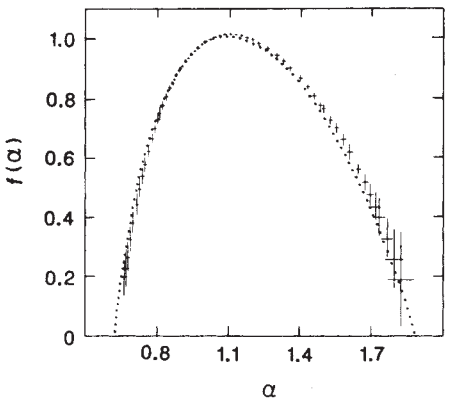

Fig. 2 The function of $f(\alpha)$ quantifying how often a given scaling index or pointwise dimension occurs on the attractor. The error bars indicate the standard deviation of the mean of three data sets. The universal circle-map prediction is shown as a dotted curve. (From Gwinn, E.G. & Westervelt, R.M. *Phys. Rev. Lett.* **59**, 157–160; 1987.)

information. Previously, the results would have been presented as a frequency power spectrum. Today the data (50,000 data points would be typical) are manipulated in the way that a theorist analyses a numerical simulation. First, the system is reduced from a continuous time recording to a discrete series of stroboscopic flashes. This method, devised a century ago by H. Poincaré, makes it possible to survey the dynamics visually. The experimental Poincaré map is shown in Fig. 1. The value of the current at each period of the external drive is plotted against its value at the next period. (The first hundred or so cycles, the transients, are not plotted.) The fact that the response is quasiperiodic implies that the dots on the figure would eventually fill up some closed curve. If the transients had been shown on Fig. 1, we would see points initially far away rapidly approaching that curve, which is therefore an 'attractor'. Precisely at the onset of chaos — which was reached in the experiment by varying the amplitude of the drive — the kinky structure visible on the figure emerges. It is called a 'strange attractor' because of the unusual way points are distributed on it and this distribution contains information about universal features of the transition to chaos.

The strangeness of the attractor can be probed by looking at the distribution of points around some reference point. For a reference point, P, on the attractor we define $N_P(r)$ as the number of neighbours within distance r along the attractor. On a usual (non-strange) quasiperiodic attractor, the points are distributed smoothly; a segment of the attractor looks like a line. Thus, $N_P(r)$ scales with r as $N_P(r) \propto r$ for any point P. For the strange attractor in the figure this is not necessarily true. If we pick a point at random, the theory predicts $N_P(r) \propto r^{\alpha}$ with α varying between 0.6326 . . . and 1.8980 . . ., and the point P is said to have the pointwise dimension α.

A powerful formalism for confronting the experiment with the predictions of the theory was developed recently by T.C. Halsey *et al.* (*Phys. Rev.* **A33**, 1141–1151; 1986). They look at the attractor as a superposition of 'subfractals'; namely, for each α, the set of points with pointwise dimension α. A function $f(\alpha)$ is introduced to quantify how often a given value α appears on the attractor — more precisely, $f(\alpha)$ is the Hausdorff dimension of the set of points with pointwise dimension α. Figure 2 shows this curve for the theory and the experiment. The dots are the theoretical prediction computed by iterating a so-called circle-map. The crosses represent $f(\alpha)$ calculated from the experimental attractor shown in Fig. 1. Given that there are no adjustable parameters, the agreement between the theory and the experiment is remarkable. (The error bars at the edges of the α-interval come from the sparseness of points contributing in those limits; here the finiteness of the data sets and noise play a large part.)

Theory and experiment thus interact in a fruitful way, and it is fascinating that the fractal properties of strange attractors can be measured with such precision in physical systems. Theoretically the most striking fact, not anticipated until a decade ago, is that the dynamical systems approaching chaos do so in a universal fashion. Other fields of physics, notably those concerned with growth or aggregation, reveal all kinds of fractal behaviour, but it is not yet clear what kind of universality (if any) to expect there. □

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Intermediate filaments

Looking for a function

Benjamin Geiger

STUDIES on the molecular properties of the cytoskeleton are largely motivated by the desire to understand the functions of these cytoplasmic filaments in cells and tissues. Physiological studies, morphological observations and biochemical characterization of proteins in the cytoskeleton have allowed molecular models, albeit tentative, of the possible cellular activities in which the various classes of filaments take part. These models, despite their tendency to be oversimplified, have contributed a great deal to current concepts of mechanisms of cell motility, mitosis, transcellular transport, adhesion, modulation of membrane activity and cellular morphogenisis. Now, however, experimental work[1–4] is providing a test for many of these ideas about the physiological functions of intermediate filaments, one class of cytoskeletal filaments.

