

**Mini Review**

# Epigenetic Modification and Retinal Degeneration: Evidence of New Potential Therapeutic Targets

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**Received:** 10 December, 2018**Accepted:** 22 December, 2018**Version of Record Online:** 08 January, 2019**Citation**

Fan Y, Chen D (2019) Epigenetic Modification and Retinal Degeneration: Evidence of New Potential Therapeutic Targets. J Eye Stud Treat 2019(1): 21-27.

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Retinitis Pigmentosa (RP) is a group of hereditary neurodegenerative retinal diseases affecting photoreceptor cells and causing blindness in humans. Epigenetic modification, including DNA methylation, histone post-translational modifications and changes in nucleosome positioning, regulates gene expression, cellular differentiation and development that do not result from alterations in the DNA sequences. In the pathogenesis of RP, epigenetic modifications played an important role, including DNA Methyltransferases (DNMTs), Poly-ADP-Ribose Polymerase (PARP), Histone Deacetylases (HDACs), Bmi1, histone H3 lysine trimethylation at H3K27 (H3K27me3), and PI3K-Akt pathway. At present, we do not have effective therapy for RP, but epigenetic modification may shed light on its therapy. In this review, we provided an overview of the epigenetic modifications involved in RP and evidence of new potential therapeutic targets for RP.

**Facts**

- Epigenetic modification played an important role in the pathogenesis of RP.
- Epigenetic modification involved in RP includes DNA Methyltransferases (DNMTs), Poly-ADP-ribose Polymerase (PARP), Histone Deacetylases (HDACs), Bmi1, histone H3 lysine trimethylation at H3K27 (H3K27me3), and PI3K-Akt pathway.
- Blocking certain epigenetic modifications may protect photoreceptor cells and prolong their survival, which suggests a potential therapeutic strategy for RP.

**Open Questions**

- How can therapy targeting on epigenetics modification be translated from preclinical studies into clinical trials?
- How to specialize the epigenetic target with minimal off-target effects and maximal therapeutic benefits?
- Would the blockers of certain epigenetic modifications work for patients with gene mutation as well?

Retinitis Pigmentosa (RP) is a set of heredity retinal diseases that feature the degeneration of rod and cone photoreceptors, with a worldwide prevalence of approximately 1:4000 [1]. Though RP is a highly variable disorder, many patients fall into a classic pattern of progression. The degeneration of peripheral rod photoreceptors causes initial night vision loss. As rod degeneration continues, patients experience tunnel vision. Finally, patients

will lose daylight vision and progress to complete blindness due to macular cone loss [2]. Although most of RP cases are non-syndromic (lesions are confined to the eye), 20-30% of patients with RP have extraocular symptoms [3]. Such cases fall within more than 30 different syndromes. The most frequent syndromic form is Usher's syndrome, in which hearing impairment is involved [4]. Hardest-Biedl syndrome is another major form of syndromic RP, in which RP is associated with obesity, cognitive impairment, polydactyl, hypogenitalism, and renal disease [5,6]. Other rare syndromic forms of RP include Bassen-Kornzweig syndrome, Refsum's disease and  $\alpha$  tocopherol transport protein deficiency [7]. RP is a major cause of visual disability and blindness, and the most common Inherited Retinal Dystrophy (IRD) [3]. However, like most of the neurodegenerative diseases, an effective treatment remains an unmet medical need. Present treatments for RP include vitamin supplementation, neuro-protective factor-secreting intraocular implants, and electronic retinal prostheses [8-12]. However, these treatments are only minimally effective in slowing down the progression of the disease or merely rescuing vision.

