Cell biology

Muscle-bound bacteria and weak worms

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FOR myosin to function properly in muscle, its bipolar filaments must be assembled in ordered arrays. A major problem facing cell biologists is the control of local assembly of the filaments. Within non-muscle cells, the filaments are continually assembling and disassembling according to local signals. In muscle cells, however, myosin must be turning over continuously within a permanent array and, therefore, the cells must be replacing myosin subunits or whole filaments in an organized fashion. Two different approaches have now been applied to find out how this is achieved. The first is a classical genetic approach in which mutants of the nematode worm *Caenorhabditis elegans* with incorrect myosin assembly are isolated[1]; and the second is by inducing expression of portions of the myosin molecule in bacteria[2]. The differences in the information about myosin filament assembly provided by these two methods offer a nice contrast between genetic and molecular-biology approaches to a cell biology problem. Analysis of mutants reveals behaviours requiring molecular explanations, whereas the expression of pieces of the molecule gives information about the behaviour of specific domains of the molecule.

On the basis of the amino-acid sequences of the myosin molecules, it is believed that repeating stretches of residues in the tail of the monomers produce the tertiary structure responsible for their assembly into filaments[3,4]. The conserved nature of these domains, and the fact that the assembly behaviour of myosin can be reproduced with proteolytically derived tail fragments, suggests that assembly is a function of the tail alone. There must be regulatory sites which when given the proper signal will modulate the assembly of bipolar filaments.

It is remarkable that Jim Spudich and collaborators now find[2] that expression of a fragment of relative molecular mass 56,000 (56K) of myosin tail from the amoeba *Dyctyostelium* in bacteria forms filaments with a 14-nm repeat like native myosin from muscle. This result means it is now possible to test rapidly for the effects of various amino-acid substitutions and deletions on assembly of the filaments. As an indication of the speed of progress, smaller fragments of the tail have already been expressed which demonstrate that filaments can form from as little as 34K of the carboxy terminus of the myosin molecule[5] (see figure).

As might be expected for non-muscle myosins, there is a site(s) that can regulate filament assembly and disassembly. In some non-muscle myosins, the phosphorylation of the regulatory light chain seems to be responsible for promoting assembly, whereas in *Dyctyostelium* myosin it is dephosphorylation of the tail which promotes assembly. The phosphorylation of this site occurs normally in the 56K and 68K fragments from bacteria but will not occur in the 34K fragment. This opens up the possibility of determining *in vitro* the portions of the myosin sequence involved in filament formation.

Is all the information relevant to the assembly of myosin filaments contained within the tail sequences? It is possible that physiological ligands could act through sites outside the tail to regulate filament assembly. It is difficult, if not impossible, to predict which sites on the molecule would affect filament assembly; therefore, the screening of mutants could uncover other physiologically important sites. *C. elegans* worms with weak muscles often do not form normal bipolar skeletal

Luis F. Leloir (1906–1987)

LUIS LELOIR, the outstanding biochemist, died on 4 December. One of his earliest contributions, which attracted immediate attention, was the discovery of glucose-1,6-diphosphate and its role as the cofactor for phosphoglucomutase. This served as a model for the proposal of a similar role for 2,3 bis-diphosphoglycerate for phosphoglycerate mutase by Cori, Sutherland and Pasternak. Then followed his main discovery, that of uridinediphosphate glucose (UDPG) and its role in galactose metabolism. Soon thereafter, Leloir and others found new reactions involving sugars, for example, in sucrose and lactose biosynthesis and in plant glycosides. In 1957 Leloir, with Cardini, discovered glycogen synthetase and that the enzyme used UDPG. He received the Nobel prize in chemistry in 1970, becoming, after Houssay, the second Nobel laureate in science from Argentina.

The discovery of the uridine nucleotide-sugar compounds by Leloir and others led to the isolation of other substances having either a different nucleoside moiety, such as adenosine, guanosine, cytidine and thymidine, or of derivatives in which the nucleoside diphosphate moiety is linked to compounds other than sugars.

Later, Leloir became interested in the role played by polyprenols in the synthesis of complex polysaccharides. Starting in 1970, he and his colleagues showed the presence in animal tissues of a microsomal acceptor lipid which accepts glucose residues from UDPG. He also showed that dolichol, a polyprenol from liver, accepts glucosyl residues from UDPG to form UDP and dolichol-phosphoglucose, and that this compound can transfer its glucosyl residues to proteins. These processes are operative in the synthesis of glucoproteins.

Although Leloir was born in Paris, his parents were Argentinians and he lived there all his life except for periods of study abroad. He studied medicine at the University of Buenos Aires. On graduating in 1932, he worked with Houssay at the Institute of Physiology, where his interest in carbohydrate metabolism began. In 1936 he went to Cambridge, UK, to the laboratory of Sir Frederick Gowland Hopkins. On his return to Buenos Aires he worked on fatty acid oxidation with J.M. Muñoz.

Houssay was dismissed by Peron in 1943; many of his students and colleagues, including Leloir, resigned in protest. Leloir went to the United States, where he spent some months with Cori in St Louis and then with Green at Columbia University in New York. Meanwhile, Houssay had obtained private support for a research institute for Leloir, so he returned to Argentina in 1945 to head the Instituto de Investigaciones Bioquímicas (Fundación Campomar).

A key point in Leloir's career and in his recognition at home, as Deulofeu pointed out in a publication in his honour in 1973, was his invitation to the now classical symposia on metabolism initiated by McElroy, in 1951, in Baltimore (many participants became Nobel prize winners), where he presented his work on UDPG.

The institute where Leloir's studies began was both modest and limited in resources, but was not limited in ingenuity, shown, for example, by the construction of a fraction collector using a toy train. As more students were attracted there, more suitable facilities were obtained. Leloir pursued his research with determination in the face of the most adverse circumstances, and he had an enormous influence on scientific development not only in Argentina but throughout Latin America. He was a modest man with a dry sense of humour, graced by charm and simplicity. I remember being with him in Buenos Aires in the late 1950s when he confided how at one point it had almost been necessary for him to choose between polo and science. Although his health had not been robust for several years, he attended the Institute daily until his death. Santiago Grisolía

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