finely poised balance between the regulation of viral gene expression and the immune system, particularly T cells (see ref. 3 for review).

That equilibrium can be upset by infections (for instance with HIV), or clinical or inherited impairment of the immune system. This may lead to the fatal form of infectious mononucleosis (glandular fever); or to progressively growing immunoblast cells that may turn into monoclonal lymphoma, malignant tumours of the lymph nodes. But immune control of EBV-transformed immunoblasts is remarkably robust. For example, the immune systems of transplant patients are strongly suppressed by drugs, but only a minority of recipients develop lymphoproliferative disease; even then they can sometimes be successfully treated by the infusion of appropriate T cells.

Inherited immunodeficiencies that allow lymphoproliferative disease to occur may point to the Achilles heel of the host defence system. The X-linked lymphoproliferative syndrome, described by David Purtilo in 1969, is the most prominent of these diseases and has alternative EBV-induced outcomes[4,5]. The syndrome manifests itself from 2.5 years of age and onwards, depending on the time of EBV infection, and all sufferers die by the time they are 40. Male carriers of the XLP trait respond to primary EBV infection with uncontrolled proliferation of both T and B cells. Fatal infectious mononucleosis occurs in 51% of patients; acquired hypogammaglobulinaemia (immunoglobulin deficiency) in 31%; and malignant lymphoma alone or in combination with the other symptoms in 26%.

Almost a decade ago genetic linkage research localized the *XLP* locus to region 24–25 on the long arm of the X chromosome (Xq24–25)[6]. Subsequently, the critical region was narrowed down considerably[7,8], but attempts to clone the gene failed. Now, however, two groups have done so.

Coffey *et al.*[1] report the positional cloning of the *XLP* gene, which they call *SH2D1A*. It has four exons and encodes a hitherto unknown protein, of 128 amino acids, that contains a single SH2 (src homology 2) domain; this is a protein module that specifically binds to tyrosyl phosphorylated peptides on signalling proteins. *SH2D1A* is expressed mainly in thymus and lung and in all lymphocyte populations assayed. Coffey *et al.* found that it was mutated in 9 out of 16 unrelated XLP patients, but not in male family members of those patients and other controls unaffected by the disease.

Sayos *et al.*[2] have reached the same goal but by a different route. They studied SLAM (signalling lymphocyte activation molecule), a glycosylated transmembrane protein also known as CDw150. SLAM has a high affinity for itself and is centrally involved in the bi-directional stimulation of T and B cells[9]. When activated, it mediates expansion of activated T cells during immune responses[10], induces production of interferon-γ and changes the functional profile of subsets of T cells. Signalling through SLAM–SLAM binding during mutual interaction between B cells, and between B cells and T cells, increases the expansion and differentiation of activated B cells[11].

Sayos *et al.* used the human SLAM cytoplasmic domain as bait in the yeast two-hybrid system. From a human T-cell library, they isolated eight DNA clones that encoded a 128-amino-acid polypeptide, designated SLAM-associated protein (SAP). As well as a single SH2 domain, this protein has a short tail, 26 amino acids in length, that is unlike any known protein domain. SAP is expressed in T cells (but not in B cells), both in humans and in mice. It turns out that SLAM and SAP interact in T cells through SAP's SH2 domain.

Using a clone that contained all four exons of mouse SAP, Sayos *et al.* localized the gene to part of the mouse X chromosome corresponding to human Xq25. To test the possibility that SAP was encoded by the *XLP* gene, SAP complementary DNAs were isolated from the blood cells of three XLP patients. All three cDNAs were mutated or deleted, in contrast to those from a healthy brother and other controls. The mutant SAPs did not bind SLAM.

In thinking how the mutation of SAP can account for the XLP diseases, Sayos *et al.* suggest that SAP is a natural inhibitor of SLAM. Consistent with this idea, they found that SAP binding blocks the recruitment of the tyrosine phosphatase SHP2 to the phosphorylated cytoplasmic domain of SLAM. Upon T-cell activation, SLAM may switch from a

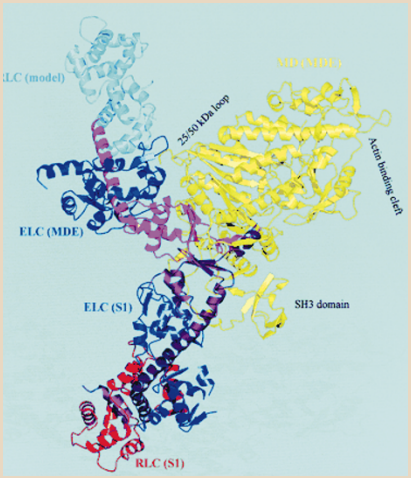
Motor proteins

Sighting of the swinging lever arm of muscle

The first sight of the structure of muscle's power stroke is shown in this figure, taken from a paper by Carolyn Cohen and colleagues published on 4 September (*Cell* 94, 559–571; 1998). The authors report the crystallographic structure, at around 3 Å resolution, of the motor domain (MD) of myosin from the thick filaments of smooth (chicken gizzard) muscle in complex with its essential light chain (ELC). This complex (MDE) forms the main part of the myosin head, which converts chemical to mechanical energy via a conformational change induced by the hydrolysis of ATP (catalysed by actin in the thin filaments). Understanding the mechanism by which myosin (and other motor proteins) converts chemical to mechanical force — manifested as sliding between the thick and thin filaments of muscle fibres — is a long-sought goal, and the new data provide an exciting glimpse of the structural basis of this mechanism.

The tail of the myosin head contains a very long α-helical region, thought to be a 'lever arm' that rotates when ATP binds and is hydrolysed — this rotation is the basis of the power stroke. The crystallographic structure of the end of the power stroke has been described previously, and there have been indications that there is a swinging lever arm. But until the new results of Cohen and colleagues, which show the beginning of the power stroke, there has been no unequivocal structural evidence for this hypothesis.

The figure consists of two superimposed structures. The motor domain of myosin is in yellow, and the magenta and pink regions of the molecule are the lever arm. The bottom structure represents the end of the power stroke, in which the molecule is free of bound nucleotide. The top structure represents the beginning of the power stroke, in which an ATP analogue is bound to the myosin. In this structure, the light-blue region of the molecule is a model, necessary because the construct used lacks



a regulatory light chain (RLC). The angle between the ends of the two lever-arm conformations is about 70°, which would produce a filament displacement of about 10 Å. This distance is consistent with measurements obtained from functional studies of muscle fibres, and from *in vitro* motility assays of the component proteins. **Maxine Clarke**