## Mechanism of Pathogenesis

The retinal degeneration 1 (rd1 or rd) human homologous mouse is one of the most-studied models for RP. It is characterized by a loss-of-function mutation in the gene encoding for the  $\beta$ -subunit of rod photoreceptor cGMP Phosphodiesterase 6 (PDE6) [13]. About 4-5% of patients are suffering from mutations in the PDE6 gene [14]. Non-functional PDE6 leads to accumulation of cGMP which play a key role in the phototransduction cascade. Excessive cGMP triggers the degeneration of photoreceptors [15,16]. The mechanisms of rd1 retina pathogenesis may shed light on its therapy, including apoptotic and non-apoptotic cell death, cell-intrinsic factors, disrupted intracellular  $Ca^{2+}$  homeostasis, and epigenetic modifications [17-21].

## Gene Mutations

Currently, 84 genes and 7 candidate genes have been linked to non-syndromic RP, while 40 genes are related to syndromic RP (RP accompanied by extraocular symptoms) [3,22,23]. These genes encode proteins that play a role in phototransduction cascade, visual cycle, ciliary structure and transport, interphotoreceptor matrix, and so on [3].

## Epigenetic Modifications

Although gene mutations play a role in the pathogenesis of RP, epigenetic mechanism is another powerful factor. Epigenetic modification regulates gene expression, cellular differentiation and development that do not result from alterations in the

DNA sequences but via the chemical modifications of DNA and histones [24]. Previous studies have reported epigenetic modifications play a role in a variety of retinal diseases, including retinal fibrosis, retinoblastoma, RP, age-related macular degeneration, and diabetic retinopathy [25-29]. Recently, dysregulation of DNA methylation and histone acetylation has been found to be involved in the pathogenesis of RP [20,30-32].

## DNMTs

DNA hypermethylation catalyzed by DNA Methyltransferases (DNMTs) is one important epigenetic factor for RP [33]. DNMTs catalyze the transfer of methyl groups from S-Adenosyl-L-Methionine (SAM) to the 5-position carbon in cytosines within DNA to generate 5-methylcytosine (5mC) [34]. Increased cytosine methylation as well as increased DNMT expression was detected in dying photoreceptors in the rd1, rd2, P23H, and S33ter rodent models for RP [35]. DNA hypermethylation of several individual genes were found in rd1 mice, including important transcription factors YY1, E2F3 and NRL [35]. The transcriptional repression of these target genes contributes to critical dysregulation of cellular events to precipitate photoreceptor cell death [35]. The use of DNMT inhibitor, decitabine, reduced DNA hypermethylation and decreased the number of dying photoreceptors in short term [35], which suggests inhibition of DNA methylation as a potential treatment for RP.

## PARylation

In cellular physiology, Poly-ADP-Ribose Polymerase (PARP) group is the important mediator that facilitates the DNA repair process and strongly protects cells against genotoxic stressors [36,37]. However, excessive PARP activation may overstrain the cellular metabolism, leading to an energetic collapse and followed by cell death [37,38]. In conjunction with its antagonist Poly-ADP-Ribose-Glycohy-Drolase (PARG), free PAR polymers generate. In rd1 mice, free PAR will cause photoreceptors death through nuclear translocation of Apoptosis Inducing Factors (AIF) [39], and oxidative DNA damage related to Transient-Receptor-Potential (TRP) ion channels [40,41]. When PARP-specific inhibitor PJ34 was used in a long-term setting, the number of surviving photoreceptors increased, suggesting a protective effect as well as a possible therapeutic target for RP [42].

## HDAC

Histone Deacetylases (HDACs) regulates the structure of chromatin through deacetylation of histone in neurons [43,44]. There are three main classes of HDAC family, HDAC I (HDAC 1-3 and 8), II (HDAC 4-7, 9, and 10), and III. HDAC

