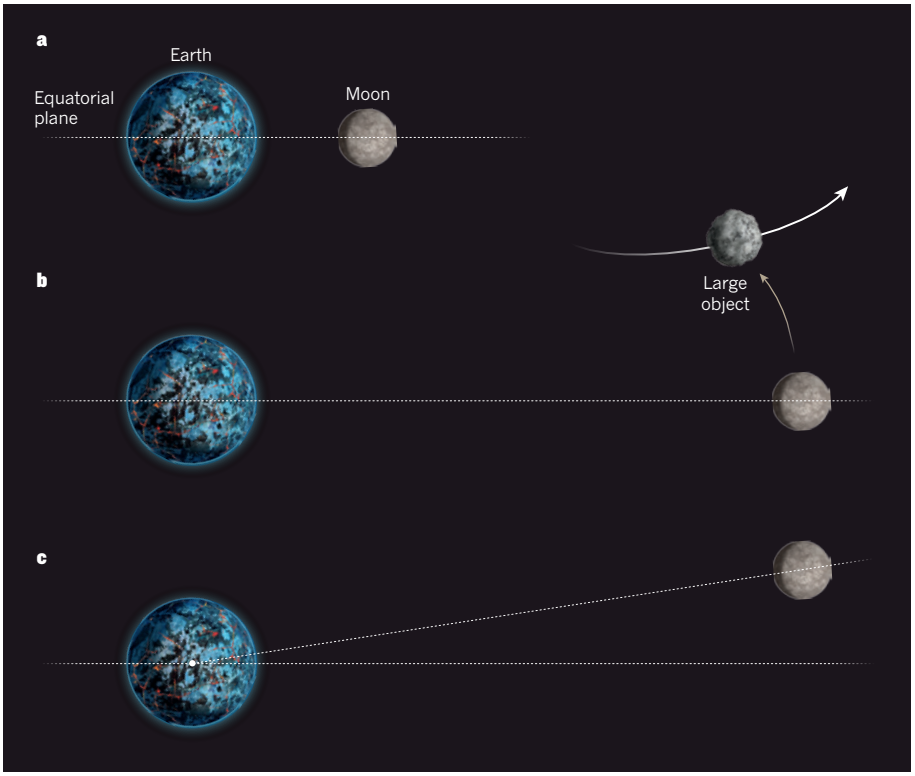

Figure 1 | Collisionless interactions could have altered the early Moon's orbit. **a**, When the Moon first formed, its orbit was approximately in the plane of Earth's Equator. Over time, its orbit then expanded. **b**, Pahlevan and Morbidelli[2] propose that collisionless interactions with large objects passing through the early Solar System would have strongly perturbed the Moon's orbit. **c**, The cumulative effect of such interactions would have tilted the Moon's orbital plane sufficiently to explain the current inclination of the Moon to Earth's orbital plane around the Sun. The Moon's orbital radius in **b** and **c** is not shown to scale.

direction may increase or decrease the Moon's orbital tilt. But just as a series of steps, each equally likely to be forward or backward, causes the standard deviation in the net distance travelled to increase with time, so too does a series of randomly oriented kicks to the lunar orbit lead to a general increase with time in the probability of exciting a minimum tilt.

Pahlevan and Morbidelli's results show a high likelihood that such random scattering events can cumulatively produce the necessary early tilt in the Moon's orbit, as long as the number of objects that deliver the final approximately 1% of Earth's mass is small (fewer than 5) and the rate of early tidal expansion of the Moon's orbit is sufficiently rapid. The rate of early tidal expansion needed is broadly consistent with the average tidal properties inferred for Earth on the basis of the expansion of the Moon's orbit to its current orbital distance. However, the specific values that would have applied to the earliest Earth remain uncertain.

The magnitude of the excited tilt scales roughly linearly with the late mass delivered to Earth. It is not known what fraction of the siderophiles that were concentrated in the cores of such large impactors would have been retained in Earth's upper layers. Improved models of late-veneer impacts should therefore be used to better constrain the late-accreted mass; this would in turn allow a closer approximation of the inclination expected from scattering. Moreover, the new scattering model is most effective if the Moon's inclination has been damped only by tides. If other forms of inclination damping have occurred, then — depending on the timing of this damping — the required initial inclination might increase, and with it the required mass of background objects, perhaps to unrealistically high values.

Previously reported models for the origin of the Moon's inclination rely on more-complex processes involving either a periodic gravitational interaction (gravitational resonance) with the Sun[6] or a resonant interaction between the Moon and its precursor disk[7]. Both require rather narrow sets of conditions for success. The new mechanism is simpler than these models, and the population of late lunar-sized objects that it requires is compellingly consistent with that needed to account for the delivery of Earth's precious metals, a completely independent constraint. Had such a population of objects not existed, the Moon might be orbiting in Earth's orbital plane, with total solar eclipses occurring as a spectacular monthly event. But our jewellery would be much less impressive — made from tin and copper, rather than from platinum and gold. ■

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BLINDNESS

Assassins of eyesight

A molecular cascade involving the transcription factor SIX6 and its target gene *p16INK4a* causes the death of neurons that link the eye to the brain. This discovery deepens our understanding of a common form of blindness, glaucoma.

ANDREW D. HUBERMAN & RANA N. EL-DANAF

Vision might feel easy, but an immense number of neurons are required to perform routine visual functions, such as reading, navigating the street or recognizing faces. Tightly lining the back of the eye is a layer of approximately 1 million neurons called retinal ganglion cells (RGCs), which take information encoded by the retina and pass it to the brain[1]. Glaucoma — a disease marked by progressive, irreversible degeneration of RGCs — is a common form of blindness, affecting more than 60 million people worldwide[2]. Although many studies have sought to understand the cellular and molecular basis of glaucoma[3], the mechanisms that drive RGC death in this debilitating disease have remained mysterious. But writing in *Molecular Cell*, Skowronska-Krawczyk *et al.*[4] report that certain glaucoma-associated mutations in humans are linked to a defined molecular pathway that accelerates RGC ageing and death.

A constellation of risk factors has been

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.

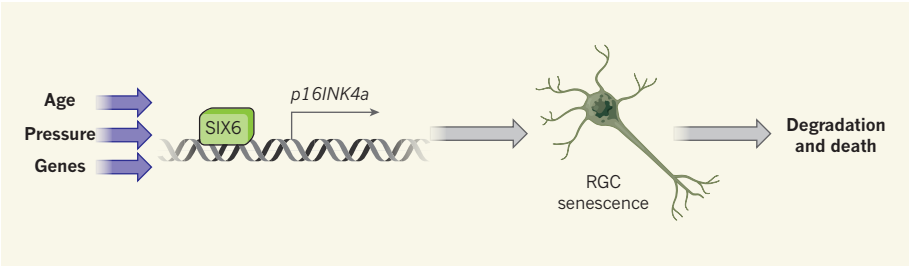

Figure 1 | Molecular pathways that underlie glaucoma. Age, elevated pressure in the eye and certain genetic mutations are all associated with an increased risk of glaucoma, a form of blindness linked to the degradation of retinal ganglion cells (RGCs). Skowronska-Krawczyk *et al.*[4] report that these 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.