measured as a percentage of egg length, the range in position of Bicoid concentration thresholds for activation of the expression of the *hunchback* gene (x_{bcd}) was found to be six times that for the *hb* border it nominally controls (x_{hb}). Moreover, x_{hb} correlated with embryo size, whereas x_{bcd} did not, raising the question of how the Hunchback border scales with the size of the egg.

Gregor *et al.* present *in vivo* data from 15 live embryos imaged side by side. These data indicate that, based on absolute distance — rather than percentage of egg length — the range in x_{bcd} is about twice that of x_{hb} (Fig. 1). I think these results indicate that the anomalous positional-accuracy problem still exists, but that the anomaly is smaller than was thought. The small range of x_{bcd} in absolute distance units may mean that the apparently different scaling properties of x_{bcd} and x_{hb} were a fixation artefact, a point that has serious implications for theoreticians.

Gregor and colleagues argue that a 10% change in Bicoid concentration is detectable and that the Bicoid gradient is sufficiently accurate to be used for specifying the position of the border of *hb* expression in the anterior domain. To make this point, they marshal an intricate set of quantitative arguments that are ultimately unconvincing, because they are based on a picture in which Bicoid is the only input to *hb* expression. This assumption is demonstrably false. The mean position of x_{hb} is altered in embryos that have mutations in *giant* and other gap genes — genes involved in allocating domains in the insect embryo. Furthermore, the variance of x_{hb} is doubled when one chromosome arm is removed[6]. Although such effects are much smaller than is seen for other gap genes, it is dangerous to ignore them in a study that aims to obtain a complete quantitative characterization of the control of *hb* expression.

The most radical elements of the authors' conclusions are not well supported. But there is no question that this work is a landmark that may prove to be as revolutionary as were the methods for imaging protein and RNA in fixed tissue that were developed 25 years ago. Moreover, these findings confirm that it is unlikely that either experimentalists or theoreticians will run out of fascinating phenomena to investigate in the *Drosophila* embryo any time soon. ■

John Reinitz is in the Department of Applied Mathematics and Statistics, Stony Brook University, Stony Brook, New York 11794-3600, USA.
e-mail: reinitz@odd.bio.sunysb.edu

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INFLAMMATORY DISEASE

Assault on the guardian

Richard M. Ransohoff

In multiple sclerosis, the immune system attacks 'self' tissues. Ten years after the discovery of one target of this autoimmunity, work with mice identifies it as a guardian protein produced in response to inflammation.

On page 474 of this issue, Ousman and her co-workers[1] describe how autoimmunity to a protein known as αB-crystallin (CRYAB) can contribute to inflammatory injury of the central nervous system. They show that autoimmune attack on CRYAB does not directly cause tissue damage. Rather, it worsens the severity of damage by simultaneously eliminating two of the protein's functions — its action as a restraining element for inflammation, and its ability to inhibit programmed cell death of glial cells in the nervous system.

The clinical context for this research is multiple sclerosis (MS), an inflammatory disorder of the human central nervous system. This disease selectively targets myelin, the complex, lipid-rich membrane that enwraps some nerve axons. Its connection with CRYAB began with an experiment that challenged orthodoxy: in 1995, van Noort *et al.*[2] reported CRYAB to be a predominant target of autoimmunity in MS. They discovered CRYAB's significance by isolating myelin proteins from MS autopsy material, and determining these proteins' ability to act as autoantigens in evoking a reaction from T cells. These are major players in the immune system, and both produce and are stimulated by cytokine messenger molecules.

The group's finding[2] came as a surprise. During many years of research on autoimmune models of MS (known collectively as experimental autoimmune encephalomyelitis, or EAE), investigators had identified several myelin proteins with encephalitogenic potential. Encephalitogenicity implies that immunization with the protein, or with a peptide derived from it, could elicit an autoimmune reaction, characterized by inflammation, demyelination and weakness of the limbs. Known encephalitogenic agents included the principal proteins of myelin — myelin basic protein and myelin proteolipid protein — as well as minor components, such as myelin oligodendroglial glycoprotein (MOG).

