the inflammatory environment and Müller cells are just beginning to be explored. TNF- α and IL-6-family cytokines were for instance shown to promote injury-induced Müller glial cell reprogramming and proliferation in the chick and/or the fish retina [45,50–52]. A novel player impacting Müller cell cycle progression was recently identified as being the Midkine cytokine. Its loss-of-function in zebrafish mutants triggers reactive Müller glia to behave as in the mouse, initiating a reprogramming response, entering the G1 phase of the cell cycle following injury, but failing to progress further into S phase [53]. It is thus likely that comparing the cytokine repertoire between fish and mouse may help bringing new insights into the mechanisms that maintain Müller cells in a reactive state without cell cycle progression. As mentioned above, mTOR signalling is required for MGPC generation in chick and zebrafish injured retinas [11,12]. Interestingly, inflammation was recently shown to be necessary for mTOR signalling activation and to enhance retinal regeneration in a mTOR-dependent manner [12]. Finally, a recent study in chick revealed that pro-inflammatory signals from microglia induce NF- κ B activation and consequent inhibition of Müller glia reprogramming [54]. Remarkably however, forcing NF- κ B activation following microglial cell depletion (i.e. in a context when NF- κ B levels are low), results in an opposite effect with increased formation of MGPCs. The authors thus propose that microglia-induced NF- κ B activation is required to initiate Müller glia reprogramming, but becomes detrimental to the process if sustained. Such mechanism might be at work in the mouse retina where, in contrast to the fish situation, NF- κ B signalling components are significantly up-regulated following retinal damage [9]. Differences in inflammatory signalling may thus contribute to different regenerative capacities in different species. A better understanding of the mechanisms underlying the bilateral communication between Müller cells and the innate immune system in regenerative and non-regenerative species thus awaits further investigation.

Conclusion

Recent studies have shed new light onto the mechanisms underlying retinal regeneration and revealed potential strategies to stimulate Müller cell-dependent retinal repair in mammals. This review of the most recent literature in the field highlights the necessity of taking into account the different regulatory mechanisms that may affect expression of key regeneration genes. This includes genetic networks, epigenetic modifications and miRNA-mediated post-transcriptional gene silencing. The influence of Müller cell microenvironment is also starting to be scrutinized, in particular inflammatory regulatory molecules. Successful execution of retinal regeneration in mammals may thus rely on combined therapeutic strategies, comprising immune- genetic- or epigenetic-targeted approaches. Deepening our comprehension of these various regulatory modules will thus be critical to translate this knowledge into therapeutic tools to restore vision in patients afflicted with degenerative retinal diseases.

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FIGURE LEGENDS

Figure 1. Müller cell dependent retinal regeneration. (A) Upon retinal damage, zebrafish, *Xenopus laevis* or post-hatched chick Müller cells dedifferentiate, re-enter into the cell cycle and regenerate some types of neurons. Several signalling pathways were shown to be required for the reprogramming and proliferation events. The list has recently been broadened with the discovery that YAP, retinoic acid or mTOR are also key players in these processes [12,13,15]. Notch and FGF8a, on the other hand, are required for maintaining the quiescence of adult Müller cells [14,51]. **(B)** In the mouse damaged retina, although Müller cells initiate reprogramming, an event that requires the YAP-EGFR axis [15], they do not proliferate. Following acute retinal injury, these reactive Müller cells rapidly return to quiescence, a transition mediated by NFI factors [9]. **(C)** It is possible to awake the regenerative potential of mouse Müller glia. Overexpressing YAP or inhibiting the Hippo pathway in Müller cells is sufficient to induce their reprogramming and proliferation, even in undamaged retina [15,16]. Following gene transfer of β -catenin to stimulate Müller cell proliferation, photoreceptors can be regenerated by forcing the expression of transcription factors promoting rod cell fate specification [19].

Figure 2. Multiple regulatory mechanisms underlying Müller cell reprogramming. (A) In zebrafish, DNA demethylation predominates after injury, although some pluripotency-associated genes are already hypomethylated in quiescent Müller cells [23]. Changes in histone modifications also likely underlie Müller cell reprogramming. For instance, the histone methyltransferase Dot1l acts as an epigenetic modifier required for Müller cell dedifferentiation and MGPC proliferation [30]. HDAC1 activity, which triggers condensed chromatin architecture that limits transcription, is decreased in reactive Müller cells, likely leading to the derepression of regeneration-associated genes. Yet, HDAC acts as a repressor of Her4 (an effector of Notch signalling, a pathway associated with Müller glia quiescence [51,56]), and as such is required for efficient proliferation of MGPCs [29]. Manipulation of epigenome modifiers in the mouse may be applied to remove the epigenetic barriers limiting Müller cell reprogramming. This was illustrated by the use of HDAC inhibitors in conjunction with Ascl1 overexpression [32]. **(B)** Several miRNAs have been identified that are either upregulated or repressed in response to injury and play important roles in the proliferation of MGPCs [33]. Manipulating miRNAs was shown to be sufficient to increase the proliferation of mouse Müller glia *in vitro* [39,40,42]. **(C)** Microglia become activated in damaged retina, producing inflammatory cytokines, including TNF- α and IL-6. Müller cells are also a source of cytokines, such as Midkine. These various inflammatory mediators are required for MGPCs proliferation in zebrafish and/or chick, highlighting the influence of inflammatory signalling pathways on retinal regeneration [45,50–53].