hyperactivation would result in significantly altered rd1 gene transcription, including downregulation of the transcription factor CREB [19,45,46]. HDAC4 overexpression prolongs rod survival in rd1 mice, where the survival effect was due to its cytoplasmic activity, and relied partially upon the activity of Hypoxia Inducible Factor 1 $\alpha$  (HIF1 $\alpha$ ) [26]. HIF1 $\alpha$  plays a central role in the regulation of oxygen homeostasis [47], and it is not detectable in the mature mouse retina [48]. Exposure of retinas to hypoxia causes stabilization of HIF1 $\alpha$  and protects photoreceptors from light-induced retinal degeneration [48]. HIF1 $\alpha$  stabilization thus might provide a mechanism for HDAC4-induced photoreceptor protection in rd1 mice [26]. However, experimental evidence also suggested that excessive activation of HDACs I/II promotes cell death [49]. Therefore, the right balance between the activities of different HDAC classes seems to be crucial for cellular viability [49]. Besides, there is cross-talk between HDAC and PARP activity. As mentioned above, PARP is involved in DNA damage repair, while excessive PARP activity may lead to cell death [50]. Increased HDAC activity appeared to be responsible for an activation of PARP in degenerating rd1 photoreceptors [20].

## Bmi1

Knocking out Bmi1 results in extensive photoreceptors survival in rd1 retina [51]. CDK4, cyclin-dependent kinase 4, is re-expressed in post-mitotic neurons in various models of neurodegenerative diseases, including Alzheimer's disease [52,53], Parkinson disease [54], and amyotrophic lateral sclerosis [55]. The re-expression of CDK4 implicates the reentry into the cell cycle and in the transition from G1 to S phase, but fails to complete S phase and undergo apoptosis. In Rd1 mice, the nuclear expression of CDK4 causes the phosphorylation of Rb [51]. Then, E2F1 is released and activated upon Rb phosphorylation and is known to contribute to neuron apoptosis [51]. The upstream epigenetic regulator Bmi1 of CDK4 could promote the apoptosis of neurons and cause the neuron loss in Rd1 retinas by repressing tumor suppressor genes such as Ink4a/Arf locus [51]. Ink4a encodes p16<sup>Ink4a</sup>, the inhibitor of CDK4 [56]. And Arf encodes p19Arf that could promote expression of p53 [56]. It's reported that genetic ablation of Bmi1 could provide extensive photoreceptor survival and improvement of retinal function in Rd1 mice [51]. Therefore, Bmi1 and E2f1 could be potential targets for RP gene therapy. Some studies report Bmi1 is involved in DNA repair initiation [57,58]. In Glioblastoma Multiforme (GBM), an aggressive brain tumor, Bmi1 is enriched in CD133-positive cancer-initiating Neural Stem Cell (NSC) [57]. Bmi1 here prevents NSCs senescence, apoptosis, or differentiation by repression the transcription and activation of tumor suppressor genes [59-65]. Meanwhile, Bmi1 could recruit the DNA damage response machinery to DNA DSB sites in response

to radiation, thus promoting NSCs survival [57]. Therefore, Bmi1 may have dual effect on the survival of neural cells.

