

## 8 References

- 1 Brass, A. L. *et al.* The IFITM Proteins Mediate Cellular Resistance to Influenza A H1N1 Virus, West Nile Virus, and Dengue Virus. *Cell* **139**, 1243-1254, doi:10.1016/j.cell.2009.12.017 (2009).
- 2 Huang, I. C. *et al.* Distinct Patterns of IFITM-Mediated Restriction of Filoviruses, SARS Coronavirus, and Influenza A Virus. *PLoS Pathog* **7** (2011).
- 3 Everitt, A. R. *et al.* IFITM3 restricts the morbidity and mortality associated with influenza. *Nature* **484**, 519-523, doi:10.1038/nature10921 (2012).
- 4 Feeley, E. M. *et al.* IFITM3 Inhibits Influenza A Virus Infection by Preventing Cytosolic Entry. *PLoS Pathog* **7**, e1002337, doi:10.1371/journal.ppat.1002337 (2011).
- 5 John, S. P. *et al.* The CD225 domain of IFITM3 is required for both IFITM protein association and inhibition of influenza A virus and dengue virus replication. *J Virol* **87**, 7837-7852 (2013).
- 6 Desai, T. M. *et al.* IFITM3 Restricts Influenza A Virus Entry by Blocking the Formation of Fusion Pores following Virus-Endosome Hemifusion. *PLoS Pathog* **10**, e1004048, doi:10.1371/journal.ppat.1004048 (2014).
- 7 Bieniasz, P. D. Intrinsic immunity: a front-line defense against viral attack. *Nat Immunol* **5**, 1109-1115 (2004).
- 8 Eisele, N. A. & Anderson, D. M. Host Defense and the Airway Epithelium: Frontline Responses That Protect against Bacterial Invasion and Pneumonia. *Journal of pathogens* **2011**, 249802, doi:10.4061/2011/249802 (2011).
- 9 Alberts, B. *et al.* *Molecular Biology of the Cell*. 4 edn, (Garland Science, 2002).
- 10 Kumar, H., Kawai, T. & Akira, S. Pathogen recognition by the innate immune system. *Int Rev Immunol* **30**, 16-34, doi:10.3109/08830185.2010.529976 (2011).
- 11 Akira, S. Innate immunity and adjuvants. *Philosophical Transactions of the Royal Society B-Biological Sciences* **366**, 2748-2755, doi:10.1098/rstb.2011.0106 (2011).
- 12 Muller, U. *et al.* Functional role of Type I and Type II interferons in antiviral defense. *Science* **264**, 1918-1921, doi:10.1126/science.8009221 (1994).
- 13 Isaacs, A. & Lindenmann, J. Virus interference. I. The interferon. *Proc R Soc Lond B Biol Sci* **147**, 258-267 (1957).
- 14 Juang, Y.-T. *et al.* Primary activation of interferon A and interferon B gene transcription by interferon regulatory factor 3. *Proceedings of the National Academy of Sciences* **95**, 9837-9842, doi:10.1073/pnas.95.17.9837 (1998).

- 15 Durbin, J. E. *et al.* Type IIFN modulates innate and specific antiviral immunity. *Journal of Immunology* **164**, 4220-4228 (2000).
- 16 Takaoka, A. & Yanai, H. Interferon signalling network in innate defence. *Cellular Microbiology* **8**, 907-922, doi:10.1111/j.1462-5822.2006.00716.x (2006).
- 17 Stark, G. R., Kerr, I. M., Williams, B. R., Silverman, R. H. & Schreiber, R. D. How cells respond to interferons. *Annu Rev Biochem* **67**, 227-264 (1998).
- 18 Silvennoinen, O., Ihle, J. N., Schlessinger, J. & Levy, D. E. Interferon-induced nuclear signalling by Jak protein tyrosine kinases. *Nature* **366**, 583-585 (1993).
- 19 Samuel, C. Interferons, Interferon Receptors, Signal Transducer and Transcriptional Activators, and Interferon Regulatory Factors. *The Journal of Biological Chemistry* **282**, 20045-20046 (2007).
- 20 Shepherd, J., Waugh, N. & Hewitson, P. Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review. *Health Technol Assess* **4**, 1-67 (2000).
- 21 Ge, D. *et al.* Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* **461**, 399-401 (2009).
- 22 Vyas, J. M., Van der Veen, A. G. & Ploegh, H. L. The known unknowns of antigen processing and presentation. *Nat Rev Immunol* **8**, 607-618, doi:10.1038/nri2368 (2008).
- 23 Kolaczkowska, E. & Kubes, P. Neutrophil recruitment and function in health and inflammation. *Nat Rev Immunol* **13**, 159-175 (2013).
- 24 Boes, M. Role of natural and immune IgM antibodies in immune responses. *Mol Immunol* **37**, 1141-1149 (2000).
- 25 Brinkmann, V. *et al.* Neutrophil extracellular traps kill bacteria. *Science* **303**, 1532-1535 (2004).
- 26 Tumpey, T. M. *et al.* Pathogenicity of influenza viruses with genes from the 1918 pandemic virus: functional roles of alveolar macrophages and neutrophils in limiting virus replication and mortality in mice. *J Virol* **79**, 14933-14944 (2005).
- 27 Seki, M. *et al.* Critical role of IL-1 receptor-associated kinase-M in regulating chemokine-dependent deleterious inflammation in murine influenza pneumonia. *J Immunol* **184**, 1410-1418 (2010).
- 28 Mosser, D. M. & Edwards, J. P. Exploring the full spectrum of macrophage activation. *Nat Rev Immunol* **8**, 958-969 (2008).

