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SPOTLIGHT

Articles of Significant Interest Selected from This Issue by the Editors

Novel NF-κB Activation Pathway in RSV Infection

Respiratory syncytial virus (RSV), a leading cause of respiratory illness in infants and children, is known to induce the release of inflammatory chemokines by activating NF-κB. Choudhary et al. (p. 8948–8959) now show that RSV activates NF-κB early in response to viral infection using a novel noncanonical activation pathway involving induction of NF-κB-inducing kinase (NIK) activity. This work identifies NIK as a central mediator of an early response to RSV infection and provides a new target for therapeutic intervention.

RSV Nonstructural Proteins Subvert Host Defense

Respiratory syncytial virus (RSV) interferes with the antiviral interferon (IFN) response by using mechanisms that appear to involve the nonstructural proteins NS1 and NS2. Lo et al. (p. 9315–9319) describe the humanization of NS1 and NS2 coding sequences to allow for direct expression in host cells and consequent inhibition of Stat2 expression and IFN-α/β signaling. This inhibitory effect is more potent on human than mouse Stat2, suggesting a role for NS1 and NS2 in limiting viral host range as well as mediating immune subversion. These findings further underscore the therapeutic potential of targeting NS1 and NS2 in RSV-induced disease.

Close Encounter: HSV-1 Capsids and Glycoproteins Travel Independently and Meet at the Site of Re-Envelopment

Herpes simplex virus type 1 (HSV-1) capsids, newly assembled in the nucleus, acquire their final envelope from an intracellular compartment before reaching the cell surface. Knowing the identity of this compartment is an important step in elucidating the molecular mechanism of HSV-1 egress. Turcotte et al. (p. 8847–8860) examine this issue by directly probing this viral transient intermediate during the course of an infection. Remarkably, viral capsids and viral glycoproteins independently travel and meet at the *trans*-Golgi network, even when disrupted. These findings suggest that the glycoproteins provide the initial signal that marks this compartment for re-envelopment.

Virus-Mediated Sorting of Proteins into Axons

In their natural hosts, mammalian alphaherpesviruses are parasites of the peripheral nervous system. During infection of the nervous system, viral components travel long distances in axons via microtubule-based transport systems. Ch'ng and Enquist (p. 8835–8846) demonstrate that a single viral membrane protein, gE, of pseudorabies virus is required for efficient targeting of many viral glycoproteins and capsids to axons. Sorting of normal axonal proteins into axons is a complicated process, but alphaherpesviruses have evolved an efficient mechanism for axonal targeting. Studying viral infection of neurons offers the opportunity to understand fundamental mechanisms of axonal targeting and transport.

Plant Virus HC-Pro Facilitates Eriophyid Mite Transmission

Helper component-proteinase (HC-Pro) mediates aphid transmission of potyviruses. The tritimovirus wheat streak mosaic virus (WSMV) encodes an HC-Pro homolog but is vectored by eriophyid mites. Stenger et al. (p. 9054–9061) show that vector transmission of WSMV is abolished upon replacement of HC-Pro with the corresponding cistron of heterologous viruses. This work provides the first evidence that plant virus HC-Pro determines transmission by a vector other than aphids.

Addition of an HTLV-1 Regulatory Element Improves the Immunogenicity of DNA Vaccines

Plasmid DNA vaccines have proven highly immunogenic in mice but less immunogenic in nonhuman primates and humans. Barouch et al. (p. 8828–8834) demonstrate that addition of a regulatory element from human T-cell leukemia virus type 1 (HTLV-1) to the cytomegalovirus enhancer/promoter of HIV-1 DNA vaccines increases transgene expres-

sion and improves cellular immune responses in both mice and nonhuman primates. These data demonstrate that optimization of regulatory elements substantially enhances DNA vaccine immunogenicity, a problem that has limited the efficacy of this approach in humans. This strategy is currently being explored in clinical trials of an AIDS vaccine candidate.

Brief Opportunity To Prevent Vaginal Transmission of SIV

HIV-1 vaginal transmission accounts for over half of the newly acquired infections worldwide. Using a vaginal transmission model in rhesus macaques, Miller et al. (p. 9217–9227) show that for the first few days following exposure to SIV there are only small numbers of productively infected cells at the portal of entry. These small founder populations must expand and continually seed distal lymphatic tissue compartments to establish systemic infection. During the brief early period when viral replication is limited to the portal of entry, vaccines and other measures should have the best chance of preventing systemic infection.

Too Late, Too Little: SIV-Specific $CD8^+$ T Lymphocytes Lag behind Viral Replication

A successful HIV vaccine will likely need to elicit immune responses superior to those seen during natural infection. Reynolds et al. (p. 9228–9235) explore potential reasons for the failure of the immune system to protect against widespread dissemination of the immunodeficiency viruses. After intravaginal infection with SIV, robust $CD8^+$ T-lymphocyte responses are detected in the cervicovaginal tissues and uterus, but this occurs only after resolution of the peak of virus production. Surprisingly, only low-frequency responses were detected in the intestinal mucosa, leaving the critically important memory $CD4^+$ T-lymphocytes "unprotected." Therefore, virus-specific $CD8^+$ T lymphocytes may be "too late and too little" to clear infection and protect against severe $CD4^+$ T-lymphocyte loss.

Effective Therapeutic Vaccination Limited by Poor CD8 T-Cell Proliferation and High Viral Load

Therapeutic vaccines often fail to effectively boost T-cell responses or lead to viral control during chronic infections. Wherry et al. (p. 8960–8968) now show that properties of the T cells, rather than the vaccine, may be partly to blame. In a mouse model of chronic viral infection, low $CD8^+$ T-cell proliferative potential limited effective therapeutic vaccination. However, more effective responses were observed at lower viral loads. This study suggests that effective immunotherapy during chronic infections will have to overcome poor $CD8^+$ T-cell responsiveness and might be enhanced by combining therapeutic vaccination strategies with approaches that will lower virus levels.

IRF-3 Activates TRAIL Expression

Interferon production and apoptosis represent important aspects of the innate immune response by a cell to infections by many viruses. Kirshner et al. (p. 9320–9324) show that expression of the apoptotic ligand TRAIL and its receptor, DR5, are increased following paramyxovirus infection and identify TRAIL as a transcriptional target of IRF-3. This work underscores the role of IRF-3 in engaging more than one pathway in the cellular innate immune response and defines a novel target for IRF-3.

Human Endogenous Provirus ERV3 at 7q11 Dissected, Its Expression Studied

Human endogenous retroviral sequences (HERVs) largely are damaged by substitutions and frameshifts, rendering expression of functional proteins unlikely. However, Andersson et al. (p. 9270–9284) show that the ERV3 locus on chromosome 7, band q11, has an open reading frame in its envelope gene, a sign of possible selection for function. Using a novel bioimformatic tool, they found its structure to be typically gammaretroviral. RNA from its envelope gene has tissue-specific expression, being abundant in adrenal and sebaceous glands and in placenta. A group of ERV3-like elements in the human genome also was defined. This work will facilitate new research on possible physiological contributions of HERVs and the evolution of gammaretroviruses.