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FIGURE 1

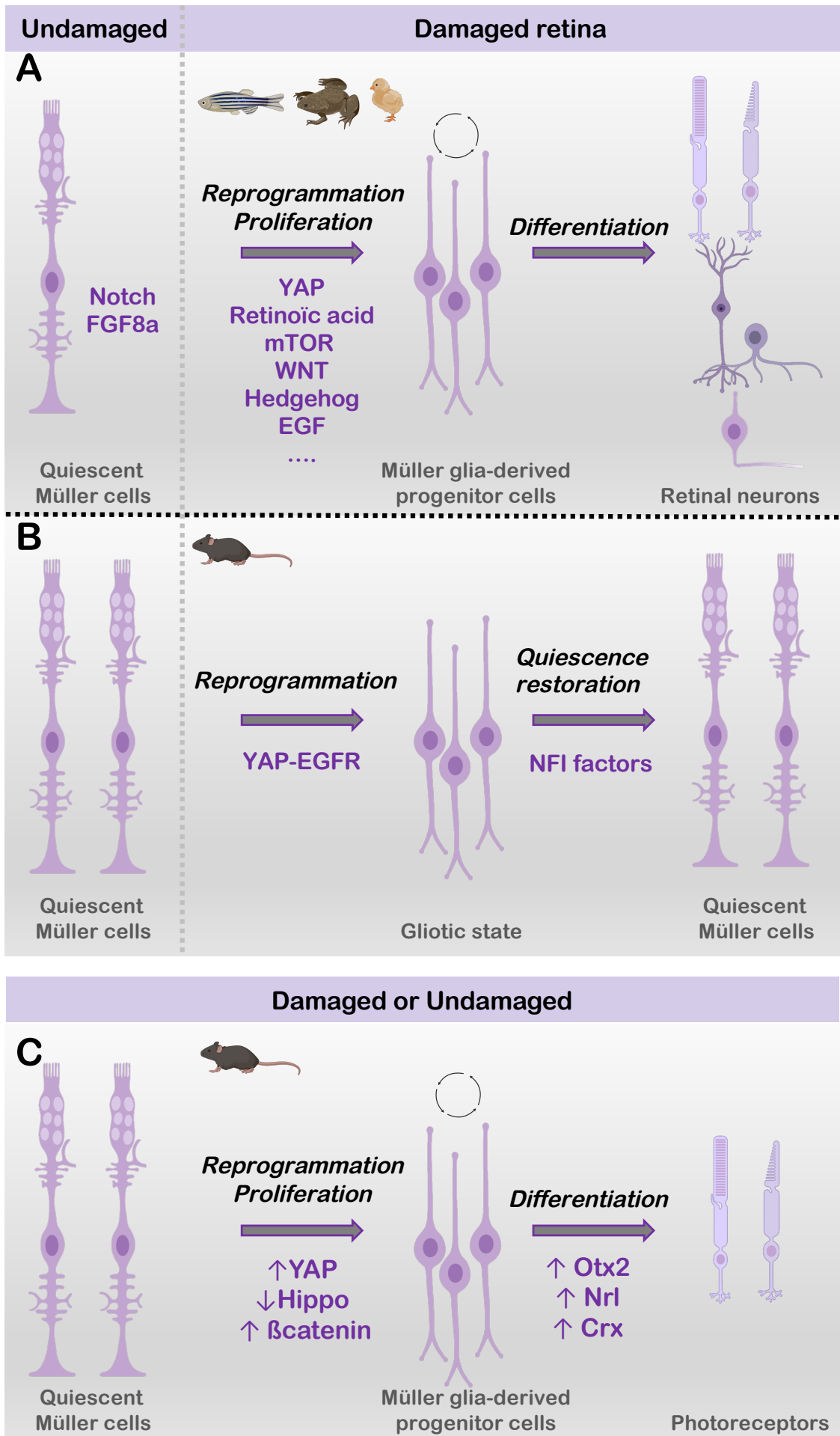


FIGURE 2