- 29 Eming, S. A., Krieg, T. & Davidson, J. M. Inflammation in wound repair: molecular and cellular mechanisms. *J Invest Dermatol* **127**, 514-525 (2007).
- 30 Kim, E. Y. *et al.* Persistent activation of an innate immune response translates respiratory viral infection into chronic lung disease. *Nat Med* **14**, 633-640 (2008).
- 31 Swann, S. A. *et al.* HIV-1 Nef blocks transport of MHC class I molecules to the cell surface via a PI 3-kinase-dependent pathway. *Virology* **282**, 267-277 (2001).
- 32 Stein-Streilein, J. & Guffee, J. In vivo treatment of mice and hamsters with antibodies to asialo GM1 increases morbidity and mortality to pulmonary influenza infection. *J Immunol* **136**, 1435-1441 (1986).
- 33 Fox, A. *et al.* Severe pandemic H1N1 2009 infection is associated with transient NK and T deficiency and aberrant CD8 responses. *Plos One* **7**, 20 (2012).
- 34 Abdul-Careem, M. F. *et al.* Critical role of natural killer cells in lung immunopathology during influenza infection in mice. *J Infect Dis* **206**, 167-177 (2012).
- 35 Duggal, N. K. & Emerman, M. Evolutionary conflicts between viruses and restriction factors shape immunity. *Nat Rev Immunol* **12**, 687-695 (2012).
- 36 Yan, N. & Chen, Z. J. Intrinsic antiviral immunity. *Nat Immunol* **13**, 214-222 (2012).
- 37 Kellam, P. & Weiss, R. A. Infectogenomics: Insights from the host genome into infectious diseases. *Cell* **124**, 695-697, doi:10.1016/j.cell.2006.02.003 (2006).
- 38 Albright, F. S., Orlando, P., Pavia, A. T., Jackson, G. G. & Albright, L. A. C. Evidence for a Heritable Predisposition to Death Due to Influenza. *Journal of Infectious Diseases* **197**, 18-24, doi:10.1086/524064 (2008).
- 39 Van Valen, L. A New Evolutionary Law. *Evolutionary Theory* **1**, 1-30 (1973).
- 40 Jiggins, F. M. & Kim, K. W. A screen for immunity genes evolving under positive selection in *Drosophila*. *Journal of Evolutionary Biology* **20**, 965-970, doi:10.1111/j.1420-9101.2007.01305.x (2007).
- 41 Stremlau, M. *et al.* The cytoplasmic body component TRIM5alpha restricts HIV-1 infection in Old World monkeys. *Nature* **427**, 848-853 (2004).
- 42 Sheehy, A. M., Gaddis, N. C., Choi, J. D. & Malim, M. H. Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein. *Nature* **418**, 646-650 (2002).
- 43 Wilson, S. J. *et al.* Inhibition of HIV-1 Particle Assembly by 22,32-Cyclic-Nucleotide 32-Phosphodiesterase. *Cell host & microbe* **12**, 585-597 (2012).

- 44 Neil, S. J., Zang, T. & Bieniasz, P. D. Tetherin inhibits retrovirus release and is antagonized by HIV-1 Vpu. *Nature* **451**, 425-430 (2008).
- 45 Goujon, C. et al. Human MX2 is an interferon-induced post-entry inhibitor of HIV-1 infection. *Nature* (2013).
- 46 García, M. A., Meurs, E. F. & Esteban, M. The dsRNA protein kinase PKR: Virus and cell control. *Biochimie* **89**, 799-811 (2007).
- 47 Silverman, R. H. Viral encounters with 2',5'-oligoadenylate synthetase and RNase L during the interferon antiviral response. *J Virol* **81**, 12720-12729 (2007).
- 48 Lindenmann, J. Resistance of mice to mouse-adapted influenza A virus. *Virology* **16**, 203-204 (1962).
- 49 Haller, O., Staeheli, P. & Kochs, G. Protective role of interferon-induced Mx GTPases against influenza viruses. *Rev Sci Tech* **28**, 219-231 (2009).
- 50 Haller, O. & Kochs, G. Interferon-induced mx proteins: dynamin-like GTPases with antiviral activity. *Traffic* **3**, 710-717 (2002).
- 51 Krug, R. M., Shaw, M., Broni, B., Shapiro, G. & Haller, O. Inhibition of influenza viral mRNA synthesis in cells expressing the interferon-induced Mx gene product. *Journal of Virology* **56**, 201-206 (1985).
- 52 Staeheli, P. & Haller, O. Interferon-induced human protein with homology to protein Mx of influenza virus-resistant mice. *Molecular and Cell Biology* **5**, 2150-2153 (1985).
- 53 Mitchell, P. S. et al. Evolution-guided identification of antiviral specificity determinants in the broadly acting interferon-induced innate immunity factor MxA. *Cell Host Microbe* **12**, 598-604 (2012).
- 54 Kane, M. et al. MX2 is an interferon-induced inhibitor of HIV-1 infection. *Nature* **502**, 563-566 (2013).
- 55 Liu, Z. et al. The Interferon-Inducible MxB Protein Inhibits HIV-1 Infection. *Cell host & microbe* **14**, 398-410, doi:<http://dx.doi.org/10.1016/j.chom.2013.08.015> (2013).
- 56 Gao, S. et al. Structure of Myxovirus Resistance Protein A Reveals Intra- and Intermolecular Domain Interactions Required for the Antiviral Function. *Immunity* **35**, 514-525, doi:<http://dx.doi.org/10.1016/j.jimmuni.2011.07.012> (2011).
- 57 Nakayama, E. E. & Shioda, T. Anti-retroviral activity of TRIM5 alpha. *Rev Med Virol* **20**, 77-92 (2010).
- 58 Diaz-Griffero, F. et al. Requirements for capsid-binding and an effector function in TRIMCyp-mediated restriction of HIV-1. *Virology* **351**, 404-419 (2006).

- 59 Perez-Caballero, D., Hatzioannou, T., Yang, A., Cowan, S. & Bieniasz, P. D. Human tripartite motif 5 alpha domains responsible for retrovirus restriction activity and specificity. *Journal of Virology* **79**, 8969-8978, doi:10.1128/jvi.79.14.8969-8978.2005 (2005).
- 60 Anderson, J. L. *et al.* Proteasome inhibition reveals that a functional preintegration complex intermediate can be generated during restriction by diverse TRIM5 proteins. *J Virol* **80**, 9754-9760 (2006).
- 61 Chatterji, U. *et al.* Trim5alpha accelerates degradation of cytosolic capsid associated with productive HIV-1 entry. *J Biol Chem* **281**, 37025-37033 (2006).
- 62 Nepveu-Traversy, M. E., Berube, J. & Berthoux, L. TRIM5alpha and TRIMCyp form apparent hexamers and their multimeric state is not affected by exposure to restriction-sensitive viruses or by treatment with pharmacological inhibitors. *Retrovirology* **6**, 1742-4690 (2009).
- 63 Mische, C. C. *et al.* Retroviral restriction factor TRIM5alpha is a trimer. *J Virol* **79**, 14446-14450 (2005).
- 64 Pertel, T. *et al.* TRIM5 is an innate immune sensor for the retrovirus capsid lattice. *Nature* **472**, 361-365 (2011).
- 65 Javanbakht, H. *et al.* Effects of human TRIM5 alpha polymorphisms on antiretroviral function and susceptibility to human immunodeficiency virus infection. *Virology* **354**, 15-27, doi:10.1016/j.virol.2006.06.031 (2006).
- 66 Sawyer, S. L., Wu, L. I., Akey, J. M., Emerman, M. & Malik, H. S. High-frequency persistence of an impaired allele of the retroviral defense gene TRIM5alpha in humans. *Curr Biol* **16**, 95-100 (2006).
- 67 Sayah, D. M., Sokolskaja, E., Berthoux, L. & Luban, J. Cyclophilin A retrotransposition into TRIM5 explains owl monkey resistance to HIV-1. *Nature* **430**, 569-573, doi:[http://www.nature.com/nature/journal/v430/n6999/supplinfo/nature02777\\_S1.html](http://www.nature.com/nature/journal/v430/n6999/supplinfo/nature02777_S1.html) (2004).
- 68 Lim, S.-Y. *et al.* TRIM5 alpha Modulates Immunodeficiency Virus Control in Rhesus Monkeys. *Plos Pathogens* **6** (2010).
- 69 Sawyer, S. L., Wu, L. I., Emerman, M. & Malik, H. S. Positive selection of primate TRIM5 alpha identifies a critical species-specific retroviral restriction domain. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 2832-2837, doi:10.1073/pnas.0409853102 (2005).
- 70 Ishikawa, J. *et al.* Molecular cloning and chromosomal mapping of a bone marrow stromal cell surface gene, BST2, that may be involved in pre-B-cell growth. *Genomics* **26**, 527-534 (1995).

