which mutations develop in the presence of an antibiotic by isolating individual cells from a bacterial population — is essential for optimizing a dynamic strategy for prescribing antibiotics. Such information can help in assessing the need for changes in the dosage and duration of treatments, for example. The approach also highlights the fact that interaction between different communities of resistant mutants that form in a bacterial population can enable them to mount a more formidable defence against antibiotics. Single-cell behaviour that is markedly different from that at the population level has been a subject of intense investigation in systems biology. Lee *et al.* provide another valuable example of such studies.

Furthermore, the collective behaviour of single-celled organisms — as seen in the phenomena of quorum sensing[3] and metabolism in a biofilm[4], and now in antibiotic resistance — shows that a pool of microbes can act in concert. Apart from its implications for research in tackling antibiotic resistance, the new work[2] adds to previous studies in challenging the conventional definition of what constitutes a multicellular organism. ■

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ASTROPHYSICS

Unexpected warm water

Bengt Gustafsson

The detection of water vapour in a carbon star has challenged the understanding of ageing stars. The discovery that such water can be warm shows that our knowledge of these objects is still rudimentary.

In the short time since its launch on 14 May 2009, the European Space Agency's Herschel Space Observatory has delivered several astronomical discoveries in the infrared and submillimetre regions of the electromagnetic spectrum. On page 64 of this issue, Decin *et al.*[1] report yet another of Herschel's exciting findings: the detection of warm water vapour in the circumstellar envelope of the carbon star IRC +10216.

Carbon stars were first recognized in the 1860s by William Huggins and Angelo Secchi. On the basis of his purely visual inspection of spectroscopic observations, Secchi defined this new group of objects as class IV in his classification system of stellar spectra. These extremely red stars, he noted[2], were remarkably different from the orange stars of class III: "we cannot identify precisely the sources of the lines and the bands. We can say however that there is a marked analogy with the reversed spectrum of carbon." Further observations by Hermann Carl Vogel and Nils Dunér later strengthened his conclusion.

The distinctive spectral features that characterize carbon stars — notably the dominant spectral bands of carbon compounds, such as the C_2 Swan bands in the green part of the spectrum, and the lack of bands from oxides such as TiO and H_2O, which are characteristic of other types of cool star — is due to their atmospheres being richer in carbon than in oxygen, as was suggested by Charles Donald Shane[3] and demonstrated by Henry Norris Russell[4]. If there is more carbon than oxygen, oxygen is mostly bound to carbon in the form of carbon monoxide (CO) because the molecule has a high binding energy (11 electronvolts). As a result, little oxygen is left free to form other oxides in such stellar atmospheres, whereas carbon atoms are available to form other carbon compounds. By contrast, in normal stars such as the Sun, the atmosphere contains more oxygen than carbon and the opposite occurs: carbon-containing molecules other than CO become rare.

During the 1950s, investigators showed that a peculiar class of ageing red giant stars known as asymptotic giant branch (AGB) stars — to which carbon stars belong — have important roles in nucleosynthesis processes. For example, the heavy 's-elements' found in the Milky Way (so called because they are created by relatively slow, hence the 's', neutron capture by heavy atomic nuclei), as well as nitrogen and carbon[5], are believed to be produced in AGB stars and later expelled into the interstellar medium. But the details of these processes have remained unclear: we still lack a complete understanding of key mechanisms, not least of those that drive the intensive winds from such stars.

There is therefore good reason to study carbon stars — not least, as we shall see, the Milky Way's pulsating star IRC +10216. This visually faint, extended object is, as seen by an observer on Earth, the brightest source outside the Solar System in the 5-micrometre waveband[6]. Radio observations have demonstrated that the optically thick, dusty shell that surrounds the star is a rich source of complex molecules. More than 70 molecular species, which are characteristic of a carbon-rich chemistry, had already been detected there before the Herschel era[7]. In fact, about 50% of all molecules observed in astronomy have been detected in this object[8].