Until recently, most information has come from the other two classes of cytoskeletal filaments, microfilaments and microtubules, which, together with batteries of associated proteins, have been extensively characterized. Moreover, the availability of excellent and well-studied model systems such as the contractile unit of skeletal muscle or the interaction of dynein with microtubules in cilia and flagellae have provided clues about the cytoplasmic activities in which actin and tubulin are involved.

The structure–function relationships of the third cytoskeletal network, the intermediate filaments, are less well characterized. Despite the fact that the primary structure of many intermediate-filament subunits is known and their cellular distribution extensively documented, only limited molecular information has so far been available on their behaviour *in vivo*. In the absence of specific data, it has been suggested that intermediate filaments are involved in mechanical integration of cytoplasmic space[5] or in a skeletal framework of the cytomatrix (see refs. 6,7 for reviews). Well-controlled experiments relating their molecular properties to specific cytoplasmic events are, however, still needed to understand their functions in more detail.

Inagaki *et al.*[1] recently investigated specific phosphorylation events in modulating the assembly of vimentin molecules into intermediate filaments. These authors show that vimentin is an excellent *in vitro* substrate for protein kinase C and cyclic AMP-dependent protein kinase, but not of several other kinases. Moreover, phosphorylation by the cyclic-AMP-dependent kinase induces the dramatic disassembly of vimentin filaments. Analysis of tryptic phosphopeptide maps indicates that the sites of phosphorylation with the two kinases are distinct, and the authors suggest that a single, site-specific phosphorylation of vimentin (as well as its

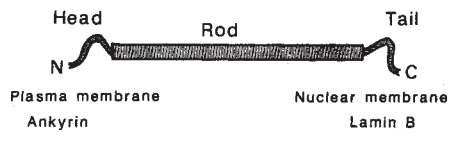

Fig. 1 Intermediate-filament subunit (vimentin or desmin) presenting binding sites for plasma-membrane-associated ankyrin at the amino-terminal head domain, and binding sites for lamin B at the carboxy-terminal tail region.

dephosphorylation) is important in the modulation of filament structure and organization.

These new findings could be related to earlier observations[5-10] which correlated changes in intermediate-filament structure in cells with phosphorylation events. The phosphorylation-dependent disassembly of intermediate filaments may produce a molecular solution for a cellular dilemma: how do dynamic cellular processes such as cytokinesis or changes in cell shape occur in the presence of the notoriously insoluble network of intermediate filaments? Data obtained using the immunofluorescence and electron microscopes indicate that cells can transiently dissociate their intermediate filaments and pack their subunits into non-filamentous spheroidal structures[11-13]. It is not clear whether a site-specific phosphorylation-dependent dissociation similar to the one documented by Inagaki *et al.*[1] is involved, or whether other modifications are effective during the dynamic rearrangement of the cytoplasm *in vivo*. To elucidate this question, it is necessary to define and localize the critical phosphorylation site along the vimentin molecule and to determine directly if specific, spatially controlled phosphorylation–dephosphorylation events are indeed involved in the physiological modulation of filament integrity and structure.

Another related matter concerns the native interactions of vimentin or other intermediate filaments with various cytoplasmic organelles. Many previous studies, based on immunocytochemistry and localization in the electron microscope, pointed to an apparent association of intermediate filaments with many cellular structures. It had been claimed that in addition to their well-documented interactions with desmosomes, intermediate filaments are often detected in close association with the nucleus, the plasma membrane, dense bodies of smooth muscle, microtubules, fat globules of adipocytes and other elements (see ref. 6 for a review). These observations stimulated much speculation concerning the roles of intermediate filaments as specific cytoplasmic organizers, yet the basis for the presumptive interactions remained obscure.