- 71 Matsuda, A. *et al.* Large-scale identification and characterization of human genes that activate NF-kappaB and MAPK signaling pathways. *Oncogene* **22**, 3307-3318 (2003).
- 72 Hotter, D., Sauter, D. & Kirchhoff, F. Emerging role of the host restriction factor tetherin in viral immune sensing. *J Mol Biol* **425**, 4956-4964 (2013).
- 73 Andrew, A. J., Miyagi, E., Kao, S. & Strelbel, K. The formation of cysteine-linked dimers of BST-2/tetherin is important for inhibition of HIV-1 virus release but not for sensitivity to Vpu. *Retrovirology* **6**, 1742-4690 (2009).
- 74 Evans, D. T., Serra-Moreno, R., Singh, R. K. & Guatelli, J. C. BST-2/tetherin: a new component of the innate immune response to enveloped viruses. *Trends Microbiol* **18**, 388-396 (2010).
- 75 Hinz, A. *et al.* Structural basis of HIV-1 tethering to membranes by the BST-2/tetherin ectodomain. *Cell Host Microbe* **7**, 314-323 (2010).
- 76 McNatt, M. W. *et al.* Species-specific activity of HIV-1 Vpu and positive selection of tetherin transmembrane domain variants. *PLoS Pathog* **5**, e1000300, doi:10.1371/journal.ppat.1000300 (2009).
- 77 Gupta, R. K. *et al.* Mutation of a Single Residue Renders Human Tetherin Resistant to HIV-1 Vpu-Mediated Depletion. *Plos Pathogens* **5** (2009).
- 78 Winkler, M. *et al.* Influenza A Virus Does Not Encode a Tetherin Antagonist with Vpu-Like Activity and Induces IFN-Dependent Tetherin Expression in Infected Cells. *PLoS ONE* **7**, e43337, doi:10.1371/journal.pone.0043337 (2012).
- 79 Yondola, M. A. *et al.* Budding capability of the influenza virus neuraminidase can be modulated by tetherin. *J Virol* **85**, 2480-2491, doi:10.1128/jvi.02188-10 (2011).
- 80 Mangeat, B. *et al.* Influenza virus partially counteracts restriction imposed by tetherin/BST-2. *J Biol Chem* **287**, 22015-22029, doi:10.1074/jbc.M111.319996 (2012).
- 81 Watanabe, R., Leser, G. P. & Lamb, R. A. Influenza virus is not restricted by tetherin whereas influenza VLP production is restricted by tetherin. *Virology* **417**, 50-56, doi:10.1016/j.virol.2011.05.006 (2011).
- 82 Galao, R. P., Le Tortorec, A., Pickering, S., Kueck, T. & Neil, S. J. Innate sensing of HIV-1 assembly by Tetherin induces NFkappaB-dependent proinflammatory responses. *Cell Host Microbe* **12**, 633-644 (2012).
- 83 Fensterl, V. & Sen, G. C. The ISG56/IFIT1 gene family. *J Interferon Cytokine Res* **31**, 71-78 (2011).

- 84       Guo, J., Peters, K. L. & Sen, G. C. Induction of the human protein P56 by interferon, double-stranded RNA, or virus infection. *Virology* **267**, 209-219 (2000).
- 85       Daffis, S. *et al.* 2'-O methylation of the viral mRNA cap evades host restriction by IFIT family members. *Nature* **468**, 452-456 (2010).
- 86       Pichlmair, A. *et al.* IFIT1 is an antiviral protein that recognizes 5'-triphosphate RNA. *Nat Immunol* **12**, 624-630 (2011).
- 87       Harris, R. S., Petersen-Mahrt, S. K. & Neuberger, M. S. RNA editing enzyme APOBEC1 and some of its homologs can act as DNA mutators. *Mol Cell* **10**, 1247-1253 (2002).
- 88       Vartanian, J. P., Meyerhans, A., Asjo, B. & Wain-Hobson, S. Selection, recombination, and G---A hypermutation of human immunodeficiency virus type 1 genomes. *J Virol* **65**, 1779-1788 (1991).
- 89       Sawyer, S. L., Emerman, M. & Malik, H. S. Ancient adaptive evolution of the primate antiviral DNA-editing enzyme APOBEC3G. *Plos Biology* **2**, 1278-1285 (2004).
- 90       Khan, M. A. *et al.* Encapsidation of APOBEC3G into HIV-1 virions involves lipid raft association and does not correlate with APOBEC3G oligomerization. *Retrovirology* **6**, 1742-4690 (2009).
- 91       Alce, T. M. & Popik, W. APOBEC3G is incorporated into virus-like particles by a direct interaction with HIV-1 Gag nucleocapsid protein. *J Biol Chem* **279**, 34083-34086 (2004).
- 92       Sadler, A. J. & Williams, B. R. Interferon-inducible antiviral effectors. *Nat Rev Immunol* **8**, 559-568 (2008).
- 93       Giannakopoulos, N. V. *et al.* Proteomic identification of proteins conjugated to ISG15 in mouse and human cells. *Biochem Biophys Res Commun* **336**, 496-506 (2005).
- 94       Shi, H. X. *et al.* Positive regulation of interferon regulatory factor 3 activation by Herc5 via ISG15 modification. *Mol Cell Biol* **30**, 2424-2436 (2010).
- 95       Malakhova, O. A. & Zhang, D. E. ISG15 inhibits Nedd4 ubiquitin E3 activity and enhances the innate antiviral response. *J Biol Chem* **283**, 8783-8787 (2008).
- 96       Harris, R. S. & Liddament, M. T. Retroviral restriction by APOBEC proteins. *Nat Rev Immunol* **4**, 868-877 (2004).
- 97       Chakrabarti, A., Jha, B. K. & Silverman, R. H. New insights into the role of RNase L in innate immunity. *J Interferon Cytokine Res* **31**, 49-57, doi:10.1089/jir.2010.0120 (2011).
- 98       Bergmann, M. *et al.* Influenza virus NS1 protein counteracts PKR-mediated inhibition of replication. *J Virol* **74**, 6203-6206 (2000).

