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Poring over channels

Ion transport across biological membranes is critical for maintenance of the intracellular milieu; for conversion of energy derived from respiration or light to forms directly usable by the cell; and, most spectacularly, in generation of action potentials by excitable tissues. Study of the last phenomenon was initiated by Luigi Galvani, who hypothesized an 'animal electricity' as the basis of nerve activity. The efforts of Helmholtz and Bernstein, of Cole and Curtis, and of Hodgkin, Huxley and Katz led to a model of channels or pores through the membrane that were exquisitely selective for either Na^+ or K^+ and could be switched between open and closed states by the membrane potential. The existence of these channels was demonstrated by Neher and Sakmann with their patch-clamp technique in the seventies, by which time it had become apparent that there were many additional types of channels—some selective for specific ions and others broadly selective for either cations or anions and triggered by chemical rather than electrical stimuli.

Sodium and calcium-selective channels as well as a cation-selective channel that is triggered by the neurotransmitter acetylcholine (the acetylcholine receptor) were purified in the seventies and reconstituted into artificial membrane systems. Electrical recordings from these preparations confirmed the proteinaceous nature of the channels. Correlating form and function became possible only after cloning the genes for Na^+, K^+ and Ca^{2+} channels as well as a variety of neurotransmitter receptors. The K^+ channel is the simplest of the voltage-activated ion channels, the Na^+ and Ca^{2+} channels each appearing to be constructed of four K^+-channel-like subsections. The simplicity of the K^+ channels makes them the system of choice for structure–function studies. Mani Ramaswami (**page 341**) reviews the explosion of information that has appeared over the last five years or so relating the sequences of genetically engineered channel polypeptides to their function. He has also summarized almost 200 years of research leading from Galvani to the current bonanza and sets the stage for a discussion of current ideas on the structures of these molecules and a dissection of their architecture into functional domains.

Chimaera

The **cover photograph** shows a spontaneous bilateral mosaic fly of the species *Drosophila ananassae*. Genetic mosaics, or animals in which some cells are genetically different from others, can be detected if suitable genetic markers are present. In the case of the fly shown on the cover, the left half expresses several mutant markers and the right half the wild-type ('normal') copies of these genes (B. N. Singh and Sujata Mohanty **page 372**). Mosaics, both spontaneous and induced, have been very powerful tools in *Drosophila melanogaster* genetics. Mutations in many genes result in lethality when homozygous. However, many of these organism-lethal mutants are viable when only a small patch of cells in the animal are homozygous mutant. Examination of the cellular phenotype of lethal mutants in mosaics has yielded much information on the role of genes during development. By using genetic markers mutant cells can be distinguished from neighbouring wild-type cells. Such mosaics are informative in understanding the roles of genes in cell–cell communication. The *D. ananassae* mosaic in the article by Singh and Mohanty is unusual because it is a half-body mosaic. The authors discuss possible mechanisms by which this may happen for an autosome, as distinct from the X chromosome, where the mechanism of generation of such mosaics is known. Even though the report is of one event, it is of interest, and is an occasion for *melanogaster* workers to remember the existence of other fly species where interesting genetics can be done. Incidentally, study of a transposable element in *D. ananassae* that preferentially inserts in the regulatory sequences of eye-specific genes has resulted in identification of new genes involved in eye development.

Molecular motifs

The three-dimensional structures of hundreds of proteins are currently available, thanks mainly to the efforts of protein crystallographers over the last four decades. Analysis of these structures has led to several basic principles pertaining to protein architecture. One such principle is that, broadly speaking, a globular protein is largely made up of one or more loosely defined structural motifs. Yet another principle is that similar amino-acid sequences generally lead to similar peptide folds, although the reverse is not always true. These principles and approaches developed over the years to predict secondary-structure features from amino-acid sequences form the basis of much of what is described as knowledge-based prediction of homologous protein structures. The predicted structures are necessarily tentative, and must be confirmed experimentally using X-ray crystallography or NMR techniques, which are expensive and time-consuming. In the meantime, the predictions provide valuable insights into the structure and the biological role of the concerned proteins. The work of H. M. Gupta and D. M. Salunke (**page 374**) is an example of the effective use of knowledge-based prediction for illuminating a biologically important problem. On the basis of detailed sequence comparisons and other available evidences, they establish structural homology of a polypeptide inhibitor of prolactin secretion with negative regulators of developmental-gene transcription. The predicted tertiary structure of the inhibitor shows the helix-loop-helix motif characteristic of the transcriptional negative regulators.