Van Noort and colleagues took the road "less traveled by" and focused on myelin from patients with MS. Previously, the usual assumption had been that any autoantigen present in myelin would be a constituent of the healthy tissue. CRYAB was distinctly an outlier, because it is expressed only at low levels in myelin derived from the non-diseased central nervous system[3]. It belongs to the family of small heat-shock proteins that are produced by all cells in response to stress. CRYAB is also an oddity among heat-shock proteins, however, being expressed selectively in the eye lens, in skeletal and cardiac muscle, and in glial cells, including oligodendrocytes (the cells that produce myelin) and astrocytes.

It soon emerged that both MS patients and healthy individuals have a strong immune response to CRYAB[4]. As with previous candidate MS antigens, it was assumed that clinically relevant autoimmune targets should themselves be encephalitogenic. Exasperatingly, however, attempts to demonstrate this property in rodents, the most widely used host species for EAE, were unsuccessful. One proposed explanation was that the immune system was 'tolerized' to Cryab by destruction, in the thymus, of T cells that recognize the protein[5]. This possibility was addressed in ingenious ways that involved using Cryab to immunize Cryab-deficient mice ($Cryab^{-/-}$ mice)[6] to uncover an encephalitogenic portion of the Cryab molecule. However, these approaches, which had been successful in other systems[7], failed to reveal an encephalitogen.

Enter Ousman and colleagues[1], who also took an unorthodox approach — studying Cryab's functions by immunizing $Cryab^{-/-}$ mice to develop EAE using a peptide from MOG, a known encephalitogen. These mice developed disease at the expected frequency and time after immunization, but became noticeably sicker, and remained so for longer, than their normal counterparts. This observation became the focal point for the authors' subsequent studies.

The actions of individual components in the EAE model usually occur either in the immune compartment (where autoimmunity or inflammation is made more or less severe), or in the central nervous system (where cells can be more or less susceptible to dying during the inflammatory process). Ousman *et al.* show that Cryab violates this dichotomy

by mediating both the immune and neural functions. On stimulation with the MOG peptide antigen, T cells from *Cryab*$^{-/-}$ mice proliferated more and secreted higher levels of inflammatory cytokines than did those from EAE controls. Other immune cells, macrophages, were also hyper-reactive, producing high levels of cytokines after challenge with lipopolysaccharide, a well-characterized macrophage stimulant. In addition, increased numbers of glial cells underwent programmed cell death in the inflamed central nervous system of *Cryab*$^{-/-}$ mice with EAE, extending *in vitro* studies[8] that suggested Cryab could protect these cells.

Ousman *et al.* then went further. They looked at two cell-signalling pathways (NF-κB and MAP kinase) involved in inflammation, and found that alterations in these pathways in cells from *Cryab*$^{-/-}$ mice correlated not only with a heightened immune reaction, but also with the vulnerability of astrocytes to programmed cell death. They also explored the clinical relevance of their findings by testing the cerebrospinal fluid of MS patients, and found CRYAB antibodies to be present. Finally, they injected Cryab protein into mice with EAE, and showed that it reduced disease.

Overall, Ousman *et al.*[1] show that Cryab is produced early on in response to inflammation associated with EAE (and possibly MS): the protein itself becomes an autoimmune target, its destruction exacerbating inflammatory damage but not directly causing demyelination. In humans, the disease cascade presumably begins with generation of autoreactivity to unknown primary encephalitogens. This is followed by upregulation of CRYAB production as part of the stress response, followed in some patients by the onset of autoimmunity to CRYAB and acceleration of the disease process.