- 99 Lewin, A. R., Reid, L. E., McMahon, M., Stark, G. R. & Kerr, I. M. Molecular analysis of a human interferon-inducible gene family. *Eur J Biochem* **199**, 417-423 (1991).
- 100 Evans, S. S., Lee, D. B., Han, T., Tomasi, T. B. & Evans, R. L. Monoclonal antibody to the interferon-inducible protein Leu-13 triggers aggregation and inhibits proliferation of leukemic B cells. *Blood* **76**, 2583-2593 (1990).
- 101 Tanaka, S. S. & Matsui, Y. Developmentally regulated expression of mil-1 and mil-2, mouse interferon-induced transmembrane protein like genes, during formation and differentiation of primordial germ cells. *Gene expression patterns : GEP* **2**, 297-303 (2002).
- 102 Lange, U. C. *et al.* Normal germ line establishment in mice carrying a deletion of the Ifitm/Fragilis gene family cluster. *Mol Cell Biol* **28**, 4688-4696 (2008).
- 103 Siegrist, F., Ebeling, M. & Certa, U. Phylogenetic analysis of interferon inducible transmembrane gene family and functional aspects of IFITM3. *Cytokine* **48**, 87-89, doi:10.1016/j.cyto.2009.07.315 (2009).
- 104 Hickford, D. E., Frankenberg, S. R., Shaw, G. & Renfree, M. B. Evolution of vertebrate interferon inducible transmembrane proteins. *BMC Genomics* **155**, 1-7 (2012).
- 105 Moffatt, P. *et al.* Bril: a novel bone-specific modulator of mineralization. *J Bone Miner Res* **23**, 1497-1508 (2008).
- 106 Sällman Almén, M., Bringeland, N., Fredriksson, R. & Schiöth, H. B. The *Dispanins*: A Novel Gene Family of Ancient Origin That Contains 14 Human Members. *Plos One* **7**, e31961, doi:10.1371/journal.pone.0031961 (2012).
- 107 Bailey, C. C., Huang, I. C., Kam, C. & Farzan, M. Ifitm3 Limits the Severity of Acute Influenza in Mice. *PLoS Pathog* **8**, e1002909, doi:10.1371/journal.ppat.1002909 (2012).
- 108 Anafu, A. A., Bowen, C. H., Chin, C. R., Brass, A. L. & Holm, G. H. Interferon Inducible Transmembrane Protein 3 (IFITM3) Restricts Reovirus Cell Entry. *J Biol Chem* **24**, 17261-17271 (2013).
- 109 Everitt, A. R. *et al.* Defining the range of pathogens susceptible to Ifitm3 restriction using a knockout mouse model. *Plos One* **8** (2013).
- 110 Warren, C. J. *et al.* The Antiviral Restriction Factors IFITM1, 2 and 3 Do Not Inhibit Infection of Human Papillomavirus, Cytomegalovirus and Adenovirus. *Plos One* **9** (2014).
- 111 Jia, R. *et al.* The N-terminal region of IFITM3 modulates its antiviral activity by regulating IFITM3 cellular localization. *J Viro* **86**, 13697-13707 (2012).
- 112 Chutiwitoonchai, N. *et al.* Characteristics of IFITM, the newly identified IFN-inducible anti-HIV-1 family proteins. *Microbes Infect* **15**, 280-290 (2013).

- 113 Lu, J., Pan, Q., Rong, L., Liu, S.-L. & Liang, C. The IFITM Proteins Inhibit HIV-1 Infection. *Journal of Virology* **85**, 2126-2137, doi:10.1128/jvi.01531-10 (2011).
- 114 Zhao, X. et al. Interferon induction of IFITM proteins promotes infection by human coronavirus OC43. *Proc Natl Acad Sci U S A* **21**, 21 (2014).
- 115 Li, K. et al. IFITM Proteins Restrict Viral Membrane Hemifusion. *PLoS Pathog* **9**, e1003124, doi:10.1371/journal.ppat.1003124 (2013).
- 116 Mellman, I., Fuchs, R. & Helenius, A. Acidification of the endocytic and exocytic pathways. *Annu Rev Biochem* **55**, 663-700 (1986).
- 117 Mudhasani, R. et al. Ifitm-2 and Ifitm-3 but Not Ifitm-1 Restrict Rift Valley Fever Virus. *J Virol* (2013).
- 118 Yount, J. S. et al. Palmitoylome profiling reveals S-palmitoylation-dependent antiviral activity of IFITM3. *Nature Chemical Biology* **6**, 610-614, doi:10.1038/nchembio.405 (2010).
- 119 Yount, J. S., Karssemeijer, R. A. & Hang, H. C. S-palmitoylation and ubiquitination differentially regulate IFITM3-mediated resistance to influenza virus. *The Journal of Biological Chemistry* **287**, 19631-19641 (2012).
- 120 Bailey, C. C., Kondur, H. R., Huang, I.-C. & Farzan, M. Interferon-Induced Transmembrane Protein 3 is a Type II Transmembrane Protein. *Journal of Biological Chemistry*, doi:10.1074/jbc.M113.514356 (2013).
- 121 Smith, S. E., Weston, S., Kellam, P. & Marsh, M. IFITM proteins - cellular inhibitors of viral entry. *Current Opinion in Virology* **4**, 71-77, doi:<http://dx.doi.org/10.1016/j.coviro.2013.11.004> (2014).
- 122 Amini-Bavil-Olyaei, S. et al. The Antiviral Effector IFITM3 Disrupts Intracellular Cholesterol Homeostasis to Block Viral Entry. *Cell Host Microbe* **13**, 452-464 (2013).
- 123 Hinners, I. & Tooze, S. A. Changing directions: clathrin-mediated transport between the Golgi and endosomes. *Journal of cell science* **116**, 763-771 (2003).
- 124 Jia, R. et al. Identification of an endocytic signal essential for the antiviral action of IFITM3. *Cell Microbiol* **20**, 12262 (2014).
- 125 Bonifacino, J. S. & Traub, L. M. Signals for sorting of transmembrane proteins to endosomes and lysosomes. *Annu Rev Biochem* **72**, 395-447, doi:10.1146/annurev.biochem.72.121801.161800 (2003).
- 126 Shiratori, T. et al. Tyrosine Phosphorylation Controls Internalization of CTLA-4 by Regulating Its Interaction with Clathrin-Associated Adaptor Complex AP-2. *Immunity* **6**, 583-589, doi:[http://dx.doi.org/10.1016/S1074-7613\(00\)80346-5](http://dx.doi.org/10.1016/S1074-7613(00)80346-5) (1997).

