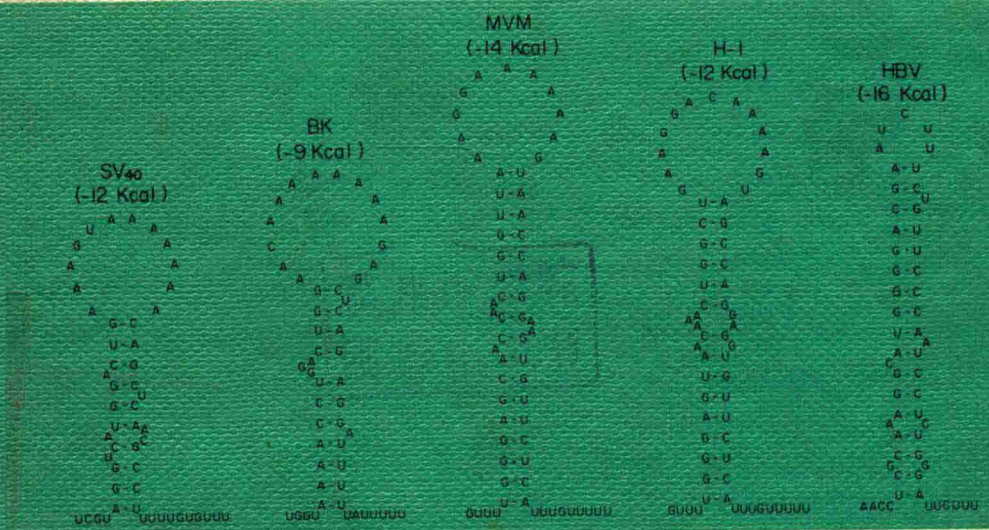
Mechanisms of Viral Pathogenesis:

From Gene to Pathogen

edited by A. Kohn and P. Fuchs



DEVELOPMENTS IN
MOLECULAR VIROLOGY

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MECHANISMS OF VIRAL PATHOGENESIS

From Gene to Pathogen

Proceedings of 28th OHOLO Conference, held at Zichron Ya'acov, Israel, March 20–23, 1983

Edited by

A. Kohn
P. Fuchs

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WELCOMING ADDRESS

Ladies and Gentlemen

The OHOLO conferences were initiated 28 years ago by the Israel Institute for Biological Research, and take their name from the site of the first meeting on the shores of Lake Kinnereth. The purpose of these meetings is, as it was at their initiation, "to foster interdisciplinary communication between scientists in Israel, and to provide added stimulus by the participation of invited scientists from abroad".

I thought at first that as the OHOLO conferences are so well established, there is no need for formal introduction to the present one. However, going through the topics of the next one (which is mathematics and energy), it occurred to me that the present conference is of a singular nature. It is the last conference of a continuum of 27 meetings dealing with various aspects of biochemistry, biology and molecular genetics.

It is not by chance that the topics of our conferences followed outstanding achievements in Biology. We started with bacterial genetics (1956), followed by biological synthesis and function of nucleic acids (1962), cellular control mechanisms of macromolecular synthesis (1963), molecular aspects of immunology (1964), strategies for the control of gene expression (1973), extrachromosomal inheritance in bacteria (1978) and finally to this year's topic—viral pathogenesis—or more appropriately named "from gene to pathogen."

Our present topic represents the peak of scientific endeavour which started with the initiation of the study of bacterial genetics at Cold Spring Harbor, and which achieved a profound understanding of basic molecular processes underlying the inheritance of genes and gene expression. Great names in molecular biology were connected with our conferences: Lwoff, Luria, Monod, Benzer, Spiegelman, S. Cohen, Gorini, Levinthal, Magasanik, Kabat and others. This year's conference is certainly in line with the tradition of the past. There is no doubt that the progress in molecular genetics represents the most dramatic scientific breakthrough in our century and every one who witnessed the flowering of this discipline, and had even a modest part in it, may be proud of this victory of the human mind.

It is with this sense of deep appreciation that I welcome the participants of the 28th OHOLO conference and wish our guests a very pleasant time in Zichron Ya'acov. Thank you.

I. Hertman, Director
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PREFACE AND ACKNOWLEDGMENTS

This conference is devoted to the elucidation of the various molecular mechanisms determining the virulence or persistence and latency of animal viruses.

The concept of virulence entails not only the infecting microorganism but also the host which is affected by it. The host may be a cell or it may be an organism. The term "virulence" is associated with those properties of the virus which lead to the death of the cells or to disease symptoms in an organism.

