using the radial-velocity technique, which is an indirect method based on measuring the periodic change in speed of a star caused by the gravitational tug of orbiting bodies. Until this year, most planet discoveries were made with this method. But there has been a widely held opinion that the radial-velocity technique will not be able to find candidate habitable Earth-mass planets despite its success at finding Jupiter-mass planets. The reasoning behind this is that the variability of the visible surfaces of stars, as a result of magnetic activity, pulsations and the turbulence of the plasma in their atmospheres, creates noise in radial-velocity measurements, and this noise is larger than the signal induced by an Earth-sized planet in the habitable zone. Also, the technical challenge of building instruments sensitive enough to detect the subtle indications of such planets, even around perfectly 'quiet' stars, was considered too challenging.

Pepe and colleagues' detections[1] were enabled by a combination of exquisite instrumentation, painstaking analysis and an ingenious observational technique. Using an ultra-stable instrument on a dedicated telescope, and with the benefit of ten years' experience in refining their calibration strategy, the authors set out to intensively monitor ten of the quietest known nearby stars. Their monitoring campaign involved making multiple measurements per night to average over the stellar noise cycles that had plagued previous studies. Using this approach, they have broken through the previously inviolate one-metre-per-second radial-velocity barrier and detected planets that have signals less than tenfold larger than that of an Earth analogue, for which the signal is 9 cm s^{-1}. Pepe *et al.* were also careful to show that the detected signals were most probably attributable to orbiting planets rather than to intrinsic variations in the stars themselves. They did this by demonstrating that the orbital periods determined for the planets were distinct from the host stars' rotation periods, and also that there were no correlations between the detected signals and the diagnostics of stellar activity.

Despite being a clear breakthrough, there are some limitations to Pepe and colleagues' study. One limitation is that the newly detected planets are poorly characterized. We do not know the compositions of the planets because the radial-velocity method yields no information about the densities of the planets it detects. Also, we have little knowledge of how elliptical the planets' orbits are (their orbital eccentricity), because the detected signals are relatively small. Both composition and orbital eccentricity are crucial parameters for assessing a planet's habitability.

Furthermore, although Pepe and colleagues' results[1], and those described in another paper from the same group[2], hint at a large population of small planets orbiting Sun-like stars, the statistics are weak because these planets are difficult to detect and therefore the samples are incomplete by an unknown amount. Identifying a large sample of similar planets, and studying them by different methods, would advance the field. However, Pepe *et al.* show that the full potential of the radial-velocity technique has not yet been realized. This work warrants the building of a generation of radial-velocity instruments that are even more stable than those now in use, so that instrumental noise is no longer a barrier to the discovery of Earth-like planets with this method.

One of the planets is only 3.6 times the mass of Earth and is in an orbit that teases the inner edge of its host star's 'habitable' zone.

NASA's ongoing Kepler mission, which finds planets using the transit technique, announced a haul of more than 1,000 new planet candidates earlier this year, and is on track to identify habitable-zone planets[3]. Because the transit technique detects planets by measuring periodic decreases in a star's brightness when a planet passes in front of it, the issue of stellar variability is also a limiting factor for this approach, and early results indicate that the stars Kepler is looking at are significantly more variable than expected[4]. This means that an extension beyond the nominal 3.5-year mission duration might be necessary for Kepler to securely detect Earth-sized planets in the habitable zones of Sun-like stars.

In the long run, astronomers aim to study the atmospheres of the small worlds revealed by radial-velocity and transit surveys to obtain further insight into the planets' habitability and even, perhaps, their state of inhabitance. The investigations that will be enabled by NASA's planned James Webb Space Telescope, which is currently at risk of cancellation, are the cornerstone of astronomers' next plans in this area. Nevertheless, it is clear that the search for other Earths is gathering pace. The exciting results from Kepler, and the remarkable advances in the radial-velocity technique demonstrated by Pepe *et al.*, show that the race is well and truly on. ■

Jacob Bean *is at the Harvard-Smithsonian Center for Astrophysics, 60 Garden Street, Cambridge, Massachusetts 02138, USA.*
e-mail: jbean@cfa.harvard.edu

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MOLECULAR MEDICINE

Defence against oxidative damage

Macular degeneration is a leading cause of blindness in the elderly in the developed world. Hope for prevention and treatment comes from the discovery of a protective mechanism against oxidative damage to the eye. SEE LETTER P.76

FERNANDO CRUZ-GUILLOTY & VICTOR L. PEREZ

Dangerous oxygen radicals that are sometimes generated during metabolic processes can damage cellular components. The eye, with its constant exposure to light and its high metabolic rate, is particularly susceptible to such damage, or oxidative stress. If left unchecked, this can be cumulative, leading to age-related macular degeneration. Almost two-thirds of people over the age of 80 have this condition, and between 30 million and 50 million individuals are affected worldwide, with a frequency in industrialized countries similar to that of cancer[1]. On page 76 of this issue, Weismann *et al.*[2] describe how a protein normally associated with an immune pathway also protects against inflammation induced by oxidative stress in age-related macular degeneration. By combining *in vitro* and *in vivo* data from human patients and animal models, the authors provide a plausible explanation for the cause of this devastating chronic disease.