- 127 Chesarino, N. M., McMichael, T. M., Hach, J. C. & Yount, J. S. Phosphorylation of the Antiviral Protein Interferon-inducible Transmembrane Protein 3 (IFITM3) Dually Regulates Its Endocytosis and Ubiquitination. *J Biol Chem* **289**, 11986-11992 (2014).
- 128 Sieczkarski, S. B. & Whittaker, G. R. Viral entry. *Curr Top Microbiol Immunol* **285**, 1-23 (2005).
- 129 Igonet, S. & Rey, F. A. SnapShot: Viral and eukaryotic protein fusogens. *Cell* **151**, 1634-1634 (2012).
- 130 Lin, T. Y. et al. Amphotericin B increases influenza A virus infection by preventing IFITM3-mediated restriction. *Cell Rep* **5**, 895-908 (2013).
- 131 Lau, S. L. et al. Interferons induce the expression of IFITM1 and IFITM3 and suppress the proliferation of rat neonatal cardiomyocytes. *J Cell Biochem* **113**, 841-847 (2012).
- 132 Zhang, Z., Liu, J., Li, M., Yang, H. & Zhang, C. Evolutionary Dynamics of the Interferon-Induced Transmembrane Gene Family in Vertebrates. *Plos One* **7**, e49265, doi:10.1371/journal.pone.0049265 (2012).
- 133 Kerns, J. A., Emerman, M. & Malik, H. S. Positive selection and increased antiviral activity associated with the PARP-containing isoform of human zinc-finger antiviral protein. *Plos Genetics* **4** (2008).
- 134 Hultquist, J. F. et al. Human and rhesus APOBEC3D, APOBEC3F, APOBEC3G, and APOBEC3H demonstrate a conserved capacity to restrict Vif-deficient HIV-1. *J Virol* **85**, 11220-11234 (2011).
- 135 Bogerd, H. P., Doehle, B. P., Wiegand, H. L. & Cullen, B. R. A single amino acid difference in the host APOBEC3G protein controls the primate species specificity of HIV type 1 virion infectivity factor. *Proc Natl Acad Sci U S A* **101**, 3770-3774 (2004).
- 136 Santa-Marta, M., Brito, P., Godinho-Santos, A. & Goncalves, J. Host factors and HIV-1 replication: clinical evidence and potential therapeutic approaches. *Frontiers in Immunology* **4**, doi:10.3389/fimmu.2013.00343 (2013).
- 137 Larue, R. S., Lengyel, J., Jonsson, S. R., Andresdottir, V. & Harris, R. S. Lentiviral Vif degrades the APOBEC3Z3/APOBEC3H protein of its mammalian host and is capable of cross-species activity. *J Virol* **84**, 8193-8201 (2010).
- 138 Guyader, M., Emerman, M., Montagnier, L. & Peden, K. VPX mutants of HIV-2 are infectious in established cell lines but display a severe defect in peripheral blood lymphocytes. *Embo J* **8**, 1169-1175 (1989).
- 139 Laguette, N. et al. SAMHD1 is the dendritic- and myeloid-cell-specific HIV-1 restriction factor counteracted by Vpx. *Nature* **474**, 654-657 (2011).

- 140 McNatt, M. W., Zang, T. & Bieniasz, P. D. Vpu binds directly to tetherin and displaces it from nascent virions. *PLoS Pathog* **9**, 25 (2013).
- 141 Andrew, A. J., Miyagi, E. & Strelbel, K. Differential effects of human immunodeficiency virus type 1 Vpu on the stability of BST-2/tetherin. *J Virol* **85**, 2611-2619 (2011).
- 142 Hatada, E. & Fukuda, R. Binding of influenza A virus NS1 protein to dsRNA in vitro. *J Gen Virol* **73**, 3325-3329 (1992).
- 143 Gack, M. U. et al. Influenza A virus NS1 targets the ubiquitin ligase TRIM25 to evade recognition by the host viral RNA sensor RIG-I. *Cell Host Microbe* **5**, 439-449 (2009).
- 144 Twu, K. Y., Noah, D. L., Rao, P., Kuo, R. L. & Krug, R. M. The CPSF30 binding site on the NS1A protein of influenza A virus is a potential antiviral target. *J Virol* **80**, 3957-3965 (2006).
- 145 Marazzi, I. et al. Suppression of the antiviral response by an influenza histone mimic. *Nature* **483**, 428-433, doi:10.1038/nature10892 (2012).
- 146 García-Sastre, A. et al. Influenza A Virus Lacking the NS1 Gene Replicates in Interferon-Deficient Systems. *Virology* **252**, 324-330, doi:<http://dx.doi.org/10.1006/viro.1998.9508> (1998).
- 147 Talon, J. et al. Influenza A and B viruses expressing altered NS1 proteins: A vaccine approach. *Proc Natl Acad Sci U S A* **97**, 4309-4314, doi:10.1073/pnas.070525997 (2000).
- 148 Brzozka, K., Finke, S. & Conzelmann, K. K. Identification of the rabies virus alpha/beta interferon antagonist: phosphoprotein P interferes with phosphorylation of interferon regulatory factor 3. *J Virol* **79**, 7673-7681 (2005).
- 149 Vidy, A., El Bougrini, J., Chelbi-Alix, M. K. & Blondel, D. The nucleocytoplasmic rabies virus P protein counteracts interferon signaling by inhibiting both nuclear accumulation and DNA binding of STAT1. *J Virol* **81**, 4255-4263 (2007).
- 150 Guerra, S., Cáceres, A., Knobeloch, K.-P., Horak, I. & Esteban, M. Vaccinia Virus E3 Protein Prevents the Antiviral Action of ISG15. *PLoS Pathog* **4**, e1000096, doi:10.1371/journal.ppat.1000096 (2008).
- 151 White, S. D. & Jacobs, B. L. The amino terminus of the vaccinia virus E3 protein is necessary to inhibit the interferon response. *J Virol* **86**, 5895-5904, doi:10.1128/jvi.06889-11 (2012).
- 152 Wiley, D. C. & Skehel, J. J. The structure and function of the hemagglutinin membrane glycoprotein of influenza virus. *Annu Rev Biochem* **56**, 365-394, doi:10.1146/annurev.bi.56.070187.002053 (1987).
- 153 Webster, R. G., Monto, A.S., Braciale, T. J., Lamb, R.A. *Textbook of Influenza*. 2nd edn, (John Wiley and Sons, 2013).