## H3K27me3 and PI3K-Akt

In rd1 retina, pan-trimethyllysine of histone significantly increase, especially histone H3 lysine trimethylation at H3K27 (H3K27me3) [66]. Downregulating H3K27me3 with PCR2 inhibitor DZNep can delay the photoreceptors degeneration in rd1 mice, which is related with multiple signaling pathways, including PI3K-Akt, rod differentiation and calpains [67]. One mechanism of DZNep protective effect is through activating PI3K-Akt pathway [67]. It's reported that Rd1 retina has high levels of H3K27me3. H3K27me3 is a repressive chromatin mark and mediates epigenetic silencing, which is catalyzed by Ezh2-containing PRC2 [66]. It's shown that DZNep inhibited Ezh2 protein level, H3k27me3 deposition in ex vivo retinal explants of rd1 mice. Ezh2 is the core part of PRC2, and its HMT enzyme activity could catalyze the addition of methyl groups to H3K27 [67]. Akt could phosphorylate serine 21 on Ezh2 and impedes its binding to H3 [68]. PI3K is the upstream regulator of Akt [67]. Its activation leads to production of PIP3 which recruits Akt to the plasma membrane, where Akt gets phosphorylated and activated on Thr308 and Ser473 by Pdk1 [69] and mTORC2 [70]. PI3K inhibitor LY294002 had the opposite effect of DZNep on rd1 retinas, which confirmed the role of Akt [67]. When treated with DZNep, the reduced H3K27me3 interacts with PI3K-Akt pathway through de-repressing Pik3r1 and Pik3r3 [67]. Together, Akt-mediated phosphorylation of Ezh2 and H3K27me3-mediated repression of PI3K subunits expression form a negative feedback loop [67]. This network contributes to the photoreceptor survival in rd1 retina. Another possible mechanism is DZNep's inhibitory effect on photoreceptor genes, Nrl and its downstream target Nr2e3 [67]. Nrl plays an important role in rods differentiation. Precursors that turn on Nrl differentiate into rods and those that do not become cones [71]. CRISPR/Cas9-mediated genome editing targeted on Nrl can protect rod and cone photoreceptors, and restore visual function in mouse RP models [72,73]. Therefore, through down-regulating of Nrl-Nr2e3, DZNep could rescue rods and cones. Calpains are a group of calcium-activated proteases with 14 known isoforms [74], which are strongly activated in degenerating rd1 mouse photoreceptors, in contrast to those of their wt counterparts [75]. DZNep treatment significantly suppressed its elevation in rd1 *ex vivo* explants, suggesting DZNep can protect rd1 retina by suppressing calpain activity [67].

## Treatment for RP

As mentioned at the beginning, present treatments for RP include dietary changes (vitamin A and/or the fish oil docosahexaenoic

acid), electronic retinal implants and neuro-protective factors (brain-derived neurotrophic factors [76], basic fibroblast growth factor [77], ciliary neurotrophic factor [78] and others), which have very limited effect [3]. Several gene-specific and mutation-specific treatments are emerging, including RPE65 gene therapy [79-82], REP1 gene for choroideremia [83]. In preclinical studies, gene therapeutics is almost always delivered before the onset of cell degeneration, because these approaches require the presence of the cells that will be targeted [3]. However, most neurodegenerative diseases are diagnosed after the onset of degeneration [84]. Other emerging therapeutic strategies involve Antisense Oligonucleotides (AONs) [85], genome editing using CRISPR/Cas system [86], and cell replacement therapy with retinal progenitor cells or embryonic stem cells [87]. Modifications of histone and DNA are reversible, which makes them good targets for therapeutic intervention. We have already had drugs targeted on the epigenetic machinery such as DNMTs, HDACs. For example, DNMT inhibitors include decitabine, zebularine, while for HDAC inhibitors, we have valproic acid, phenylbutyrate, nicotinamide, AGK2 and so on [33]. But these drugs are mainly designed for stroke, AD, HD or PD. We still do not have any commercial epigenetic-targeting drugs for RP at present. Meanwhile, most of drugs mentioned above are nonspecific. Targeting a specific epigenetic modification rather than affect global modifications would be the possible solution to overcome the off-target effects and the lack of specificity.

## Conclusion

In summary, we provided a review of the mechanisms of RP pathogenesis, especially the epigenetic modifications. DNA methylation and post-transcriptional histone modifications, including DNMTs, PARP, HDAC4, Bmi1, H3K27me3 and PIK3-Akt pathways, have a great potential for developing novel therapeutic strategies. Besides RP, the past decade has witnessed the accumulation of evidence that collectively points to a role for epigenetic modifications in Huntington's Disease (HD) [88,89], Parkinson's Disease (PD) [90], Ataxia-Telangiectasia (AT) [91], and Alzheimer's Disease (AD) [92]. In this scenario, we saw great potentials for histone modifications in neurodegenerative disease including retinitis pigmentosa.

## Acknowledgements

This study was supported by grants to DC from the National Natural Science Foundation of China (81371022, 81570860, and 81870665).

## Competing Financial Interests Statement

The authors declare no competing financial interests.

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