Capsule

Human MX2 is an interferon-induced post-entry inhibitor of HIV-1 infection

Animal cells harbor multiple innate effector mechanisms that inhibit virus replication. For the pathogenic retrovirus human immunodeficiency virus type 1 (HIV-1), these include widely expressed restriction factors, such as APOBEC3 proteins, TRIM5-α, BST2 and SAMHD1, as well as additional factors that are stimulated by type 1 interferon (IFN). Goujon and co-authors used both ectopic expression and gene-silencing experiments to define the human dynamin-like, interferon (IFN)-induced myxovirus resistance 2 (MX2, also known as MXB) protein as a potent inhibitor of HIV-1 infection and as a key effector of IFNα-mediated resistance to HIV-1 infection. MX2 suppresses infection by all HIV-1 strains tested, has equivalent or reduced effects on divergent simian immunodeficiency viruses, and does not inhibit other retroviruses such as murine leukemia virus. The Capsid region of the viral Gag protein dictates susceptibility to MX2, and the block to infection occurs at a late post-entry step, with both the nuclear accumulation and chromosomal integration of nascent viral complementary DNA suppressed. Finally, human MX1 (also known as MXA), a closely related protein that has long been recognized as a broadly acting inhibitor of RNA and DNA viruses, including the orthomyxovirus influenza A virus, does not affect HIV-1, whereas MX2 is ineffective against influenza virus. MX2 is therefore a cell-autonomous, anti-HIV-1 resistance factor whose purposeful mobilization may represent a new therapeutic approach for the treatment of HIV/AIDS.

Nature 2013; 502: 559

Eitan Israeli

Capsule

Temperature triggers immune evasion by *Neisseria meningitidis*

Neisseria meningitidis has several strategies to evade complement-mediated killing, and these contribute to its ability to cause septicemic disease and meningitis. However, the Meningococcus is primarily an obligate commensal of the human nasopharynx, and it is unclear why the bacterium has evolved exquisite mechanisms to avoid host immunity. Loh and colleagues demonstrate the mechanisms of meningococcal immune evasion and resistance against complement increase in response to an increase in ambient temperature. The authors identified three independent RNA thermosensors located in the 5′ untranslated regions of genes necessary for capsule biosynthesis, the expression of factor H binding protein, and sialylation of lipopolysaccharide, which are essential for meningococcal resistance against immune killing. Therefore, increased temperature (which occurs during inflammation) acts as a 'danger signal' for the Meningococcus, enhancing its defense against human immune killing. Infection with viral pathogens, such as influenza, leads to inflammation in the nasopharynx with an increased temperature and recruitment of immune effectors. Thermoregulation of immune defense could offer an adaptive advantage to the Meningococcus during co-infection with other pathogens and promote the emergence of virulence in an otherwise commensal bacterium.

Nature 2013; 502: 237

Eitan Israeli

Capsule

Mucin protein MUC2 as guardian of the gut

The intestine is able to tolerate continual exposure to large amounts of commensal bacteria and foreign food antigens without triggering an inappropriate inflammatory immune response. In the large intestine, this immunological tolerance is thought to occur via a physical separation between environment and host imposed by a continuous mucous layer built up from the secreted mucin protein, MUC2. However, in the small intestine, this mucous layer is porous, necessitating an additional layer of immune control. Shan et al. report that in the small intestine, MUC2 plays an active role in immunological tolerance by activating a transcription factor in resident dendritic cells, thereby selectively blocking their ability to launch an inflammatory response. This work identifies MUC2 as a central mediator of immune tolerance to maintain homeostasis in the gut and possibly on other mucosal surfaces in the body.

Science 2013; 342: 447

Eitan Israeli

Capsule

Immune clearance of highly pathogenic SIV infection

Established infections with the human and simian immunodeficiency viruses (HIV and SIV, respectively) are thought to be permanent with even the most effective immune responses and antiretroviral therapies only able to control, but not clear, these infections. Whether the residual virus that maintains these infections is vulnerable to clearance is a question of central importance for the future management of millions of HIV-infected individuals. Hansen and team recently reported that approximately 50% of rhesus macaques (RM; *Macaca mulatta*) vaccinated with SIV protein-expressing rhesus cytomegalovirus (RhCMV/SIV) vectors manifest durable, aviremic control of infection with the highly pathogenic strain SIVmac239. They show that regardless of the route of challenge, RhCMV/SIV vector-elicited immune responses control SIVmac239 after demonstrable lymphatic and hematogenous viral dissemination, and that replication-competent SIV persists in several sites for weeks to months. Over time, however, protected RM lost signs of SIV infection, showing a consistent lack of measurable plasma- or tissue-associated virus using ultrasensitive assays, and a loss of T cell reactivity to SIV determinants not in the vaccine. Extensive ultrasensitive quantitative polymerase chain reaction (PCR) and quantitative PCR with reverse transcription analyses of tissues from RhCMV/SIV vector-protected RM necropsied 69–172 weeks after challenge did not detect SIV RNA or DNA sequences above background levels, and replication-competent SIV was not detected in these RM by extensive co-culture analysis of tissues or by adoptive transfer of 60 million hematolymphoid cells to naive RM. These data provide compelling evidence for progressive clearance of a pathogenic lentiviral infection, and suggest that some lentiviral reservoirs may be susceptible to the continuous effector memory T cell-mediated immune surveillance elicited and maintained by cytomegalovirus vectors.