- 154 Sriwilaijaroen, N. & Suzuki, Y. Molecular basis of the structure and function of H1 hemagglutinin of influenza virus. *Proceedings of the Japan Academy. Series B, Physical and biological sciences* **88**, 226-249 (2012).
- 155 Medina, R. A. & Garcia-Sastre, A. Influenza A viruses: new research developments. *Nat Rev Microbiol* **9**, 590-603 (2011).
- 156 Russell, R. J. et al. Structure of influenza hemagglutinin in complex with an inhibitor of membrane fusion. *Proc Natl Acad Sci U S A* **105**, 17736-17741, doi:10.1073/pnas.0807142105 (2008).
- 157 Tate, M. D. et al. Playing hide and seek: how glycosylation of the influenza virus hemagglutinin can modulate the immune response to infection. *Viruses* **6**, 1294-1316, doi:10.3390/v6031294 (2014).
- 158 Skehel, J. J. & Wiley, D. C. Receptor binding and membrane fusion in virus entry: the influenza hemagglutinin. *Annu Rev Biochem* **69**, 531-569, doi:10.1146/annurev.biochem.69.1.531 (2000).
- 159 Martin, J. et al. Studies of the binding properties of influenza hemagglutinin receptor-site mutants. *Virology* **241**, 101-111 (1998).
- 160 Lakadamyali, M., Rust, M. J. & Zhuang, X. Endocytosis of influenza viruses. *Microbes Infect* **6**, 929-936, doi:10.1016/j.micinf.2004.05.002 (2004).
- 161 Matlin, K. S., Reggio, H., Helenius, A. & Simons, K. Infectious entry pathway of influenza virus in a canine kidney cell line. *J Cell Biol* **91**, 601-613 (1981).
- 162 Samji, T. Influenza A: understanding the viral life cycle. *Yale J Biol Med* **82**, 153-159 (2009).
- 163 Mas, V. & Melero, J. A. Entry of enveloped viruses into host cells: membrane fusion. *Subcellular biochemistry* **68**, 467-487, doi:10.1007/978-94-007-6552-8\_16 (2013).
- 164 Chernomordik, L. V. & Kozlov, M. M. Mechanics of membrane fusion. *Nature structural & molecular biology* **15**, 675-683, doi:10.1038/nsmb.1455 (2008).
- 165 Gorlich, D. & Kutay, U. Transport between the cell nucleus and the cytoplasm. *Annu Rev Cell Dev Biol* **15**, 607-660 (1999).
- 166 Jardetzky, T. S. & Lamb, R. A. Virology: a class act. *Nature* **427**, 307-308, doi:10.1038/427307a (2004).
- 167 Krug, R., Alonso-Caplen, F., Julkunen, I. & Katze, M. in *The Influenza Viruses The Viruses* (ed RobertM Krug) Ch. 2, 89-152 (Springer US, 1989).

- 168 Punpanich, W. & Chotpitayasunondh, T. A review on the clinical spectrum and natural history of human influenza. *Int J Infect Dis* **16**, 10 (2012).
- 169 Carrat, F. et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *Am J Epidemiol* **167**, 775-785 (2008).
- 170 Mertz, D. et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. *Bmj* **23** (2013).
- 171 Nobusawa, E. & Sato, K. Comparison of the mutation rates of human influenza A and B viruses. *J Virol* **80**, 3675-3678 (2006).
- 172 Hanada, K., Suzuki, Y. & Gojobori, T. A large variation in the rates of synonymous substitution for RNA viruses and its relationship to a diversity of viral infection and transmission modes. *Mol Biol Evol* **21**, 1074-1080 (2004).
- 173 Koel, B. F. et al. Substitutions near the receptor binding site determine major antigenic change during influenza virus evolution. *Science* **342**, 976-979, doi:10.1126/science.1244730 (2013).
- 174 Neumann, G., Noda, T. & Kawaoka, Y. Emergence and pandemic potential of swine-origin H1N1 influenza virus. *Nature* **459**, 931-939 (2009).
- 175 Lindstrom, S. E., Cox, N. J. & Klimov, A. Genetic analysis of human H2N2 and early H3N2 influenza viruses, 1957-1972: evidence for genetic divergence and multiple reassortment events. *Virology* **328**, 101-119, doi:10.1016/j.virol.2004.06.009 (2004).
- 176 Worobey, M., Han, G. Z. & Rambaut, A. Genesis and pathogenesis of the 1918 pandemic H1N1 influenza A virus. *Proc Natl Acad Sci U S A* **111**, 8107-8112, doi:10.1073/pnas.1324197111 (2014).
- 177 Baillie, G. J. et al. Evolutionary dynamics of local pandemic H1N1/2009 influenza virus lineages revealed by whole-genome analysis. *J Virol* **86**, 11-18 (2012).
- 178 Manz, B. et al. Pandemic influenza A viruses escape from restriction by human MxA through adaptive mutations in the nucleoprotein. *PLoS Pathog* **9**, 28 (2013).
- 179 Flahault, A., Deguen, S. & Valleron, A. J. A mathematical model for the European spread of influenza. *Eur J Epidemiol* **10**, 471-474 (1994).
- 180 Hale, B. G. et al. Inefficient control of host gene expression by the 2009 pandemic H1N1 influenza A virus NS1 protein. *J Virol* **84**, 6909-6922 (2010).
- 181 Fineberg, H. V. Pandemic preparedness and response--lessons from the H1N1 influenza of 2009. *N Engl J Med* **370**, 1335-1342 (2014).

- 182 Van Kerkhove, M. D. *et al.* Risk Factors for Severe Outcomes following 2009 Influenza A (H1N1) Infection: A Global Pooled Analysis. *PLoS Med* **8**, e1001053, doi:10.1371/journal.pmed.1001053 (2011).
- 183 Dawood, F. S. *et al.* Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. *The Lancet Infectious Diseases* **12**, 687-695 (2012).
- 184 Viboud, C., Miller, M., Olson, D., Osterholm, M. & Simonsen, L. Preliminary Estimates of Mortality and Years of Life Lost Associated with the 2009 A/H1N1 Pandemic in the US and Comparison with Past Influenza Seasons. *PLoS Curr* **20** (2010).
- 185 Cromer, D. *et al.* The burden of influenza in England by age and clinical risk group: a statistical analysis to inform vaccine policy. *The Journal of infection* **68**, 363-371, doi:10.1016/j.jinf.2013.11.013 (2014).
- 186 van Riel, D. *et al.* Human and avian influenza viruses target different cells in the lower respiratory tract of humans and other mammals. *Am J Pathol* **171**, 1215-1223 (2007).
- 187 Chan, M. C. *et al.* Proinflammatory cytokine responses induced by influenza A (H5N1) viruses in primary human alveolar and bronchial epithelial cells. *Respir Res* **6**, 135 (2005).
- 188 Cheung, C. Y. *et al.* Induction of proinflammatory cytokines in human macrophages by influenza A (H5N1) viruses: a mechanism for the unusual severity of human disease? *Lancet* **360**, 1831-1837 (2002).
- 189 Majumdar, S. R., Eurich, D. T., Gamble, J. M., Senthilselvan, A. & Marrie, T. J. Oxygen saturations less than 92% are associated with major adverse events in outpatients with pneumonia: a population-based cohort study. *Clin Infect Dis* **52**, 325-331 (2011).
- 190 Montalto, N. J. An office-based approach to influenza: clinical diagnosis and laboratory testing. *Am Fam Physician* **67**, 111-118 (2003).
- 191 Dolan, G. P. *et al.* The comparative clinical course of pregnant and non-pregnant women hospitalised with influenza A(H1N1)pdm09 infection. *Plos One* **7**, 3 (2012).
- 192 Samuel, N., Attias, O., Tatour, S. & Brik, R. Novel influenza A (H1N1) and acute encephalitis in a child. *Isr Med Assoc J* **12**, 446-447 (2010).
- 193 Fraser, C. *et al.* Pandemic potential of a strain of influenza A (H1N1): early findings. *Science* **324**, 1557-1561 (2009).
- 194 Sridhar, S. *et al.* Cellular immune correlates of protection against symptomatic pandemic influenza. *Nat Med* **19**, 1305-1312, doi:10.1038/nm.3350 (2013).

