al.[2] have knocked out the AID gene in mice, and found that these animals are normal except that their B cells completely lack the ability to undergo CSR. The problem seems to lie specifically in CSR, as all known cellular events leading up to this process are normal.

In complementary studies, Revy *et al.*[1] have tracked down the gene that is mutated in a rare form of human immunodeficiency known as hyper-IgM syndrome — a disease in which the B cells can produce only the IgM class of antibody. Remarkably, all the patients with this disease had mutations in the AID gene. The symptoms of this disease[1] are very similar to the characteristics seen in the AID-knockout mice[2]. The specific effect of the AID mutation on CSR is reminiscent of the highly specific inactivation of *V(D)J* recombination in mice that lack the recombination-activating genes[3]. These genes encode the components of the *V(D)J* 'recombinase'.

Significantly, humans and mice without the AID protein also failed to undergo somatic hypermutation[1,2] — a fact that came as a surprise. Even more surprising is the nature of AID. Both CSR and somatic hypermutation involve the cutting and pasting of DNA, so one might have expected the proteins needed for these processes would be DNA-recombination enzymes such as nucleases or helicases. But AID belongs to a family of enzymes that 'edit' RNA, changing the base cytosine to uridine by deamination[6].

Although AID cannot yet be declared the long-sought 'CSR recombinase', it is certainly crucial to CSR. But how can RNA editing be linked to the DNA recombination that clearly occurs during this process? The easiest answer would be that CSR requires a recombinase protein, somatic hypermutation needs a 'mutator', and AID edits the RNA transcripts encoding both. AID is akin to APOBEC-1, a cytosine deaminase that edits the RNA transcript encoding apolipoprotein B. The cytosine-to-uridine change in this transcript creates a 'stop' codon, and so produces a truncated protein with new functions[7]. Perhaps AID works in a similar way. Alternatively, AID might have functions independent of its deaminase activity, and may act directly in DNA recombination.

A final possibility relates to the apparent role of RNA transcripts in CSR[2]. CSR occurs within large regions of 'repetitive' DNA sequences ('switch' regions) that precede each exon encoding a heavy-chain constant region. Transcription through switch regions is induced by stimuli that lead to CSR, and is a prerequisite for this recombination process. Moreover, switch regions transcribed *in vitro* form stable RNA–DNA complexes called 'R loops', which can recruit certain DNA-repair endonucleases[8]. Perhaps AID recognizes and alters the structure of this RNA–DNA complex, enhancing its recognition by recombination or repair systems. Such RNA–DNA complexes have also been proposed to function in somatic hypermutation[8]; if so, this might explain why AID is needed in both recombination processes.

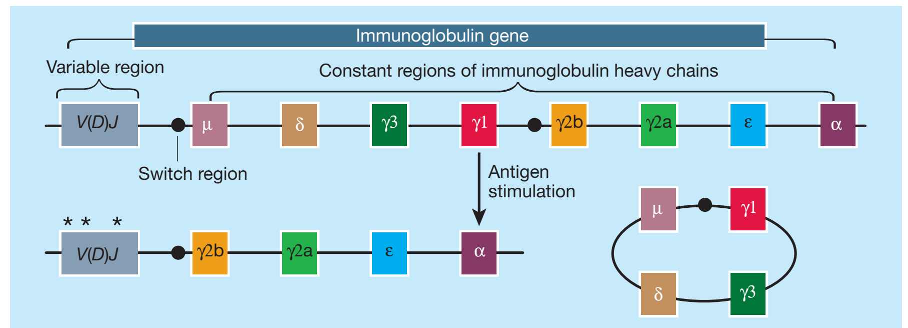

Figure 1 **Shuffling antibody genes. The immunoglobulin genes encode antibodies — protective molecules produced by B cells in the vertebrate immune system. The class of antibody produced is determined by the constant-region exon next to the *V(D)J* exon. During an infection, the 'switch' segment of the μ exon recombines with the switch segment of one of the downstream exons (switching with γ2b is shown here). This 'class switch recombination' process results in the replacement of the μ exon by γ2b, and the deletion of the intervening sequence. Immunoglobulin G protein is then produced by the cell, instead of immunoglobulin M. Somatic hypermutation also accompanies infection, and occurs (asterisks) within the *V(D)J* exon. The two processes tailor the antibody to the infection. Revy *et al.*[1] and Muramatsu *et al.*[2] have identified activation-induced deaminase as being crucial to both reactions.**

