Strategies to treat neurodegeneration in neuronal ceroid lipofuscinosis: a view onto the retina

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Neuronal ceroid lipofuscinosis (NCL), also known as Batten disease, is the umbrella term for a group of autosomal recessive lysosomal storage disorders with onset mainly in childhood. The total 13 genetically distinct NCLs are caused by mutations in genes encoding soluble or transmembrane lysosomal enzymes, and have been classified according to the affected gene into CLN1 to CLN8. Another study showed that degeneration in CLN6 disease (Kleine Holthaus et al., 2018). Intracerebroventricular injections of an AAV9 vector encoding human CTNS in neonatal Cln6 mice attenuated the pathology in visual centers of the brain. Of note, the brain-directed treatment in CLN6 mice was significantly slower than intravitreal injections of a control vector, suggesting that the subretinal route is not suitable for delivering therapeutic proteins. The limited outcome of the ERT and the NSC-based enzyme replacement therapy is among the potential treatment options for the CLN2 dog model. The CLN2 canine model might be more effective in attenuating retinal degeneration in the Ctsd knockout mutant. To this aim, NSCs were lentivirally modified to overexpress CTSD and transplanted into the vitreous cavity at P7. While the cell-based treatment reduced lysosomal storage accumulation and lysosomal hypertrophy and neuroinflammation, it neither restored the disrupted autophagic flux nor improved retinal function in a CLN2 dog model (Murray et al., 2021). The most prevalent NCL, CLN3 disease, is caused by mutations in the CLN3 gene, which encodes cystathionine β-synthase (CBS). CLN3 patients usually present with progressive visual deterioration at the early stages of the disease, CLN3 mouse models display a relatively mild retinal dystrophy phenotype, and partial loss of CTSD enzymatic activity accounted for ~44% of normal at the time of analysis at P22 (Liu et al., 2022). Possible explanations for this paradoxical observation include (i) preferential uptake of the protease by cell types facing the vitreous cavity (i.e. astrocytes, Müller cells, ganglion cells, and displaced amacrine cells) and/or (ii) slow diffusion of functional CTSD from the vitreous into the retina, resulting in stage-wise therapeutic benefits. Differences in genotype-phenotype relationships suggest that restoration of CTSD enzymatic activity to 10% or less of normal is sufficient to attenuate disease progression. While the result of the combined treatment effects on the retina of the CLN2 canine model (Tracy et al., 2016), indicating that ex vivo gene therapy is among the potential treatment options for vision loss in certain NCLs. The limited outcome of the ERT and the NSC-based enzyme substitution approach suggest that autologous mesenchymal stem cells might be due to insufficient levels of functional CTSD. The continuous intravitreal administration of CTSD might be effective in attenuating retinal degeneration in the Ctsd knockout mutant. To this aim, NSCs were lentivirally modified to overexpress CTSD and transplanted into the vitreous cavity at P7. While the cell-based treatment reduced lysosomal storage accumulation and lysosomal hypertrophy and neuroinflammation, it neither restored the disrupted autophagic flux nor improved retinal function in a CLN2 dog model.
neuroinflammation were markedly attenuated. Furthermore, and different from the NSC-based enzyme substitution strategy, the intravitreal gene therapy fully restored the disrupted autophagic flux as indicated by normalized levels of the autophagy marker SQSTM1/p62 (Figure 1E and F) and microtubule-associated protein 1 light chain 3-II. More importantly, the treatment effectively promoted cone and rod photoreceptor survival (Figure 1G and H) and significantly slowed the loss of rod bipolar cells (Liu et al., 2022), demonstrating the potential of ocular gene therapy to ameliorate this severe and rapidly progressing retinal dystrophy. An AAV vector-mediated gene transfer of lysosomal enzymes or secreted proteins to dystrophic retinas has also shown promise in animal models of other NCLs. For instance, an AAV2 vector-mediated expression of tripeptidyl peptidase 1 (PPT1) – the enzyme affected in CLN1 disease – in retinal ganglion cells of Ppt1 knockout mice slowed the decline in retinal function as demonstrated by electroretinogram recordings and resulted in a better organization of the photoreceptor layer (Griffey et al., 2022). Ocular gene therapy may also attenuate deterioration of retinal structure and function in sheep deficient in CLN5, a putative lysosomal enzyme. Intravitreal injections of scAAV9.CLN5 in presymptomatic animals prevented lysosomal storage accumulation, ameliorated reactive astroglisis, markedly preserved visual function as evaluated in electroretinogram recordings and significantly slowed photoreceptor degeneration (Murray et al., 2021). CLN1 disease is caused by biallelic loss-of-function mutations in the GRN gene encoding progranulin (PGRN), a secreted protein implicated in the regulation of cell survival, inflammation, and lysosomal homeostasis. While an intravenous gene therapy in young postnatal Gnr knockout mice using an AAV9-2YF capsid attenuated retinal thinning, retina structure was either not preserved or even adversely affected after intravitreal injections of AAV2-7m8.PGRN in mutant mice aged one month or older. Findings indicate that the therapeutic outcome in this CLN1 animal model is determined by the route of vector administration and/or age at treatment.

