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Discussion Letter

Organization of soluble enzymes in the cell

Relay at the surface

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A model is proposed uniting two groups of facts: the adsorption of enzymes on subcellular structures and the direct ('from hand to hand') transfer of metabolites between enzymes. The basic idea is that the binding of metabolites (substrates and/or products) results in desorption of the enzymes from subcellular structures during each catalytic act. This makes the enzymes mobile and capable of directly (from hand to hand) transferring metabolites to other enzymes adsorbed on subcellular structures. The model leads to a mechanism by means of which soluble enzymes can be compartmentalized in defined regions of the cytoplasm.

Supramolecular enzyme organization; Intracellular organization; Metabolite transfer; Enzyme compartmentation

There is a body of evidence that the majority of the soluble enzymes, at least in the eukaryotic cell, are associated with various subcellular structures, such as membranes, the cytoskeleton and polyribosomes. This conception of enzyme organization, although not strictly proven, is nevertheless supported by numerous experimental data (see recent reviews [1–9]). Thus, for example, glycolytic enzymes are often found in a complex with structural proteins and membranes (see [1–7,9]), and translational machinery proteins are in a complex with polyribosomes (see [8,9]) upon subcellular fractionation. Recently developed methods of determining the diffusion of proteins in a living cell, such as the reference phase technique [10] and fluorescence recovery after photobleaching [11–13], also indicate that the soluble proteins are associated with the subcellular structures in vivo.

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On the other hand, Srivastava and Bernhard have recently reported convincing data showing that metabolites, when transferred between enzymes, do not diffuse freely through the environment but are directly transferred from one active center to another, as if 'from hand to hand' in a short-lived enzyme-metabolite-enzyme complex (see reviews [14–16]). This kind of mechanism is clearly demonstrated in the case of the transfer of 1,3-diphosphoglycerate between phosphoglycerate kinase and glyceraldehyde-3-phosphate dehydrogenase, and also NADH between dehydrogenases (see [14–16]). The model of direct transfer presumes that it is not the metabolites themselves, but their complexes with enzymes that diffuse in the cell. This means that enzymes must be mobile. This requirement, however, runs contrary to the fact that enzymes in the cell exist predominantly in an adsorbed state.

The only way of reconciling these two groups of facts is to assume that at alternating periods of time enzymes are either in a fixed (adsorbed) state or mobile (diffuse freely). However, what could be

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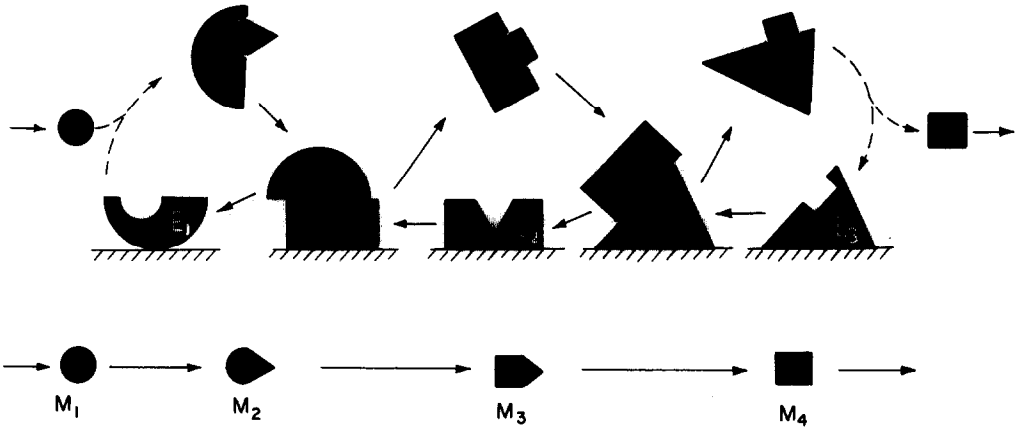

Fig.1. Enzyme organization according to relay at the surface model. See text for details.

the mechanism in action? It can be understood if enzymes are desorbed from subcellular structures by metabolites (substrates and/or products). Indeed, the phenomenon of the desorption of enzymes by metabolites has been shown in numerous cases of enzyme association with subcellular structures (see reviews [9,17]). If an enzyme is desorbed by a metabolite during every catalytic act (which seems likely [9,17]), then there is a mechanism allowing enzymes both to be in an adsorbed state and to diffuse freely alternately.

The functioning of multienezyme systems consisting of several soluble enzymes may be described as follows (fig.1). An enzyme E_1 is adsorbed on a subcellular structure while it is not at work, i.e. when not bound with a substrate. Enzyme E_1 desorbs either upon binding the substrate or immediately after the catalytic act. Now enzyme E_1 in the complex with its product diffuses within the cell until it meets the subsequent (along the metabolic chain) enzyme E_2 adsorbed on the surface of the subcellular structure. Consequently, an enzyme-metabolite-enzyme complex appears and a direct from hand to hand transfer of a metabolite takes place. Then, enzyme E_1 adsorbs again on the surface, while enzyme E_2 desorbs either immediately or after the catalytic act. Enzyme E_2 undergoes the same transformations as enzyme E_1. This chain of interactions can be termed as 'relay at the surface'.

The most significant consequence of the model is that it can explain how the local accumulation of enzymes in the regions of final product consumption is achieved (Shakhnovich, E.I., Gutin, A.M. and Ryazanov, A.G. in preparation). Indeed, if an enzyme carrying the final product of a multienzyme chain transfers the product to the 'consumer', it will be adsorbed somewhere nearby on the surface of the subcellular structure. The preceding enzyme transfers the metabolite to this adsorbed enzyme and thus also adsorbs not far from the place where the final product is consumed, etc. It turns out that the entire chain of enzymes catalyzing subsequent reactions leading to the formation of the final consumed product is localized precisely where this product is required. Thus, in the absence of long-range interactions, it can be conceived how molecules can accumulate at certain points in space, at the same time remaining mobile.

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