The discovery of a crucial role for AID in both CSR and somatic hypermutation may well be what is needed to stimulate progress in this field. On another front, switch regions are often involved in the movements of chunks of chromosomes that occur in certain B-cell lymphoma cancers. Conceivably, processes that lead to the unusual properties of switch regions might underlie the instability of related sequences elsewhere in the genome. If so, AID may be important for more than shuffling antibody genes. ■

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Chemical physics

Spinning molecules to bits

Manish Gupta and Richard N. Zare

The speed at which a jet can travel or a centrifuge can spin is limited by rotor disintegration. As the turbine of a jet or the rotor of a centrifuge goes round, it experiences a centrifugal force, which increases in proportion to the square of its rotational velocity. As the rotor speeds up there is some point beyond which the mechanical strength of the rotor cannot withstand the centrifugal force and the rotor breaks. In two papers in *Physical Review Letters*, Corkum and co-workers[1,2] demonstrate that rotor disintegration will also happen to individual molecules if they are made to spin rapidly enough.

Corkum and colleagues break chlorine molecules (Cl_2) apart by using femtosecond laser technology, which produces short, intense pulses of light whose frequency is made to change with time (to chirp). The oscillations of the electric field of the light pulse, which are perpendicular to the pulse direction, induce a dipole moment (charge separation) in a molecule. The magnitude of the dipole moment depends on the polarizability of the molecule, which varies with the spatial orientation of the molecule in the electric field. When the electric field oscillations are made to rotate, the dipole moment follows the direction of the electric field, causing the molecule to rotate.

In their optical centrifuge, Corkum and colleagues accelerate the rotating electric field of the light up to terahertz frequencies, forcing chlorine molecules to spin ever more rapidly. In this process, each molecule is excited to increasingly higher rotational states, *J*. As the molecule is driven step by step up the 'ladder' of rotational states, it spins faster and faster, causing the molecule to elongate. Eventually, the centrifugal force exceeds the strength of the molecular bond and the chlorine molecule dissociates into

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two chlorine atoms that fly off tangentially to the direction of rotation.

The chlorine atom fragments are then detected by multiphoton ionization, and their velocity measured by time of flight. The results show that many of the atoms have a velocity consistent with centrifugal dissociation. The energy spacing between rotational states varies with J, making it necessary to adjust the frequency of rotation of the light's electric field so that it stays in step with the molecular rotation. This adjustment is accomplished by controlling the chirp of the laser pulse. This experiment is a beautiful example of the power of strong laser fields to manipulate matter. In strong-field optics the strength of the radiation must be comparable to or greater than the electrostatic field of the charged particles in the matter.

The physics behind molecular and rotor disintegration are strikingly similar, despite the different driving forces involved. For a spinning rod, whenever the peripheral velocity (of the outer parts) reaches 2–20% of the speed of sound in the material, the rotor is in danger of flying to bits. A similar calculation can be performed for the chlorine molecule. The peripheral velocity is found from its classical motion in the highest rotational level before dissociation occurs. In the same way as for a solid, the speed of sound is calculated by assuming that it is given by the square root of the ratio of the modulus of elasticity (the second derivative of the potential energy function) to the density of the molecule. For Cl_2 we find that centrifugal dissociation takes place when the peripheral velocity is 13.7% of the speed of sound, which is approximately the same value as for a plastic rod. Remarkably, the same considerations apply to the disintegration of both molecular and macroscopic rotating objects.

When a rotating rod breaks by centrifugation it tears apart at the centre of rotation, which coincides with its centre of mass. This behaviour might seem paradoxical in that this point is stationary, but the force on the rotor at the centre of rotation is the greatest because it is the sum of all the forces from more distant points. The same reasoning applies to spinning chlorine atoms. In this sense, rotational destruction of a molecule could be a new way to select and control bond breaking in polyatomic molecules, a long-sought goal in physical chemistry[3]. For example, consider a linear polymer of N equally spaced monomer units. In the optical centrifuge built by Corkum and colleagues it would dissociate into polymers of $N/2$ monomer units — break in the middle — in sharp contrast to thermal dissociation (simply heating the molecules up), which yields a wide range of different polymer lengths.