Nature 2013; 502: 100

Eitan Israeli

Capsule

Pathogenesis and transmission of avian influenza A (H7N9) virus in ferrets and mice

On 29 March 2013, the Chinese Center for Disease Control and Prevention confirmed the first reported case of human infection with an avian influenza A(H7N9) virus. The recent human infections with H7N9 virus, totaling over 130 cases with 39 fatalities to date, have been characterized by severe pulmonary disease and acute respiratory distress syndrome (ARDS). This is worrying because H7 viruses have typically been associated with ocular disease in humans, rather than severe respiratory disease. This recent outbreak underscores the need to better understand the pathogenesis and transmission of these viruses in mammals. Besler et al. assessed the ability of A/Anhui/1/2013 and A/Shanghai/1/2013 (H7N9) viruses, isolated from fatal human cases, to cause disease in mice and ferrets and to transmit to naive animals. Both H7N9 viruses replicated to higher titer in human airway epithelial cells and in the respiratory tract of ferrets compared to a seasonal H3N2 virus. Moreover, the H7N9 viruses showed greater infectivity and lethality in mice compared to genetically related H7N9 and H9N2 viruses. The H7N9 viruses were readily transmitted to naive ferrets through direct contact but, unlike the seasonal H3N2 virus, did not transmit readily by respiratory droplets. The lack of efficient respiratory droplet transmission was corroborated by low receptor-binding specificity for human-like α2,6-linked sialosides. These results indicate that H7N9 viruses have the capacity for efficient replication in mammals and human airway cells and highlight the need for continued public health surveillance of this emerging virus.

Nature 2013; 501: 556

Eitan Israeli

Capsule

Cerebral organoids model human brain development and microcephaly

The complexity of the human brain has made it difficult to study many brain disorders in model organisms, highlighting the need for an in vitro model of human brain development. Lancaster et al. have developed a human pluripotent stem cell-derived three-dimensional organoid culture system, termed cerebral organoids, that develops various discrete, although interdependent, brain regions. These include a cerebral cortex containing progenitor populations that organize and produce mature cortical neuron subtypes. Furthermore, cerebral organoids are shown to recapitulate features of human cortical development, namely characteristic progenitor zone organization with abundant outer radial glial stem cells. Finally, the authors used RNA interference and patient-specific induced pluripotent stem cells to model microcephaly, a disorder that has been difficult to recapitulate in mice. They demonstrate premature neuronal differentiation in patient organoids, a defect that could help to explain the disease phenotype. Together, these data show that three-dimensional organoids can recapitulate development and disease even in this most complex human tissue.

Nature 2013; 501: 373

Eitan Israeli

Capsule

Limited airborne transmission of H7N9 influenza A virus between ferrets

Wild waterfowl form the main reservoir of influenza A viruses, from which transmission occurs directly or indirectly to various secondary hosts, including humans. Direct avian-to-human transmission has been observed for viruses of subtypes A(H5N1), A(H7N2), A(H7N3), A(H7N7), A(H9N2) and A(H10N7) upon human exposure to poultry, but a lack of sustained human-to-human transmission has prevented these viruses from causing new pandemics. Recently, avian A(H7N9) viruses were transmitted to humans, causing severe respiratory disease and deaths in China. Because transmission via respiratory droplets and aerosols (hereafter referred to as airborne transmission) is the main route for efficient transmission between humans, it is important to gain an insight into airborne transmission of the A(H7N9) virus. Richard et al. show that although the A/Anhui/1/2013 A(H7N9) virus harbors determinants associated with human adaptation and transmissibility among mammals, its airborne transmissibility in ferrets is limited, and it is intermediate between that of typical human and avian influenza viruses. Multiple A(H7N9) virus genetic variants were transmitted. Upon ferret passage, variants with higher avian receptor binding, higher pH of fusion, and lower thermostability were selected, potentially resulting in reduced transmissibility. This A(H7N9) virus outbreak highlights the need for increased understanding of the determinants of efficient airborne transmission of avian influenza viruses among mammals.

