news and views

Cytochalasin action

from Dennis Bray

CERTAIN chemicals have come to stand for particular areas of biological research. Think of fluorescein isothiocyanate; 2-deoxyglucose; bis-acrylamide; α-bungarotoxin, anti-mouse immunoglobulin. Substances such as these are hitched so firmly to a line of research that you could almost use their monthly sales figures to measure scientific fortunes. They can be important for practical reasons and are often essential to a new technique, but sometimes the link is of a more fundamental nature and arises because their site of action is so close to the heart of a biological phenomenon. This is well-illustrated by the cytochalasins — a group of secondary mould metabolites with a remarkable ability to paralyse the movements of vertebrate cells (see Tanenbaum (ed.) *Cytochalasins: Biochemical and Cell Biological Aspects,* North-Holland, 1978).

When the discovery came in the mid-1960s, that the cytochalasins had an effect on the migration and division of tissue cells there was, at first, little interest. In those days cell motility was an obscure subject — a few anchorites here and there watched amoebae crawl around or produced extracts of blood platelets but that was all. And then, within a few years, both the drug and the discipline took the centre of the stage. Everyone, from the most myopic graduate student to the most harried administrator knew that cells move, and that they do so by a sort of muscle contraction, and that this is blocked by a new drug called cytochalasin — or is it colchicine?

The history of how it happened has yet to be written, but a timely article in *Science* (**171**, 135; 1971) from a group at Stanford, led by Wessells, certainly had great influence. Touching most of the bases it surveyed the aspects of the new science of cell motility — locomotion, intracellular movements, shape changes — and linked them to an immature knowledge of non-muscle actomyosin systems. The keystone of this edifice was the effect of the drug cytochalasin which, it was suggested, acted on cell movements by direct action on actin.

The tidal wave that followed grew because everyone realised that movements were important to the phenomenon they were studying — whether it was secretion, phagocytosis, morphogenesis or transport. An international authority on the sex life of the red kidney bean found an actin band on a gel and filaments in a micrograph and new horizons opened before him. An hypothesis was born — curiously fashioned from sliding and interdigitating filaments it needed only one test to make it fact. And yes — cytochalasin causes *coitus interruptus*. Small wonder then that there was a reaction from the establishment. To those familiar with, say, the precise world of X-ray diffraction of myofibrils, the new science was a quagmire of half truths. And nowhere was this more true than in the connection between actin and cytochalasin. The evidence was indeed slim. Little more than that the most obvious morphological disorder in cells treated with the drug was in the microfilaments. Attempts to prove a closer relationship were disappointing. Muscle contraction, actin activation of myosin ATPase, the salt-induced polymerisation of pure actin, decoration of actin with heavy meromyosin — all these were essentially unaffected. Even more incriminating was the finding that the wonder drug of motility had other effects. It was very good at blocking glucose uptake into the cell — working quickly and at low concentrations.

The use of cytochalasin continued but without a licence: in many laboratories it became *chemica non grata*. Only a few talented researchers persisted with the conviction that it was of central importance. Several strategems were developed to prove this point and one of them — that described here — has at last been sucessful. It began with the synthesis of a hydrogenated cytochalasin derivative that was free of the unwanted side-effects of membrane transport functions (Atlas & Lin *J. Cell Biol.* **76**, 360; 1978) and the use of this bait to fish for the motility receptor site. A binding complex could be found in the erythrocyte membrane which contained spectrin, actin and band 4.1 (Lin & Lin *Proc. natn. Acad. Sci. U.S.A.* **76**, 2345; 1979; see also *News and Views* **281**, 426; 1979). The complex had the property that when added to a solution of monomeric actin it caused an explosive polymerisation — an intriguing property when you consider microfilaments in the cell. When it was found that cytochalasin inhibited this polymerisation the writing was indeed on the wall (Grumet *et al. J. Cell Biol.* **83**, 316a; 1979).

Everything that has been learnt about the actin polymerising complexes recently — and a great deal is about to be published — is encouraging. It, or its close relative can be isolated from other tissues such as brain or platelets (Flanagan, *Fed. Proc.* **38**, 339a; 1979); the complex can utilise actin sequestered by profilin — a low molecular weight protein that is abundant in the cytoplasm (Lin *et al. J. Cell Biol.* **38**, 317a; 1979); the different types of cytochalasin affect actin polymerisation with the same relative potency they show towards whole cells (Lin & Lin *op. cit.*). And at last the eagerly awaited nub of the complex has been identified, the crucial molecule on which cytochalasin acts was revealed as — after all — actin (Grumet *et al. op. cit.*). Or, to be more precise, it is the growing end of an actin filament. Within the complex, it is thought that a short oligomeric fragment is held in such a way that it can act as a nucleation point. A similar effect can be produced if pure actin is bound to polylysine (Brown & Spudich *J. Cell Biol.* **80** 499, 1979) or stabilised by chemical cross-linking (Grumet *et al. op. cit.).* The induction of polymerisation by these fragments, curiously in contrast to salt-induced polymerisation, is blocked by cytochalasin; this drug moreover binds to filamentous actin with a stoichiometry that indicates binding at one end. It is similar, many will recall, to the action of colchicine on microtubules.

And so — thanks largely to the incisive experiments of Lin and his colleagues — cytochalasin has been made an honest drug. It acts on a small nucleating fragment of actin sequestered by a group of other proteins associated with the plasma membrane. The normal function of the nucleating fragment within the cell is, presumably, to cause actin subunits to assemble into microfilaments; the stimulus for this has yet to be identified and could well come from the other side of the membrane. Cytochalasin, therefore, forms a causal nexus between actin and the membrane and cellular movements, and acts — who can doubt it? — at the heart of cell motility. □

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