INTRODUCTION

Treatment strategies for retinal dystrophies

Retinal dystrophies can be caused in many different ways. Typically, they result in photoreceptor degeneration and ensuing blindness. Recent years have been an exciting time for the development of treatments for retinal dystrophies, with reports of the first major clinical successes.

This special issue explores different strategies for treating retinal dystrophies, including gene therapy, cell replacement therapies, optogenetic-based visual prosthetic devices, as well as the use of less conventional natural product remedies.

Jane Farrar, Sophia Millington-Ward, Naomi Chadderton, Fiona Mansergh, and Arpad Palfi present a comprehensive review of different gene-based therapeutic strategies currently being developed to treat retinal dystrophies. These strategies include the introduction of a wild-type gene to counter loss of function due to mutant forms of the gene, as well as the reduction of mutant gene expression in dominant inherited retinopathies. In addition to addressing a specific mutant gene, the authors also discuss modulation of secondary features associated with the disease pathology. The principle of this approach is to target problems that are common to different, polygenic disorders, focusing on cell survival (e.g., providing neurotrophic factors or antiapoptotic agents, reducing the level of oxidative stress). This strategy is specifically addressed in another review in this issue by Bisti and co-workers. Another approach, discussed more briefly, consists of assigning new functions to surviving cells. This approach is mainly about introducing genes encoding for light-sensitive molecules (optogenetics), and is taken up in greater detail by Barrett and co-workers in this issue.

Kerstin Nagel-Wolfrum, Fabian Möller, Inessa Penner, and Uwe Wolfrum write about the possibility of using translational read-through drugs (TRIDs) to treat retinal dystrophies caused by in-frame nonsense mutations. Many retinal degenerations are caused by mutations in genes that are large or express a variety of different isoforms. These degenerations do not lend themselves readily to treatment by viral delivery of wild-type cDNA. The authors argue that pharmacological treatment with TRIDs offers an effective alternative to treat some of these degenerations—ones that are caused by a mutation that results in a premature stop codon. TRIDs inhibit termination of translation at the premature stop codon. They include aminoglycosides and a small molecule, PTC124, which was identified from a high-throughput screen. The authors describe TRIDs and their mode of action, and discuss their advantages and limitations.

Carla Mellough, Joseph Collin, Evelyne Sernagor, Nicholas Wride, David Steel, and Majlinda Lako discuss recent advances made in differentiating human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs) into retinal cells. They highlight the steps that are required to generate human synthetic retinas from patient-specific iPSCs. They discuss how successful in vitro differentiation of hESCs and hiPSCs emulates human embryonic development and yields high production of photoreceptors, retinal pigment epithelium and retinal neurons when done in optimal culture conditions. They review recent progress in generating optic cups and fully laminated retinas in vitro from murine ESCs and hESCs, stressing the importance of optimizing differentiation protocols. They discuss how differentiating hESCs can endogenously upregulate factors crucial for differentiation into specific cell types and review the key signaling molecules needed for cell genesis and differentiation (Shh, transforming growth factor beta, BMP, Wnt, fibroblast growth factor, Notch, IGF-1) as well as oxygen supply and extracellular matrix components. Finally, they discuss the exciting new opportunities presented by using hiPSCs to investigate retinal disease models in vitro.

Rachael Pearson, Claire Hippert, Anna Graca, and Amanda Barber review recent progress and challenges for photoreceptor transplantation. They address remodeling of the host retina for successful photoreceptor transplantation, and the optimal developmental stage of the transplanted cells for successful integration. They discuss the problems posed by glial proliferation in the degenerating retina, and how the integrity of the extracellular matrix affects photoreceptor transplantation. In particular, they discuss how two cellular matrix metalloproteases (MMP-2 and MMP-9) expressed by Muller cells affect the integration of transplanted photoreceptors, showing that when done at the right time, MMP-2 upregulation may encourage the integration of transplanted cells. They then discuss how the outer limiting membrane presents a physical barrier to the migration of transplanted cells into the host retina, with transient fragmentation of it providing improved integration. Finally, they discuss immunological challenges associated with potential rejection of transplanted cells, which express major histocompatibility complex proteins from early differentiation stages.

John Barrett, Rolando Berlinguer-Palmini, and Patrick Degenaar discuss the use of optogenetics to induce light sensitivity in surviving retinal neurons following photoreceptor degeneration. After presenting a historical background and overview of optogenetics (including a useful discussion about the advantages of optogenetics over electrical implantable devices), they review the different optogenetic probes currently used (e.g., channelrhodopsin for excitation and halorhodopsin for inhibition) and discuss the important issue of deciding which specific cell types to target. Next, they discuss irradiance levels required for the activation of specific probes, which also imposes limitations on the engineering design. Finally, they discuss the requirements for processing visual stimuli, including fast transmission of visual information to the
display, gain control, image enhancement, encoding strategies (depending on which cells are targeted), and control of signal intensity.

**Silvia Bisti, Rita Maccarone, and Benedetto Falsini** discuss the neuroprotective effects of natural product remedies, particularly saffron, for retinal dystrophies. First, they introduce the spice saffron and its therapeutic uses throughout history. They describe the active components found in saffron, carotenoids such as zeaxanthin, crocin, crocetin (powerful antioxidants) and a plethora of other active molecules. They discuss evidence for the protective effects of dietary saffron in a rat light damage model, and the likely underlying mechanisms. Further, they review clinical trials that they performed on patients with early age-related macular degeneration. Finally, they discuss safety issues for long-term use of dietary saffron to treat retinal dystrophies.

Together, these articles demonstrate different approaches being considered to treat retinal dystrophies. Clearly, some approaches lend themselves more appropriately to some types of dystrophy than to others, as well as to different stages of the dystrophy. Once a dystrophy progresses, the focus shifts from preventing degeneration to restoring vision. As with all diseases, prevention is the best cure. At present, gene therapy applied to loss-of-function monogenic dystrophies shows the most promise as a preventative treatment. But, there is still plenty of need for restorative approaches, especially in multifactorial dystrophies and the many cases where diagnosis of the dystrophy does not occur until degeneration is well underway.

Restoration of some level of visual function may ultimately be best achieved using a combination of different approaches, although this leads to complications for clinical trials. When diagnosis occurs after degeneration is well underway, cell replacement therapies offer an attractive solution. A major problem, however, is the profound remodeling that occurs in the surviving retinal layers after photoreceptor cell death, leading to aberrant connectivity and abnormal neural activity. Efforts should be made to protect photoreceptors from dying, and to prevent surviving cells from undergoing such remodeling. Saffron, or other natural remedies with powerful antiapoptotic, antioxidant, and anti-inflammatory properties, may help preserving the integrity of the retina, setting the stage for more successful gene or cell replacement therapy, or for targeting bipolar cells for optogenetic or direct electrical stimulation with prosthetic devices. Alternatively, it may prove better to circumvent degeneration and remodeling by using direct stimulation (electrical or optical) of the retinal ganglion cells, the output cells of the retina, because these cells remain relatively unaffected. But in order to fulfill this challenging goal, we need to achieve a deeper understanding of how ganglion cells encode complex visual scenes into trains of action potentials, as they normally do via information processing in the outer and inner plexiform layers in the healthy retina.

One could hope that refining current therapeutic approaches or developing more integrative ones in the near future will help patients maintain their sight in old age.

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