

**Biomedical Research Education & Training
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Research Keywords

Apoptosis, Biochemistry, Genetics, Infectious Disease, Microbiology, Mouse, Receptors, Virology, Viral Pathogenesis

Research Specialty

Virus structure, virus-cell interactions, and viral pathogenesis

Research Description

Our laboratory uses the mammalian reoviruses as an experimental system to study mechanisms by which viruses cause cell death and disease. Reoviruses infect many mammalian species, including humans, but disease is restricted to the very young. After infection of newborn mice, reoviruses are capable of causing encephalitis, hepatitis, and myocarditis, depending on the viral strain used. We use a multidisciplinary approach to investigate mechanisms of reovirus attachment, cell entry, genome replication, and apoptosis. These studies will provide a comprehensive analysis of the steps in reovirus replication that culminate in disease.

(1) Reovirus cell-attachment. The capacity of the reovirus attachment protein, sigma 1, to bind either ependymal cells or neurons is a major determinant of the different patterns of neurologic disease caused by reovirus infection. We are conducting experiments using expressed sigma 1 proteins and viral mutants with defined alterations in receptor-binding functions to determine how independent receptor-binding domains of sigma 1 contribute to stable cell-attachment and trigger viral entry. We also are investigating the role of a newly identified reovirus receptor, junctional adhesion molecule 1, in reovirus attachment, entry, and disease. This work will be interpreted in the context of ongoing structural studies of sigma 1 with the goal of determining how sigma 1 structure relates to its function in receptor binding.

(2) Reovirus entry into cells. Reovirus enters cells by clathrin-dependent endocytosis. Reovirus entry requires endosomal acidification and proteolysis of viral outer-capsid proteins; however, mechanisms by which these processes facilitate entry are not understood. We have isolated mutant viruses altered in their requirement for acid-dependent proteolysis and mutant cells that do not support proteolytic disassembly of reovirus virions. Biochemical, genetic, and structural studies using these mutant viruses and cells are ongoing to define mechanisms of reovirus entry. This research will reveal fundamental mechanisms by

which viral and cellular factors cooperate to facilitate viral entry and illuminate new targets for therapy against viruses that use the endocytic pathway to enter cells.

(3) Reovirus-induced apoptosis. Reovirus induces apoptosis in both cultured cells and in the murine central nervous system and heart. Our studies indicate that apoptosis is triggered by a signal-transduction cascade initiated by reovirus attachment and disassembly. Experiments are in progress to identify components of the cell-signaling apparatus required for apoptosis induction by reovirus and to determine the relationship between apoptosis and reovirus virulence. These studies will establish new paradigms for the interaction of RNA-containing viruses with critical cell-signaling pathways and lead to a better understanding of how viruses injure their host cells.

(4) New work in our laboratory is focused on mechanisms of orthopoxvirus attachment to host cells. Poxvirus replication is initiated by virus binding to cell-surface receptors. The attachment step is likely to be a critical determinant of viral tropism and thus play a crucial role in disease pathogenesis. Thus far, definitive receptors have not been identified for any orthopoxvirus. We are investigating virus-cell and virus-host interactions that mediate the attachment of vaccinia virus, a model orthopoxvirus. Results of these experiments will reveal fundamental mechanisms by which viral attachment proteins and their cellular receptors mediate orthopoxvirus tropism and initiate disease.

Publications

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Postdoctoral Position Available

Yes

Postdoctoral Position Details

POSTDOCTORAL FELLOWSHIP IN VIRAL PATHOGENESIS

A postdoctoral position is available to join a dynamic and interactive group engaged in the study of molecular viral pathogenesis using the mammalian reovirus system. Problems that we are currently addressing include the organization of receptor-binding domains in the viral attachment protein, biophysics of virus-receptor interactions, and the role of discrete attachment steps in virus-induced apoptosis and disease. We also are conducting studies to understand molecular mechanisms of reovirus disassembly and genome replication through an integrated approach that includes genetic and biochemical analysis of viral mutants and identification of cellular genes required for viral disassembly and replication. Applicants should have proficiency in molecular and cellular biology and protein biochemistry. Experience in studies of viral replication and pathogenesis is desirable. Send curriculum vitae, a brief description of research experience, and the names of three references to:

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