Data from the IRAS infrared satellite have shown[9,10] that about 4% of all Galactic carbon stars have signs of silicate grains in their expanding circumstellar envelopes. This suggested — contrary to what one would expect under thermal-equilibrium conditions and for well-mixed gas mixtures — that the gas envelopes of these carbon stars contain both oxygen-rich and carbon-rich material, thereby posing a challenge to the conventional understanding of the chemistry and evolution of ageing stars. One possible explanation for this astonishing observation is that the stars' evolutionary transition from an oxygen-rich to a carbon-rich phase occurred quite recently, so that the remains of previous epochs can still be traced in the stars' outer envelopes. The subsequent detection[11], with the SWAS submillimetre satellite, of circumstellar water vapour in IRC +10216 — a characteristic of oxygen-rich stars — has caused further astonishment.

This observation[11] was based on the identification of a single water-vapour spectral line of low excitation, which corresponds to a transition between two energy levels that are populated even at low temperatures. The fact that the line is a low-excitation one may suggest that the water vapour originates from the outer, cold regions of the stellar gas envelope. Another possibility is that the vapour arises from the vaporization of icy bodies, such as comets or minor planets, in orbit around the star[11,12].

In their study, Decin *et al.*[1] identify not just one but numerous water-vapour lines in the spectra of IRC +10216 (see Fig. 1 on page 65). However, many of these are high-excitation lines, which — if the water molecules are thermally excited — means that the temperature of the gas in which the lines are formed is of the order of 1,000 kelvin. These results point to the existence of warm water vapour in the inner regions of the stellar envelope, and seem to rule out models — including the vaporization-of-icy-bodies hypothesis — that posit that water vapour originates only from the stellar envelope's cooler intermediate and outer regions.

The strength of the newly discovered lines also goes against another hypothesis: that the existence of water vapour in the envelope's inner regions is due to shock waves that are induced by the star's pulsation and generate the non-thermal-equilibrium chemistry needed to form water in a carbon-rich gas. The authors[1] suggest, instead, that the non-thermal-equilibrium chemistry is the result of the penetration of ultraviolet photons into the inner regions of the envelope, possibly from the star but more likely from interstellar space. But for these hypotheses to work, a highly clumpy circumstellar envelope is required, so that enough of the ultraviolet radiation penetrates into its

inner layers; a homogeneous envelope would shield its inner layers against the radiation.

Although models of the composition of stellar envelopes based on thermal-equilibrium chemistry have been known to be inadequate for some time[13–16], Decin and colleagues' study is a strong reminder that non-equilibrium chemistry needs to be considered in quite some detail in attempts to understand carbon-star envelopes. Whatever the explanation for the origin of warm water in IRC +10216, their work[1] demonstrates that our understanding of AGB stars is still rudimentary. This is unsatisfactory, because we — and all known life forms — are probably the result of the processes that produce and expel carbon in such stars. ■

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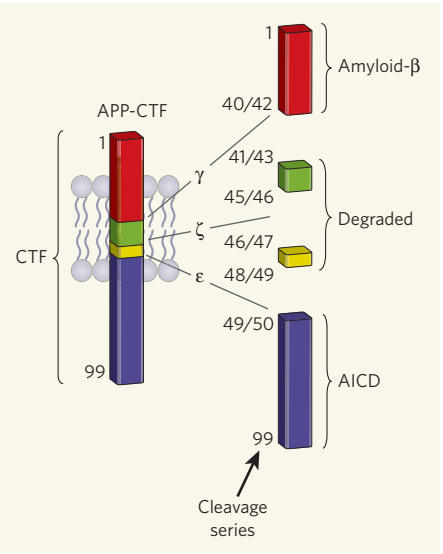

Figure 1 | Complexities of presenilin-dependent cleavage. The presenilin complex cleaves the transmembrane domain of its substrates at three main sites, ε, ζ and γ, generating various cleavage products. In the case of amyloid precursor protein (APP), for example, the cleavage products (indicated by the numbered position of the amino acids in the protein sequence) include amyloid-β and APP intracellular domain (AICD). He *et al.*[1] show that inhibition of γ-secretase activating protein (GSAP) selectively modulates APP processing, leading to reduced amyloid-β production and increased AICD levels. CTF, carboxy-terminal fragment.