The macula region of the retina is required for central vision and is heavily populated with photoreceptors. These convert the light entering the eye into electrical and molecular signals that are transmitted to the brain for visual processing. The retina's outer segments are replenished daily, and the resulting debris is cleared away by the retinal pigment epithelial cells. If these cells become dysfunctional, a build-up of debris (drusen) can occur in the vicinity of photoreceptor cells in the macula, which are then more likely to die off, leading to the irreversible loss of vision seen in patients with age-related macular degeneration (AMD). Many environmental and genetic factors have been

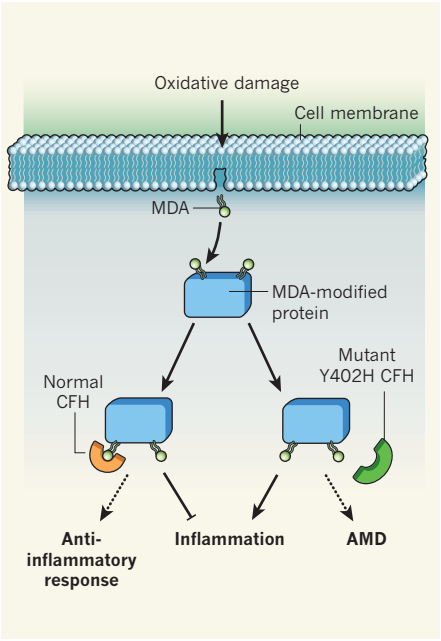

Figure 1 | Mechanisms at work in age-related macular degeneration. Oxidative damage to lipids in the cell membrane generates the reactive decomposition product malondialdehyde (MDA), which forms adducts with cell proteins. Normal complement factor H (CFH) binds MDA with high affinity, blocking inflammatory reactions. Mutant CFH, in which the amino acid histidine is substituted for tyrosine at residue 402, fails to bind MDA, so inflammation cannot be prevented, leading to age-related macular degeneration (AMD) and blindness.

correlated experimentally with AMD progression, including oxidative damage (induced by factors such as smoking and light exposure) and inflammation[3].

A collection of proteins known as complement factors form part of the innate immune system, which is the first line of defence against pathogens. These factors interact with one another in a sequence of stimulatory or inhibitory steps in a cascade known as the complement pathway. Complement proteins have been implicated in certain pathological conditions, and have been found in the accumulated drusen of patients with AMD[4]. Variations in the DNA sequence at particular sites, or polymorphisms, in genes encoding complement factors have been associated with the development of AMD, suggesting that inflammation is an important component of the disease.

A polymorphism in complement factor H (CFH) conveys a significant risk of developing AMD[5–7]. CFH is an inhibitor of the complement pathway and therefore has anti-inflammatory activity. The relevant single-nucleotide polymorphism in the *CFH* gene produces an amino-acid change from tyrosine to histidine at position 402 (the Y402H mutation) in the protein. The functional consequences of this mutation have been elusive until now, but Weismann *et al.*[2] convincingly show that it directly affects the ability of CFH to control the inflammation associated with AMD.

The story began with the group's interest in malondialdehyde (MDA) — a common decomposition product of lipid peroxidation by oxygen radicals. It reacts with cellular proteins to form adducts that can act as markers of oxidative stress. The MDA-modified proteins induce inflammatory responses and are recognized by the innate immune system. They are found in many physiological and pathological conditions, including atherosclerosis, AMD[8,9] and other chronic degenerative diseases.

Weismann *et al.* show that CFH peptides constitute the majority of MDA-binding proteins. A series of cleverly designed experiments clarified the physical and functional features of the CFH–MDA interaction. This turned out to be highly specific, with CFH binding to MDA whatever its carrier protein, but not to other oxidative products. The authors mapped the CFH domains that specified MDA binding, including a short segment known as SCR7, which contains the Y402H mutation. The Y402H CFH variant from AMD patients showed a markedly reduced ability to bind MDA compared with normal CFH (Fig. 1).

Weismann and colleagues further demonstrate that CFH and MDA co-localize in the eyes irrespective of whether these organs are affected by AMD. This suggests that in the healthy eye CFH protects the macula, and in dying (apoptotic) cells it recognizes MDA–protein adducts. Perhaps the researchers' most important result from a therapeutic viewpoint is that CFH can prevent MDA-mediated pro-inflammatory effects in at least two cell types associated with AMD — retinal pigment epithelial cells and macrophages.

Weismann and co-workers' findings[2] answer the long-standing question about the role of CFH in AMD but they also raise other questions. MDA is ubiquitously generated in a variety of inflammatory settings, but we don't know whether its connection with CFH is relevant outside the eye. The authors found that other members of the CFH family that bind MDA block CFH activity, suggesting that the subtle regulation of complement activity needs to be examined in more detail. It will be interesting to see whether other oxidation-induced modifications associated with AMD, including those induced by carboxyethylpyrrole[10], interact with proteins in a way similar to the MDA–CFH paradigm. Answers to such questions could help in the fight against AMD and other chronic inflammatory diseases. ■

Fernando Cruz-Guilloty *and* **Victor L. Perez**
are in the Department of Ophthalmology, Bascom Palmer Eye Institute, and the Department of Microbiology and Immunology, University of Miami