Nature 2013; 501: 560

Eitan Israeli

Capsule

Cross-neutralization of four paramyxoviruses by a human monoclonal antibody

Broadly neutralizing antibodies reactive against most and even all variants of the same viral species have been described for influenza and HIV-1. However, whether a neutralizing antibody could have the breadth of range to target different viral species was unknown. Human respiratory syncytial virus (HRSV) and human metapneumovirus (HMPV) are common pathogens that cause severe disease in premature newborns, hospitalized children and immune-compromised patients, and play a role in asthma exacerbations. Although antisera generated against either HRSV or HMPV are not cross-neutralizing, Corti et al. speculated that, because of the repeated exposure to these viruses, cross-neutralizing antibodies may be selected in some individuals. Now they describe a human monoclonal antibody (MPE8) that potently cross-neutralizes HRSV and HMPV as well as two animal paramyxoviruses: bovine RSV (BRSV) and pneumonia virus of mice (PVM). In its germline configuration, MPE8 is HRSV-specific and its breadth is achieved by somatic mutations in the light chain variable region. MPE8 did not result in the selection of viral escape mutants that evaded antibody targeting and showed potent prophylactic efficacy in animal models of HRSV and HMPV infection, as well as prophylactic and therapeutic efficacy in the more relevant model of lethal PVM infection. The core epitope of MPE8 was mapped on two highly conserved anti-parallel β-strands on the pre-fusion viral F protein, which are rearranged in the post-fusion F protein conformation. Twenty-six of the 30 HRSV-specific neutralizing antibodies isolated were also found to be specific for the pre-fusion F protein. Taken together, these results indicate that MPE8 might be used for the prophylaxis and therapy of severe HRSV and HMPV infections and identify the pre-fusion F protein as a candidate HRSV vaccine.

Nature 2013; 501: 439

Eitan Israeli

Capsule

Odor receptors and neurons for DEET and new insect repellents

There are major impediments to finding improved DEET alternatives because the receptors causing olfactory repellency are unknown, and new chemicals require exorbitant costs to determine safety for human use. Kain et al. identified DEET-sensitive neurons in a pit-like structure in the *Drosophila melanogaster* antenna called the sacculus. They express a highly conserved receptor, Ir40a, and flies in which these neurons are silenced or *Ir40a* is knocked down lose avoidance to DEET. The authors used a computational structure activity screen of › 400,000 compounds that identified › 100 natural compounds as candidate repellents. They tested several and found that most activate *Ir40a+* neurons and are repellents for Drosophila. These compounds are also strong repellents for mosquitoes. The candidates contain chemicals that do not dissolve plastic, are affordable and smell mildly like grapes, with three considered safe in human foods. These findings pave the way to discover new generations of repellents that will help fight deadly insect-borne diseases worldwide.

Nature 2013; 502: 507

Eitan Israeli

Capsule

Experimental viral evolution reveals major histocompatibility complex polymorphisms as the primary host factors controlling pathogen adaptation and virulence

Using an experimental evolution approach, Kubinak et al. recently demonstrated that the mouse-specific pathogen Friend virus (FV) complex adapted to specific major histocompatibility complex (MHC) genotypes, which resulted in fitness tradeoffs when viruses were exposed to hosts possessing novel MHC polymorphisms. Here, the group reports the analysis of patterns of pathogen adaptation and virulence evolution from viruses adapting to one of three hosts that differ across the entire genome (A/WySn, DBA/2J and BALB/c). They found that serial passage of FV complex through these mouse genotypes resulted in significant increases in pathogen fitness (156-fold) and virulence (11-fold). Adaptive responses by post-passage viruses also resulted in host genotype-specific patterns of adaptation. To evaluate the relative importance of MHC versus non-MHC polymorphisms as factors influencing pathogen adaptation and virulence, the researchers compared the magnitude of fitness tradeoffs incurred by post-passage viruses when infecting hosts possessing either novel MHC polymorphisms alone or hosts possessing novel MHC and non-MHC polymorphisms. MHC polymorphisms alone accounted for 71% and 83% of the total observed reductions in viral fitness and virulence in unfamiliar host genotypes, respectively. Strikingly, these data suggest that genetic polymorphisms within the MHC, a gene region representing only ~0.1% of the genome, are major host factors influencing pathogen adaptation and virulence evolution.

Genes Immun 2013; 14: 365

Eitan Israeli