substantial crustal thinning or post-tectonic subsidence¹⁴. Similarly, the massive accumulation of Jurassic and older sediments in the St George's Channel Basin followed by uplift, such that the Cretaceous is absent, then a phase of Tertiary subsidence, is indicative of a history which relates to a totally different causal mechanism.

One important line of investigation which has yet to be extensively applied in the study of extensional basins is that of deep reflection seismic profiling. In 1983 the British Institutions' Reflection Profil-

ing Syndicate (BIRPS) will study both areas in the North Sea and offshore south-west Britain. Data acquired during those experiments should provide crucial evidence on depth variation of the Moho associated with basin development and on the nature of faults deep in the crust where transition is expected to occur from brittle fracture to ductile flow during extension. □

R. McQuillin is Head of Marine Geophysics Unit in the Institute of Geological Sciences, Murchison House, West Mains Road, Edinburgh EH9 3LA.

Translation control

Protein phosphorylation and translation of messenger RNAs

from Mike Clemens

It has been known for many years that parts of the complicated cellular machinery that translate messenger RNAs into proteins can be modified by reversible phosphorylation — the initiation factor eIF-2 (responsible for placing the initiating methionyl-tRNA on the ribosome) and the protein S6 (a component of the smaller ribosomal subunit) are the best studied examples. Now, it has been suggested that a third class of proteins involved in translation, the aminoacyl-tRNA synthetases, is subject to a phosphorylation-dephosphorylation process¹.

The aminoacyl-tRNA synthetases attach amino acids to tRNA during translation. Damuni *et al.*¹ have recently shown that, in extracts of rat liver, several aminoacyl-tRNA synthetases can be inactivated by incubation with ATP, provided that care is taken to inhibit protein phosphatase activity with sodium fluoride. A crude fraction containing the activity responsible for this effect (a putative protein kinase) was identified, as well as another fraction which reversed the inactivation and is presumed to contain one or more protein phosphatases. The effects of the fraction could be mimicked by addition of highly purified protein phosphatases from skeletal muscle or liver. Although no direct evidence for changes in the phosphorylation state of the various aminoacyl-tRNA synthetases has yet been obtained, the results clearly suggest that the enzymes can be regulated by such a mechanism. The major questions are, what factors may control the phosphorylation-dephosphorylation system and what is its physiological relevance?

According to Damuni *et al.*, both nutritional and hormonal control of aminoacyl-tRNA synthetase activity may occur by the reversible phosphorylation of the enzymes. Overnight starvation of rats led to a 50–60 per cent inhibition of at least five different synthetases and inhibition could be reversed by incubating the enzyme with the reactivating (protein phosphatase) frac-

tion. Exposure of isolated hepatocytes to the hormone glucagon together with a cyclic AMP phosphodiesterase inhibitor similarly inactivated the synthetases; insulin treatment of cells from starved rats produced the opposite effect.

The question of the physiological relevance of these changes poses more of a problem. First, modulation of rates of amino acid-charging on tRNA might be expected to affect the rates at which growing protein chains are elongated (since the charged tRNAs are the precursors for that process). Most evidence indicates, however, that it is the rate of ribosome attachment to mRNAs (initiation) rather than the rate of charging which controls the overall protein synthesis rate. Second, neither overnight starvation nor acute insulin administration has much effect on the rate of protein synthesis in liver *in vivo* (as opposed to the situation in skeletal muscle where protein synthesis is sensitive to such treatment). In experiments where precursor-specific radioactivity has been rigorously controlled and measured, no decreases in the rate of hepatic protein synthesis per ribosome have been seen in up to two days of starvation^{2,3}, although there was a small decline in ribosome number. Experimentally induced diabetes has been shown by McNurlan and Garlick⁴ to cause a 28 per cent fall in protein synthesis rate per ribosome *in vivo*; in perfused liver a larger effect was observed, although it was not associated with any lowering of the polypeptide chain elongation rate⁵. Insulin treatment only appears to reverse the inhibition of protein synthesis relatively slowly in the liver (requiring 24 h or longer). Clearly, these observations leave open the question of the role of the three- to four-fold changes in aminoacyl-tRNA synthetase activities obtained within 30 min in hepatocytes by Damuni *et al.*

It is possible that the regulation of translation in liver is different from that in skeletal muscle as the latter tissue is clearly

more sensitive to physiological changes. Recent work⁶ carried out at the University of Sussex suggests that starvation, diabetes and insulin treatment have substantial effects on the levels of initiation complexes formed between methionyl-tRNA and 40S ribosomal subunits. The changes are of the same magnitude as those seen in the rate of protein synthesis in muscle in these conditions. It seems difficult to link the regulation of initiation of translation to possible modulation of charging of tRNAs with amino acids, even if such a process also occurs in muscle. Nevertheless it is tempting to speculate on a possible relationship between aminoacyl-tRNA synthetase activity and polypeptide chain initiation.

It is well established that the availability of essential amino acids controls protein synthesis in cultured tumour cells and in normal tissues. Regulation occurs through modulation of initiation and involves a change in the activity of initiation factor eIF-2 (ref. 7). Several pieces of evidence suggest that this regulation is not mediated directly by changes in tRNA charging levels, and yet recent studies⁸ at St George's Hospital Medical School on Chinese hamster ovary cell mutants containing a temperature-sensitive aminoacyl-tRNA synthetase show that initiation is controlled at the non-permissive temperature in a manner which is indistinguishable from the effects of amino acid starvation. Is there a regulatory function attributable to aminoacyl-tRNA synthetases, perhaps not directly involving tRNAs themselves? It may be relevant that many of the synthetases exist in the form of a high-molecular-weight multi-enzyme complex. Such a complex could include regulatory proteins, which might be the true substrates for the hormone-sensitive protein kinase(s) and phosphatase(s) studied by Damuni *et al.* Interestingly, the main effect of glucagon on protein synthesis in perfused liver is to prevent stimulation by added amino acids⁹.

Protein phosphorylation and translational control have proved uneasy partners in recent years. After eight years of investigation it is only now becoming apparent how eIF-2 activity may be controlled by phosphorylation, and the significance of the changes in the multiple phosphorylated forms of ribosomal protein S6 still has not been resolved. Let us hope that our understanding of the control of the aminoacyl-tRNA synthetases by protein kinases and phosphatases follows a smoother path. □

Mike Clemens is a Cancer Research Campaign Career Development Award Holder at St George's Hospital Medical School, London SW17 0RE.

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