- 195 WHO.  
[http://www.who.int/influenza/human\\_animal\\_interface/avian\\_influenza/h5n1\\_research/faqs/en/](http://www.who.int/influenza/human_animal_interface/avian_influenza/h5n1_research/faqs/en/)
- 196 Wang, H. *et al.* Probable limited person-to-person transmission of highly pathogenic avian influenza A (H5N1) virus in China. *Lancet* **371**, 1427-1434 (2008).
- 197 Kandun, I. N. *et al.* Three Indonesian clusters of H5N1 virus infection in 2005. *N Engl J Med* **355**, 2186-2194 (2006).
- 198 Herfst, S. *et al.* Airborne transmission of influenza A/H5N1 virus between ferrets. *Science* **336**, 1534-1541 (2012).
- 199 Imai, M. *et al.* Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. *Nature* **486**, 420-428 (2012).
- 200 Webster, R. G., Bean, W. J., Gorman, O. T., Chambers, T. M. & Kawaoka, Y. Evolution and ecology of influenza A viruses. *Microbiol Rev* **56**, 152-179 (1992).
- 201 Swayne, D. E. Understanding the complex pathobiology of high pathogenicity avian influenza viruses in birds. *Avian Dis* **51**, 242-249 (2007).
- 202 Reperant, L. A., Kuiken, T. & Osterhaus, A. D. Influenza viruses: from birds to humans. *Hum Vaccin Immunother* **8**, 7-16 (2012).
- 203 Garten, W. & Klenk, H. Cleavage activation of the influenza virus hemagglutinin and its role in pathogenesis. *Avian Influenza* **27**, 156-167 (2008).
- 204 Munster, V. J. *et al.* Mallards and highly pathogenic avian influenza ancestral viruses, northern Europe. *Emerg Infect Dis* **11**, 1545-1551 (2005).
- 205 West, B. & Zhou, B.-X. Did chickens go North? New evidence for domestication. *Journal of Archaeological Science* **15**, 515-533, doi:[http://dx.doi.org/10.1016/0305-4403\(88\)90080-5](http://dx.doi.org/10.1016/0305-4403(88)90080-5) (1988).
- 206 Siegel, P. B., Dodgson, J. B. & Andersson, L. Progress from chicken genetics to the chicken genome. *Poultry science* **85**, 2050-2060 (2006).
- 207 Bernasconi, D., Schultz, U. & Staeheli, P. The interferon-induced Mx protein of chickens lacks antiviral activity. *J Interferon Cytokine Res* **15**, 47-53 (1995).
- 208 Ko, J. H. *et al.* Polymorphisms and the differential antiviral activity of the chicken Mx gene. *Genome Res* **12**, 595-601 (2002).
- 209 Sironi, L. *et al.* Susceptibility of different chicken lines to H7N1 highly pathogenic avian influenza virus and the role of Mx gene polymorphism coding amino acid position 631. *Virology* **380**, 152-156 (2008).

- 210 Benfield, C. T., Lyall, J. W. & Tiley, L. S. The cytoplasmic location of chicken mx is not the determining factor for its lack of antiviral activity. *Plos One* **5**, 0012151 (2010).
- 211 Li, B. *et al.* Partial antiviral activities of the Asn631 chicken Mx against newcastle disease virus and vesicular stomatitis virus. *Mol Biol Rep* **39**, 8415-8424, doi:10.1007/s11033-012-1694-9 (2012).
- 212 Schusser, B. *et al.* Mx is dispensable for interferon-mediated resistance of chicken cells against influenza A virus. *J Virol* **85**, 8307-8315 (2011).
- 213 Yoneyama, M. *et al.* The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. *Nat Immunol* **5**, 730-737 (2004).
- 214 Kato, H. *et al.* Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. *Nature* **441**, 101-105 (2006).
- 215 Barber, M. R., Aldridge, J. R., Jr., Webster, R. G. & Magor, K. E. Association of RIG-I with innate immunity of ducks to influenza. *Proc Natl Acad Sci U S A* **107**, 5913-5918 (2010).
- 216 Liniger, M., Summerfield, A., Zimmer, G., McCullough, K. C. & Ruggli, N. Chicken cells sense influenza A virus infection through MDA5 and CARDIF signaling involving LGP2. *J Virol* **86**, 705-717 (2012).
- 217 International-HapMap-Consortium. A haplotype map of the human genome. *Nature* **437**, 1299-1320 (2005).
- 218 Manry, J. & Quintana-Murci, L. A genome-wide perspective of human diversity and its implications in infectious disease. *Cold Spring Harb Perspect Med* **3** (2013).
- 219 Nicolle, C. Les infections inapparentes. *Sciencia* **33**, 181-271 (1933).
- 220 Chapman, S. J. & Hill, A. V. Human genetic susceptibility to infectious disease. *Nat Rev Genet* **13**, 175-188 (2012).
- 221 Fellay, J. *et al.* Common genetic variation and the control of HIV-1 in humans. *PLoS Genet* **5**, 24 (2009).
- 222 van Manen, D., van 't Wout, A. B. & Schuitemaker, H. Genome-wide association studies on HIV susceptibility, pathogenesis and pharmacogenomics. *Retrovirology* **9**, 1742-4690 (2012).
- 223 Dean, M. *et al.* Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. *Science* **273**, 1856-1862 (1996).
- 224 Fellay, J. *et al.* Common genetic variation and the control of HIV-1 in humans. *PLoS Genet* **5**, e1000791, doi:10.1371/journal.pgen.1000791 (2009).

