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Epigenetic Regulation of Retinal Stem Cells

Editorial

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Epigenetics is defined as the investigation of stably heritable changes of gene expressionthat occur without alteration ofthe DNA sequence itself [1-3]. Epigenetic gene regulation usually involves DNA methylation and/or modification of histones [4]. In mammalian cells, DNA methylation mainly occurs at the fifth carbon of the cytosine residuein a 5'-CG-3' (CpG) dinucleotide and its occurrence is inversely correlated with the GC content and CpG density [5,6]. Epigenetic regulation has a role in many biological processes, including gene transcription, imprinting, and transposon activity in embryonic stem cells, germ cells, somatic cells, and tumor cells [7-9]. Histone modification represents an additional epigenetic mechanism that regulates gene expression, genomic imprinting, and X chromatin remodeling synergeticallyalong with DNA methylation [10,11].

Stem cells are able to self-renew and proliferate within the niche, where they are maintained in an undifferentiated and quiescent state by interactions with the surrounding matrix and nichecells that involve integrins and cadherins, respectively. The niche and its components protect stem cells from stress, such as accumulation of free radicals and reactive oxygen species (ROS). Therefore, keeping ROS level low is linked to the maintenance of stem cellsin an immature state. Aging of stem cells is mainly induced by telomere shortening, oxidative stress, and epigenetic changes of the genomeas in other cell types. An increase of ROS inducesup-regulation of p16INK4a and p19ARF [12]. Polycomb group (PcG) genesplay a key role in the epigenetic regulation of stem cells. Epigenetic regulation of stem cell self-renewal/proliferation and commitmen is controlled by PcG protein at amajor cell cycle checkpoint [13], through which the activated p19Arf-p53-p21-retinoblastoma protein (Rb) and p16Ink4a-Rb pathways mediate heterochromatin formation and silencing of E2F target genes during cellular senescence[14]. Epigenetic regulation is also important for the maintenance of retinal stem cells and for normal retinal development [15].

Retinal diseases (mainly age-related macular dystrophy and the hereditary retinal dystrophies) are a major cause of blindness worldwide. Lifestyle-related diseases, such as hypertension, hyperlipidemia, diabetesmellitus, and obesity, are alsoare risk factors for retinal diseases[16]. Since the main underlying problem in retinal degeneration is the loss of retinal neural cells, treatment strategies aimed at regenerating neural cells and retinal pigment epitheliumcells have been examined as potential therapeutic modalities. Transplantation studies using immature cells derived from the neural retina have demonstrated that transplanted neuronal progenitor cells are integrated into the developing retina and acquire the morphological features of retinal photoreceptors including rhodopsin [17]. Recently, transplantation of induced pluripotent stem cells (iPS) into the subretinal space has also been investigated in animal models [18-21], and these studies have demonstrated that transplanted iPS are integrated into all major retinal cell layers and express photoreceptor markers [21]. Since the risk of adverse effects due to the viral vector is not negligible, further investigation is required to establish a virus-free protocol for the transplantation of iPS. Identification of highly demethylated stem cells by application of epigenetic profiling could offer a higher potential for the therapeutic application of stem cells for retinal repair in the future.

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