There are several provocative leads for further research. It seems[9] that autoimmunity to CRYAB can be detected early in the course of MS, and an obvious step is to find out whether strategies to restore tolerance can be devised[10]. It is also of interest that infection with Epstein–Barr virus, the agent most strongly associated with MS in epidemiological studies, upregulates CRYAB expression in certain immune cells[11]. Finally, polymorphisms in the promoter genes encoding CRYAB may influence disease severity[12], and a suspected mediator of damage in MS, known as MMP9/gelatinase B, can use CRYAB as a substrate[13] — offering yet another way in which inflammation could reduce the protein's availability. ■

Richard M. Ransohoff is in the Neuroinflammation Research Center, Department of Neurosciences, Lerner Research Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA.
e-mail: ransohr@ccf.org

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QUANTUM COMPUTING

Powered by symmetry

Johannes Hecker Denschlag

Forces determine how particles move and behave. But so can symmetry, and exchange symmetry can be used to control the interactions of ultracold atoms. This could be a big step towards practical quantum computation.

Quantum computers promise to solve problems that cannot be tackled by conventional computers[1]. But they make high demands on the machinery from which they are built. The physical entities storing quantum bits — the smallest units of quantum information — must be controlled and coupled to each other with great precision. On page 452 of this issue, Anderlini *et al.*[2] present a very general method, based on a quantum-mechanical phenomenon known as exchange symmetry[3–5], that allows this degree of precision manipulation in controlled collisions of neutral atoms.

Arrays of trapped ultracold atoms are promising candidates for storing quantum information because of their weak, random coupling to the external world. During a controlled collision, the interaction between two cold atoms each carrying a bit of quantum information can be used to process that information[6,7]. But this scheme only works if the interaction between the atoms depends on the specific state of their quantum bits, and finding an appropriate atomic system is no trivial matter.

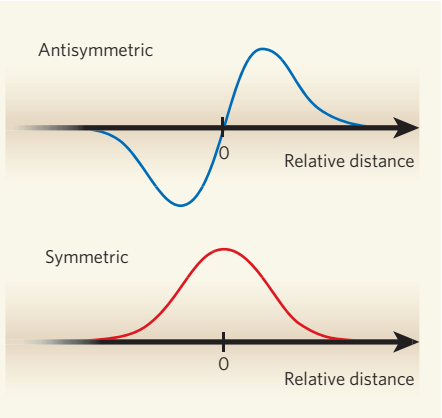

Figure 1 | Never the twain shall meet. An antisymmetric spatial wavefunction of two atoms held in a harmonic potential similar to the microscopic traps used by Anderlini *et al.*[2] vanishes at zero distance between the two atoms. As a result, atoms in an antisymmetric state can never be found in the same place. A symmetric wavefunction, by contrast, favours atoms being at the same place. By controlling the symmetry state of atoms, one can therefore control their interactions.

One option is to exploit symmetry. Symmetry is a fundamental concept throughout physics, and is the basis for all conservation laws. Angular momentum, for example, is conserved in isotropic (that is, rotationally symmetric) environments. Another type of symmetry is based on the idea that no measurable quantity should change after the exchange of identical particles. This exchange symmetry classifies particles into two groups: fermions, described mathematically by an overall antisymmetric wavefunction, and bosons, with an overall symmetric wavefunction. The antisymmetry of the fermionic wavefunction leads directly to the famous Pauli exclusion principle, which forbids two or more particles from occupying the same quantum state.

Anderlini *et al.*[2] find a way to make use of a similar symmetry-based constraint. They work with bosonic rubidium atoms, ^{87}Rb, that have a symmetric total wavefunction. This wavefunction has two components: a spin component describing the internal state of the atoms, and a spatial component describing their locations. Because of the fixed exchange symmetry of the total wavefunction, the symmetries of the spin and spatial wavefunctions are precisely related: if the spin wavefunction for ^{87}Rb atoms is symmetric, then the spatial wavefunction is also symmetric, and vice versa. Crucially, antisymmetric spatial wavefunctions hinder particles from getting close to each other, whereas symmetric spatial wavefunctions favour it (Fig. 1). Because the atoms interact effectively only when they come into contact, particles in symmetric spatial states interact with each other, whereas particles in antisymmetric spatial states do not.

Anderlini *et al.* stored quantum information in the atoms' spin wavefunction, such that the