Preclinical studies have demonstrated the efficacy of various therapeutic strategies in attenuating retinal degeneration and vision loss in NCLs caused by dysfunctions of transmembrane or soluble proteins. Whether these strategies will show similar therapeutic benefits in NCL patients remains to be seen. The future clinical trials. If successful, meaningful preservation of retina structure and function would improve the quality of life of NCL patients presenting with non-symptomatic retinopathy or with vision loss at the early stages of the disease. Evidently, effective retina-directed treatment options will be of great relevance once therapies for neurodegeneration in the brain become available, as exemplified by the brain-directed ERT for CLN2 disease.

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Perspective

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References

Bassal M, Liu J, Jankowiak W, Saftig P, Bartsch U (2021) Rapid and progressive loss of multiple retinal cell types in cathepsin D-deficient mice–an animal model of CLN10 disease. Cells 10:696.
Griffey M, Macauley SL, Ogilvie JM, Sands MS (2005) AAV2-mediated ocular gene therapy for infantile neuronal ceroid lipofuscinosis. Mol Ther 12:413-421.
Kleine Holthaus SM, Ribeiro J, Abelleira-Hervas L, Pearson RA, Duran Y, Georgiadis A, Sampson RD, Rizzi M, Hoke J, Massow R, Arzam S, Luhmann UF0, SM, Smith AJ, Mole SE, Ali RR (2018) Prevention of photoreceptor cell loss in a Cchner/nclf mouse model of Batten disease requires systemic delivery of AAV9 gene therapy partially prevents retinal degeneration in canine CLN2 neuronal ceroid lipofuscinosis. Exp Eye Res 152:77-87.
White KA, Nelvagel HR, Poole TA, Lu B, Johnson TB, Davis S, Pratt MA, Brukdj J, Assis AB, Likinte S, Meyer K, Kaspar BK, Cooper JD, Wang S, Weimer JM (2021) Intracranial delivery of AAV9 gene therapy partially prevents retinal degeneration and visual deficits in CLN6-Batten disease mice. Mol Ther Methods Clin Dev 20:497-507.
Whiting REH, Robinson K, Ota-Kurokii J, Lim S, Castaner LJ, Jensen CA, Katz ML (2021) Intravitreal implantation of TP11-transduced stem cells delays retinal degeneration in canine CLN2 neuronal ceroid lipofuscinosis. Exp Eye Res 198:101835.
Whiting REH, Pearce JW, Vanseeistenke DP, Bbi K, Lim S, Robinson K, Castaner LJ, Sinclair J, Chandra S, Nguyen A, O'Neill CA, Katz ML (2020b) Intravitreal enzyme replacement preserves retinal structure and function in canine CLN2 neuronal ceroid lipofuscinosis. Exp Eye Res 197:108130.

Marques ARA, Di Spiezio A, Thinesen N, Schmidt L, Grozinger J, Lullmann-Rauch R, Damm M, Storck SE, Pietrzik CU, Fogh J, Bartsch, Urban, Opi, others.

Figure 1 | Ocular gene therapy restores the autophagy-lysosomal pathway and slows photoreceptor loss in Ctsd knockout mice. A scAAVshH10 vector encoding CTSD was intravitreally injected at postnatal day 5, and retinas were analyzed at postnatal day 22 (B, D, F, H). Injections of a scAAV9H10 vector encoding the green fluorescent protein (GFP) into the contralateral eyes served as a control (A, C, E, G). Normalized levels of saposin D (B) and subunit of mitochondrial ATP synthase (SCMAS; D), and the absence of sequestosome 1 (p62) bodies (F) in treated retina demonstrate preservation of storage material accumulation and clearance of autophagic substrates, respectively. Restoration of the autophagy-lysosomal pathway results in significant preservation of the photoreceptor cell layer (onl; outlined with white arrowheads) and survival of numerous arrestin-positive cones (H). gcl: Ganglion cell layer; inl: inner nuclear layer. Scale bar: 50 µm. Unpublished data.

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