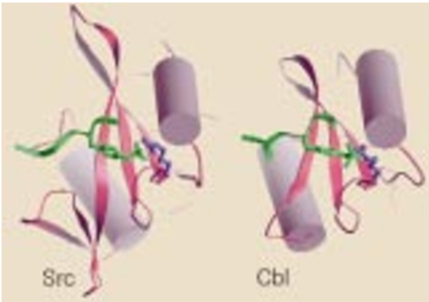

Figure 2 **A 'mainstream' SH2 domain, from the tyrosine kinase of the Rous sarcoma virus (Src, left)[11], is compared to that from Cbl (right)[3]. The backbone structure of the SH2 domain is shown in purple in both. Each of the SH2 domains is bound to a piece of protein containing a phosphorylated tyrosine residue (green). An arginine residue, conserved in all SH2 domains, interacts with the phosphate group. All the crucial aspects of phosphotyrosine recognition are similar in both SH2 domains.**

by recognizing phosphotyrosine residues specifically, and phosphotyrosines serve as beacons that attract SH2-containing protein molecules. These proteins then transmit molecular signals to key cytoplasmic proteins and genes in the nucleus, thus regulating the machinery of the cell[5,6].

The discovery of an SH2-containing signalling molecule in the slime mould *Dictyostelium discoideum*, along with the apparent absence of SH2 domains in yeast and in plants, has suggested a role for SH2 domains in the evolutionary transition to multicellular animals[7]. *Dictyostelium*, an organism that can become multicellular, spends much of its life cycle in a unicellular form. In response to environmental cues such as starvation, individual cells begin to clump together and form a 'slug', which can move as one unit. Soon, a developmental process begins. Some of the cells differentiate into a stalk, while the more fortunate ones develop into a fruiting body capable of dispersing spores. In this most simple of developmental decisions, a signalling protein known as STAT (for 'signal transducer and activator of transcription') is crucial for the determination of cell fate[7]. Although the full complexity of metazoan signalling is absent in *Dictyostelium*, the STAT protein in the slime mould is clearly related in its amino-acid sequence to STAT proteins in more complex organisms, including humans.

What is significant to the present discussion, however, is that both the human and *Dictyostelium* STAT proteins contain an SH2 domain, which allows the STAT proteins to dimerize in response to activating signals. They dimerize and thus become activated through reciprocal phosphotyrosine–SH2 interactions; the activated dimer can now bind to DNA and direct transcription. The SH2 domain in the *Dictyostelium* STAT is evolutionarily the most ancient such sequence known so far, and the slime moulds are the simplest organisms yet discovered to contain an SH2–phosphotyrosine signalling protein. It may be that the *Dictyostelium* STAT (or a STAT in some other similar ancient organism) represents an evolutionary link between single-cell and multi-cell organisms.

So what about Cbl? Cbl is a so-called 'adaptor' protein which links different signalling molecules together upon activation of the receptor. Cbl was known to bind to phosphorylated tyrosine residues, but nothing in its amino-acid sequence suggested that it harboured an SH2 domain. The three-dimensional structural analysis presented by Meng *et al.*[3] shows that the phosphotyrosine-recognition property of Cbl is conferred by a structural unit that resembles classical SH2 domains in every important way. For example, all SH2 domains have an invariant arginine residue that rises up from an interior location in the domain to engage the phosphate group of the phosphotyrosine[8]. This crucial determinant of specificity is conserved in a precise structural context in the Cbl SH2 domain (Fig. 2). Until now, the STAT SH2 domains have been among the most divergent of the known SH2 domains in terms of their amino-acid sequences. The discovery of a perfectly formed SH2 domain in Cbl indicates that the range of sequences that will form SH2 domains has an even greater spread than had been suspected.

Given the lack of sequence similarity between the Cbl SH2 domain and the more familiar ones, could the structure of the Cbl domain have arisen by convergent evolution from an unrelated ancestral protein? Although this is a possibility, it is highly unlikely. The strong conservation of three-dimensional structure between Cbl and other SH2 domains suggests to us that they have evolved from a common ancestral protein. There are examples of phosphotyrosine-binding domains that are structurally unrelated to the SH2 domain, demonstrating that the need to recognize phosphotyrosine does not place any particular constraints on protein structure[8].

In this regard, another intriguing observation is the presence in Cbl of a small helical domain located just before the SH2 domain. Strikingly, the STAT proteins also have a domain with a very similar structure located before their SH2 domains[9,10]. Although the helical domains are rotated with respect to one another in Cbl and the STATs, it is a tantalizing thought that their similar folding topology may reflect a vestigial structural remnant of an as-yet-unknown ancestral SH2-containing protein.

The identification of very distant relationships between proteins proceeds most reliably when three-dimensional information is available for representative members

100 YEARS AGO

In the history of vegetable physiology, sufficient importance has not been given to Dante's observations upon the action of solar light and heat upon plants, and to the ideas upon this action that existed in Italy in the fourteenth century. … It is not unlikely that the verses of Dante influenced Leonardo da Vinci in believing that "the sun giveth spirit and life to plants, and the soil with its moisture nourisheth them," leading him to an experiment in which the importance of leaf-function in the nourishment of plants is first noted, two hundred years before Malpighi. In this experiment Leonardo caused a water-fed plant to grow prosperously and bear fruit abundantly, although its roots had purposely been reduced to "only one tiny rootlet" (*solamente una minima radice*). Leonardo thus succeeded in causing a plant to grow chiefly by its foliage, to "*vivere della cima*" ("Paradiso", xviii. 29): an experiment that would have been too dangerous for the experimenter in Dante's days.

From *Nature* 2 March 1899.

50 YEARS AGO

Last August scientific workers from all over the world heard with deep disappointment that the Soviet Union had officially adopted an isolationist attitude on certain branches of biology. For the first time in the U.S.S.R. there was established a 'party line' in one of the natural sciences. Since then there has been speculation as to whether this attitude might extend to other natural sciences, and a recent broadcast from Moscow gives point to these speculations. On January 26, 1949, the philosopher Alexander Alexandrovitch Maximov, who is a corresponding member of the Academy of Sciences, and who belongs to the staff of its Institute of Philosophy, gave a broadcast on the Moscow Radio Home Service. The theme of his talk was the correct Bolshevik attitude to natural science. He attacks those foreign physicists who "regard as synonymous the philosophical definition of matter and the objective idea of reality", and who are responsible for other "idealistic misinterpretations" in relativity and quantum theory. He indicts by name Einstein, Niels Bohr and Heisenberg.

From *Nature* 5 March 1949.