ALZHEIMER'S DISEASE

Selectively tuning γ-secretase

Peter St George-Hyslop and Gerold Schmitt-Ulms

Presenilin proteins have a major role in normal cellular processes, but some contribute to disease, for example through the formation of amyloid-β. The way in which these different roles are regulated is now becoming clearer.

Accumulation of the amyloid-β peptide in the brain is a hallmark of Alzheimer's disease. It is generated from amyloid precursor protein by consecutive cleavage events that involve the presenilin enzyme complex. So why not target this complex for treating Alzheimer's disease? The problem is that this enzyme complex acts on several other proteins that are crucial for health and will also be affected by its inhibition. On page 95 of this issue, He *et al.*[1] describe a protein called γ-secretase activating protein (GSAP), and show that its depletion selectively prevents amyloid-β production by the presenilin complex.

The presenilin complex consists of four core proteins[2–5]: PS1/PS2, APH-1, nicastrin and PEN-2. In addition to amyloid precursor protein (APP), other notable substrates of this complex include Notch and N-cadherin proteins, which span the cell membrane. The complex cleaves these proteins at amino-acid residues within their transmembrane domain.

Several cleavage reactions are catalysed by the presenilin complex (Fig. 1). Cleavage of substrates at residues 48 and 49 — termed ε-cleavage — generates soluble intracellular-domain fragments that are involved in molecular signalling; these include APP intracellular domain and Notch intracellular domain. Cleavage at residues 45 and 46 (ζ-cleavage) generates small, short-lived fragments. And cleavages between residues 38 and 43 (γ-cleavage) produce neurotoxic amino-terminal amyloid-β fragments such as Aβ40 and Aβ42, which are secreted and are involved in the development of Alzheimer's disease[6]. Whether the different types of cleavage occur independently or sequentially, from the ε- to the γ-site, remains unknown. How these cleavage events are regulated is also debated.

The complexity of this presenilin-dependent proteolysis has frustrated attempts to suppress amyloid-β production for treating Alzheimer's disease: general inhibition of the presenilin complex also blocks essential presenilin-dependent signalling cascades, including the Notch pathway. But hopes have been raised by several lines of evidence, which — although still contentious — suggest that the molecular mechanisms of amyloid-β generation by γ-site cleavage are distinct from the mechanisms of ε-site cleavage[7]. He and colleagues' work[1] further supports this idea.

Following up on the team's previous observation[8] — that the anticancer drug imatinib (Gleevec) selectively decreases amyloid-β production, without affecting Notch cleavage — He *et al.* find that GSAP binds to imatinib, as well as to both PS1 and APP. The 16-kilodalton GSAP is itself derived by the cleavage of a larger protein called protein pigeon homologue. GSAP does not contain any protein domain that has been found previously and, despite its imatinib-binding ability, bears no apparent resemblance to the tyrosine kinase enzyme BCR–ABL — the known therapeutic target of imatinib.

He and colleagues find that, consistent with the idea that imatinib interacts with GSAP to prevent presenilin-dependent cleavage of the carboxy-terminal fragment of APP (APP-CTF), reduced GSAP expression significantly decreases amyloid-β levels, with imatinib addition having no further effect. Unexpectedly, however, reduction in GSAP is accompanied by increased levels of APP intracellular domain. Moreover, neither increasing nor suppressing GSAP expression affected Notch cleavage. These observations suggest that GSAP differentially regulates the γ- and ε-site cleavages of APP-CTF, and that it is highly substrate specific.

Further analysis of a mouse model of Alzheimer's disease shows that long-term GSAP depletion results in significant reductions in amyloid-β levels and in the rate of amyloid-β-plaque development, without affecting Notch signalling. These effects are in contrast to those of most conventional γ-secretase inhibitor compounds, which usually impair Notch processing to some extent.

This work[1] corroborates previous studies[7] indicating that Notch and APP processing by the presenilin complex are regulated separately. Indeed, several other proteins selectively modulate amyloid-β production, but spare Notch cleavage. These include TMP21 (ref. 9), CD147