Experiments on the rotational destruction of larger molecules should now be possible because the method of dissociation used by Corkum and co-workers is so universal, requiring only that the molecule be polarizable. Although polyatomic molecules are more complex and have a much richer energy-level structure, working with larger molecules does have several advantages. In addition to being more polarizable, larger molecules need not be spun as fast as smaller ones to cause dissociation. For example, compare the angular velocity ω_N required to rupture a linear polymer of N equally spaced monomer units with that necessary to break apart a molecule of $N=2$ units. If we assume the same energy for bond cleavage, a tetramer ($N=4$) requires an angular velocity that is about 3.2 times smaller than that for the dimer.

Linear polymers are just one way to use destructive molecular centrifugation. As Corkum and co-workers point out, the preparation of rotationally excited molecules that are not vibrationally excited may offer several advantages. Some possibilities include using them for etching surfaces, promoting new chemical reactions and creating tunable multi-terahertz radiation sources. Let the molecular whirling dervishes begin! ■

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Alzheimer's disease

A partner for presenilin

Dale Schenk

At the core of much of the research into Alzheimer's disease is the mechanism that generates the amyloid-β (Aβ) peptide. This peptide is the building block of the toxic 'plaques' characteristic of brain tissue from patients with Alzheimer's disease. On page 48 of this issue[1], Yu and colleagues describe a new protein — which they call nicastrin after the Italian village of Nicastro, key to early studies of this disease — that may be involved in generating the Aβ peptide. Their findings not only advance our understanding of this process and its relationship to Alzheimer's disease, but also provide a new molecular target for the design of drugs to treat this neurodegenerative disorder. More fundamentally, their work provides an insight into how cells might dispose of membrane proteins that they no longer need.

The Aβ peptide is generated from a larger precursor, the amyloid precursor protein (APP), by two sequential enzymatic 'activities' called β-secretase and γ-secretase. These activities result in the cleavage of APP in two places to produce Aβ (Fig. 1). The Aβ peptide is then released into the brain. APP stretches through the plasma membrane, with domains both inside and outside the cell — the γ-secretase activity makes its cut in part of APP that is within the membrane[2]. This activity also has a more benign and useful role: during development, it might

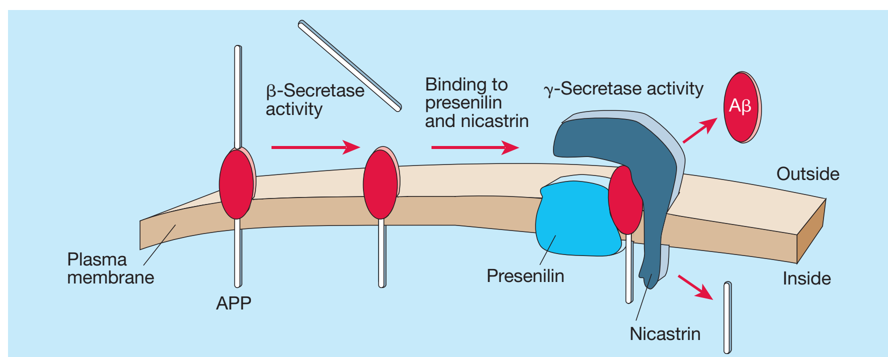

Figure 1 **Does a protein complex underlie the γ-secretase activity that generates the amyloid-β (Aβ) peptide? The Aβ peptide is found in the brain plaques of patients with Alzheimer's disease. It is produced from the amyloid precursor protein (APP) in two steps (left to right). First, APP is cut by a membrane-bound aspartyl protease, called β-secretase, resulting in a secreted segment of APP and a membrane-bound stub. This stub is then processed by the γ-secretase activity, generating the Aβ peptide. The presenilin proteins are required for this activity, and are likely to be the essential enzymatic component. Yu *et al.*[1] now show that another protein, nicastrin, is also required. It might act to position the APP stub correctly to allow presenilin to cut it at the right place; or it might regulate the activity of the γ-secretase enzyme (possibly presenilin). In the model shown, the large extracellular domain of nicastrin blocks the entry of APP (which is not cleaved by γ-secretase) and other protein substrates containing large amino-terminal domains.**

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