In a series of recent biochemical studies, Georgatos and Blobel[2,3] show that purified vimentin binds to different fractions of avian erythrocyte membranes through two distinct domains. Sites located at the carboxy-terminal tail of the vimentin molecule bind specifically to nuclear envelopes in a cooperative fashion, whereas the plasma-membrane fraction interacts in a saturable manner with the amino-terminal head of the vimentin molecule. The central rod segment of vimentin has no apparent affinity to either fraction (see Fig. 1). Binding studies reveal specific vimentin-binding constituents along these two types of membrane. It is shown that major nuclear binding sites for vimentin are lamin B or the lamin A–lamin B hetero-oligomers. Interestingly, lamins A and C, which associate with lamin B to form the nuclear lamina at the endofacial surfaces of the nuclear membrane, have a similar primary and secondary structure to intermediate filaments[14,15]. Other new work[4] shows that the membrane-skeleton protein ankyrin could provide a second type of binding site to the amino-terminal head region of vimentin or of desmin, a related intermediate-filament protein of muscle cells (Fig. 1).

The specific interaction of vementin, and possibly other intermediate-filament subunits with lamin B, raises an interesting

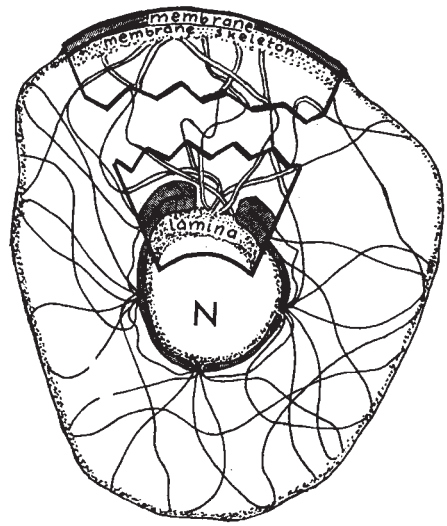

Fig. 2 Hypothetical picture of the intermediate-filament network in cells. Based on the results described in the text, vimentin- or desmin-containing filaments associate with the cell nucleus, interacting with the nuclear lamina through the nuclear pores. At the cell periphery the same intermediate filaments apparently associate with the membrane skeleton, thus forming an elaborate system of nucleolemmal/plasmalemmal interactions. The subunits carrying the two types of binding sites are distributed in a non-polar fashion along the filament.

problem. In their heteropolymeric form, lamins are known to be confined to the endofacial surfaces of the nuclear envelope, whereas intermediate filaments are located throughout the cytoplasm and outside the nucleus. Thus, physical interaction between vimentin and lamins (if and when it takes place *in vivo*) could occur through the nuclear pores, where elements of the nuclear lamina are exposed to the cytoplasm. This suggestion of a direct and specific interaction between elements of the cytoplasmic matrix and peripheral elements of the nuclear matrix is not new. Ultrastructural studies carried out several years ago suggested that such interactions exist and take place through the nuclear-pore complexes[16-20]. The identification of another binding system along the plasma membrane provides a possible mechanism for nucleolemmal/plasmalemmal anchorage and communication (see scheme in Fig. 2). The new *in vitro* results[1-4] seem to complement the existing data concerning the molecular basis and possible mechanisms underlying the physiological interactions of intermediate filaments.

It is too early to evaluate the functional significance of these new observations, yet specific questions and working hypotheses can now be put forward relating the new molecular and structural findings to specific cytoplasmic and nuclear events. Does the nuclear lamina that is exposed at the nuclear pores act as an organizing centre for intermediate-filament assembly? Is ankyrin (or a homologous molecule in non-erythroid cells) a physiological linker of intermediate filaments to the plasma membrane? Are the interactions of vimentin with the nucleus or with the plasma membrane modulated by post-translational modifications of either of the molecules involved? Do the mechanical interconnections between the nucleus and the membrane play a general role in the spatial organization of the cytoplasmic matrix or in the active or passive transport of macromolecules between the nucleoplasmic and cytoplasmic compartments? Are there other intermediate filament-associated proteins on different cellular organelles? How are the site-directed phosphorylations (or dephosphorylations) of vimentin spatially and temporally regulated? Do other intermediate filaments, such as keratins, neurofilaments or glial filaments, have binding properties similar to those of vimentin and desmin, and are they comparably affected by specific phosphorylations? The tools are now ready for concerted efforts to answer these and other questions about the organization and dynamics of the cytoplasm. □

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