Since virulence is defined as a product of interaction of virus and the host, a statement about the level of virulence of any particular strain of virus can be made only if the species and age of the host, the route of inoculation and the dose are kept constant, so that this property of "virulence" can in fact be attributed to the genomic structure and the molecular expression of it in a virus.

When viruses cause disease by multiplication in a target tissue or organ (e.g. CNS, lungs, liver) the virulence is a function of virus multiplication and the extent of cell damage. Thus poliovirus is not considered virulent as long as it infects only the cells lining the intestinal tract, but when it has the ability to invade the central nervous system it is virulent. Many viruses (e.g. arboviruses) may be virulent to newborn animals, but not to adults in the same species.

On the cellular level the first requirement for the ability of a virus to infect a cell is the necessity in a cell to have proper receptors for binding the virus. Poliovirus is not virulent in chicken cells because it cannot attach to it and infect it. The opportunity for expression of virulence is thus first determined by the chemistry of virus:cell encounter. This entails cell receptors as well as the virus attachment proteins (VAP). The structure of these viral antigens is genomically determined and therefore can be affected by mutations. In addition, there are posttranslational events, such as e.g. the cleavage of hemagglutinins in myxoviruses and of F proteins in paramyxoviruses which are essential in establishing a productive infection (Choppin, Rott, Trent).

In viruses with divided genomes such as myxo, bunya and orbiviruses the reshuffling of the genomic pieces in cells infected by more than one strain of virus may result in a change in virulence to a particular host. This reassortment, which can be experimentally manipulated, permits the analysis of progeny virus and the assignment of virulence to certain genes. So, for instance, the work of Bishop already indicated that the medium-sized RNA species of the bunyavirus genome that codes for glycoproteins determines neurovirulence in the California group of virus and viscerotropism in group C bunyavirus. He has also shown that the L-RNA gene

products (transcriptase and replicase) can mitigate the virulence that is prescribed by M-RNA gene products. Reassortant viruses with a defective L-RNA are not transmitted by arthropod vectors. Genetic analysis of reassortment of influenza and bunyavirus points to a polygenic nature of pathogenicity of these viruses. In the paramyxoviruses the normal expression of M protein is involved in persistent infection, as e.g. in SSPE induced by measles virus (Norrby, Carter).

The host contribution to virulence of myxo and paramyxoviruses involves the proteolytic cleavage of HA or F proteins. Thus cells (or animal species) that do not possess the proper protease, would not be infected by these viruses (Akov).

In rabies virus Coulon and Flamand identified the antigenic site on the glycoprotein G which is associated with virulence of this virus. Mutants which are not neutralized by certain monoclonal antibodies directed to different epitopes on G, have a significantly reduced pathogenicity in mice. Thus in this virus the virulence seems to be associated with a particular antigenic structure on the G-protein.

The examples depicted till now are connected with the effects of structural changes in some viral proteins which determine virulence either per se or as a result of the structure being differently affected by host cell enzymes.

Another type of virulence depends on the regulatory functions of the viral or host genomes. Wagner shows that the inhibition of cellular RNA synthesis by vesicular stomatitis virus depends on the presence and role of a 47 nucleotide leader sequence present at the 3′ end of the viral genome, and the presence in that leader squence of TAATA-like and consensus-like nucleotide sequences.

This type of regulation of virulence is also encountered in herpes virus which needs a thymidine kinase for the phosphorylation of its nucleosides (Becker). The presence and activity of this enzyme may determine whether the virus will be actively multiplying in the infected cells or establish a latent infection, or be reactivated from its latent state. Mutants of HSV which lack the TK gene can infect epidermal cells and even proceed to nerve cells in ganglia, but they are unable to multiply there and to proceed to brain so as to cause encephalitis. The virus can multiply, however, in host cells which provide their kinase for the synthesis of viral components.

Finally one should perhaps discuss in this context the concept of oncogenes and the fact that normal animal genes become expressed as a result of finding themselves in the vicinity or association with promoter regions supplied by oncogenic viruses, or by rearrangement of the gene (Canaani, Aaronson).

Other host specific regulatory factors which may affect the expression of a gene are the attenuators and the enhancers, which have been by now quite well molecularly defined and are discussed in this conference in the context of SV40 gene expression (Aloni, Gruss) and retrovirus pathogenesis.

Research on virulence is still in its beginning stages. Many individual elements concerning either the virus or the host contributing to virulence have been studied, often in detail, but the overall picture—the orchestration effect of all contributing factors—still eludes us and remains a challenge for future research.