associated with glaucoma, one of the greatest of which is age. Like other forms of neurodegeneration, loss of RGCs occurs more often in people over 60, raising questions about whether similar mechanisms might underlie glaucoma and other age-related neurodegenerative disorders such as Alzheimer's disease[5]. There also seems to be a strong genetic component to glaucoma, with certain forms occurring four to five times more frequently in dark-skinned people[6]. Finally, the disease is often thought to be caused by elevated fluid pressure inside the eye. However, abnormally high intraocular pressures are neither 100% predictive of nor a prerequisite for glaucoma, and many people with the disease have normal eye pressures[2]. This broad range of risk factors has led many to speculate that glaucoma is caused by a variety of individual stressors that all increase RGC susceptibility to death. The key questions have therefore become: what are the common molecular pathways that trigger RGC loss, and how could those pathways be manipulated for therapies?

Skowronska-Krawczyk *et al.* analysed genetic-association studies in several human populations to find genes that are commonly mutated in people with primary open-angle glaucoma (the most common form of the disease). One screen picked up *SIX6*, which encodes a transcription factor that helps to shape the eye during embryonic and postnatal development[7]. A mutation called His141, which changes amino-acid residue 141 of the SIX6 protein from asparagine to histidine, confers a risk of glaucoma. The authors performed a careful structural analysis, which revealed that this residue probably lies outside the transcription factor's DNA-binding domain. Instead, the mutation might affect the ability of SIX6 to interact with other transcription factors or with co-factor proteins, altering the efficiency with which the protein can activate its target genes.

To identify possible target genes for SIX6, Skowronska-Krawczyk and colleagues again turned to genetic-association studies. These indicated that mutations in the *p16INK4a* gene are a strong risk factor for glaucoma. The authors found that expression of both *p16INK4a* and *SIX6* was higher in eyes of people with glaucoma than in those of healthy people. Moreover, they demonstrated that SIX6 binds to and activates *p16INK4a*.

In many cell types, *p16INK4a* is associated with a cellular ageing process called senescence. Skowronska-Krawczyk *et al.* found that approximately four times more RGCs were senescing in patients with glaucoma than in healthy people. To probe this pathway further, the authors engineered human retinal progenitor cells cultured *in vitro* to express the SIX6 His141 mutation. The mutant protein strongly upregulated *p16INK4a* and another marker of cellular senescence, the *IL-6* gene. This effect seems to be specific to the His141 mutation, because upregulation of these markers did not occur in cells producing wild-type SIX6 or forms of SIX6 mutated at different residues. Together, the results indicate that the His141 mutation increases the effectiveness with which SIX6 activates *p16INK4a* and triggers senescence pathways in RGCs.

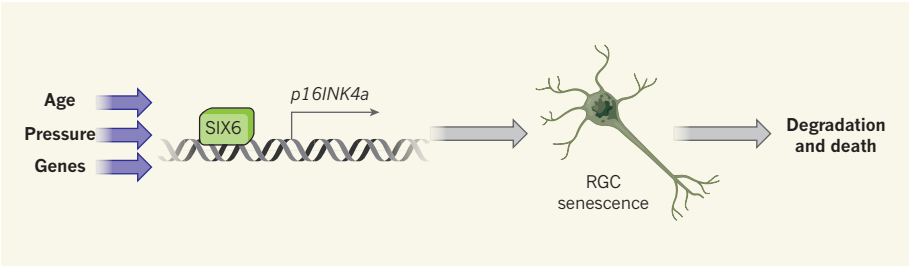

Figure 1 | Molecular pathways that underlie glaucoma. Age, elevated pressure in the eye and certain genetic mutations are all associated with an increased risk of glaucoma, a form of blindness linked to the degradation of retinal ganglion cells (RGCs). Skowronska-Krawczyk *et al.*[4] report that these risk factors converge on a single molecular cascade in which the transcription factor SIX6 binds to and activates the gene *p16INK4a*. Increased *p16INK4a* expression causes RGC senescence and, eventually, RGC degradation and death.

Skowronska-Krawczyk and colleagues next explored whether activation of *p16INK4a* was linked to RGC ageing or death in mice in which intraocular pressure was experimentally raised. They found that expression of both *SIX6* and *p16INK4a* increased markedly after experimental elevation of intraocular pressure. The evidence for an interaction between SIX6 and *p16INK4a* was further bolstered by the discovery that *p16INK4a* expression was reduced in mice lacking SIX6, and that elevated intraocular pressure increased SIX6–*p16INK4a* binding in wild-type mice. As in human glaucomatous retinas, increases in intraocular pressure dramatically elevated the number of senescent RGCs. Together, these results suggest that increased *p16INK4a* expression is a major cause of cellular-senescence pathways that ultimately lead to RGC degeneration and death in glaucoma.

In a final set of experiments, the authors performed a crucial test of this model by assessing whether genetic deletion of *p16INK4a* or partial deletion of *SIX6* impeded RGC death in a mouse model of glaucoma. Remarkably, when intraocular pressure was experimentally increased in either of these genetically mutated mouse strains, RGCs resisted death, strongly supporting the idea that SIX6-activated increases in *p16INK4a* mediate RGC loss in response to different stressors (Fig. 1).

Skowronska-Krawczyk and colleagues' study is an important step forward. First, it provides support for the long-held view that, even though different risk factors and stressors can increase the likelihood of glaucoma, there is a common molecular mechanism by which those stressors act to kill RGCs. Second, the study indicates that cellular senescence and its associated pathways are precursors to RGC degeneration and death.

Over the past few years, there has been a surge in our understanding about which RGCs are most vulnerable in early-stage glaucoma[8,9], and of the ion channels required to translate intraocular pressure increases into RGC degradation and death[10]. The current study provides a solid molecular foundation on which to integrate these findings. A more complete understanding of the biological underpinnings of glaucoma will no doubt also help to identify new targets for intervention, and might reveal mechanistic insights into the molecular basis of other age-related neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. ■

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CORRECTION

The News & Views article 'Rehabilitation: Boost for movement' by Randolph J. Nudo (*Nature* **527,** 314–315; 2015) omitted to mention that the author has declared competing financial interests. Details are available in the online version of the article.