- 225 Samson, M. *et al.* Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature* **382**, 722-725 (1996).
- 226 Mallal, S. *et al.* Association between presence of HLA-B\*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* **359**, 727-732 (2002).
- 227 Bottomly, D. *et al.* Expression quantitative trait Loci for extreme host response to influenza a in pre-collaborative cross mice. *G3 (Bethesda, Md.)* **2**, 213-221, doi:10.1534/g3.111.001800 (2012).
- 228 Srivastava, B. *et al.* Host genetic background strongly influences the response to influenza a virus infections. *PLoS One* **4**, e4857, doi:10.1371/journal.pone.0004857 (2009).
- 229 Horby, P., Nguyen, N. Y., Dunstan, S. J. & Baillie, J. K. An updated systematic review of the role of host genetics in susceptibility to influenza. *Influenza Other Respir Viruses* **7 Suppl 2**, 37-41, doi:10.1111/irv.12079 (2013).
- 230 Lin, T.-Y. & Brass, A. L. Host genetic determinants of influenza pathogenicity. *Current Opinion in Virology*, doi:<http://dx.doi.org/10.1016/j.coviro.2013.07.005> (2013).
- 231 Zhang, L., Katz, J. M., Gwinn, M., Dowling, N. F. & Khoury, M. J. Systems-based candidate genes for human response to influenza infection. *Infect Genet Evol* **9**, 1148-1157, doi:10.1016/j.meegid.2009.07.006 (2009).
- 232 Zuniga, J. *et al.* Genetic variants associated with severe pneumonia in A/H1N1 influenza infection. *The European respiratory journal* **39**, 604-610, doi:10.1183/09031936.00020611 (2012).
- 233 Hidaka, F. *et al.* A missense mutation of the Toll-like receptor 3 gene in a patient with influenza-associated encephalopathy. *Clinical immunology (Orlando, Fla.)* **119**, 188-194, doi:10.1016/j.clim.2006.01.005 (2006).
- 234 Esposito, S. *et al.* Toll-like receptor 3 gene polymorphisms and severity of pandemic A/H1N1/2009 influenza in otherwise healthy children. *Virol J* **9**, 270, doi:10.1186/1743-422x-9-270 (2012).
- 235 Zufferey, R., Nagy, D., Mandel, R. J., Naldini, L. & Trono, D. Multiply attenuated lentiviral vector achieves efficient gene delivery in vivo. *Nat Biotechnol* **15**, 871-875 (1997).
- 236 Bolte, S. & Cordelieres, F. P. A guided tour into subcellular colocalization analysis in light microscopy. *J Microsc* **224**, 213-232 (2006).
- 237 Nexo, B. A. *et al.* Restriction genes for retroviruses influence the risk of multiple sclerosis. *Plos One* **8** (2013).
- 238 Haralambieva, I. H. *et al.* Genetic polymorphisms in host antiviral genes: associations with humoral and cellular immunity to measles vaccine. *Vaccine* **29**, 8988-8997 (2011).

- 239 Seo, G. S. *et al.* Identification of the polymorphisms in IFITM3 gene and their association in a Korean population with ulcerative colitis. *Experimental and Molecular Medicine* **42**, 99-104, doi:10.3858/emm.2010.42.2.011 (2010).
- 240 Karlsson, S. & Mork, J. Deviation from Hardy–Weinberg equilibrium, and temporal instability in allele frequencies at microsatellite loci in a local population of Atlantic cod. *ICES Journal of Marine Science: Journal du Conseil* **62**, 1588-1596, doi:10.1016/j.icesjms.2005.05.009 (2005).
- 241 Thanaraj, T. A. & Clark, F. Human GC-AG alternative intron isoforms with weak donor sites show enhanced consensus at acceptor exon positions. *Nucleic Acids Research* **29**, 2581-2593, doi:10.1093/nar/29.12.2581 (2001).
- 242 Ernst, J. *et al.* Mapping and analysis of chromatin state dynamics in nine human cell types. *Nature* **473**, 43-49 (2011).
- 243 Hoffman, M. M. *et al.* Unsupervised pattern discovery in human chromatin structure through genomic segmentation. *Nat Methods* **9**, 473-476 (2012).
- 244 Solovyev, V. V., Shahmuradov, I. A. & Salamov, A. A. Identification of promoter regions and regulatory sites. *Methods in molecular biology (Clifton, N.J.)* **674**, 57-83, doi:10.1007/978-1-60761-854-6\_5 (2010).
- 245 Honda, K. & Taniguchi, T. IRFs: master regulators of signalling by Toll-like receptors and cytosolic pattern-recognition receptors. *Nat Rev Immunol* **6**, 644-658, doi:10.1038/nri1900 (2006).
- 246 Qureshi, S. A., Salditt-Georgieff, M. & Darnell, J. E., Jr. Tyrosine-phosphorylated Stat1 and Stat2 plus a 48-kDa protein all contact DNA in forming interferon-stimulated-gene factor 3. *Proc Natl Acad Sci U S A* **92**, 3829-3833 (1995).
- 247 Zhang, Y. H. *et al.* Interferon-induced transmembrane protein-3 genetic variant rs12252-C is associated with severe influenza in Chinese individuals. *Nat Commun* **4**, 1-5 (2013).
- 248 Wang, Z. *et al.* Early hypercytokinemia is associated with interferon-induced transmembrane protein-3 dysfunction and predictive of fatal H7N9 infection. *Proc Natl Acad Sci U S A* **111**, 769-774 (2014).
- 249 Mills, T. C. *et al.* IFITM3 and susceptibility to respiratory viral infections in the community. *J Infect Dis* **209**, 1028-1031 (2014).
- 250 Li, Y., Willer, C., Sanna, S. & Abecasis, G. Genotype imputation. *Annu Rev Genomics Hum Genet* **10**, 387-406 (2009).
- 251 Bowles, N. E. *et al.* Kawasaki disease patients homozygous for the rs12252-C variant of interferon-induced transmembrane protein-3 are significantly more likely to develop coronary artery lesions. *Molecular Genetics & Genomic Medicine*, n/a-n/a, doi:10.1002/mgg3.79 (2014).

- 252 Okano, M. *et al.* Human herpesvirus 6 infection and Kawasaki disease. *J Clin Microbiol* **27**, 2379-2380 (1989).
- 253 Okano, M., Thiele, G. M., Sakiyama, Y., Matsumoto, S. & Purtilo, D. T. Adenovirus infection in patients with Kawasaki disease. *J Med Virol* **32**, 53-57 (1990).
- 254 Weidner, J. M. *et al.* Interferon-Induced Cell Membrane Proteins, IFITM3 and Tetherin, Inhibit Vesicular Stomatitis Virus Infection via Distinct Mechanisms. *Journal of Virology* **84**, 12646-12657, doi:10.1128/jvi.01328-10 (2010).
- 255 Price, A. M. *et al.* Analysis of Epstein-Barr virus-regulated host gene expression changes through primary B-cell outgrowth reveals delayed kinetics of latent membrane protein 1-mediated NF-kappaB activation. *J Virol* **86**, 11096-11106 (2012).
- 256 Scott, R., Siegrist, F., Foser, S. & Certa, U. Interferon-alpha induces reversible DNA demethylation of the interferon-induced transmembrane protein-3 core promoter in human melanoma cells. *J Interferon Cytokine Res* **31**, 601-608 (2011).
- 257 Brubaker, S. W., Gauthier, A. E., Mills, E. W., Ingolia, N. T. & Kagan, J. C. A bicistronic MAVS transcript highlights a class of truncated variants in antiviral immunity. *Cell* **156**, 800-811, doi:10.1016/j.cell.2014.01.021 (2014).
- 258 Taubenberger, J. K. & Kash, J. C. Influenza virus evolution, host adaptation, and pandemic formation. *Cell Host Microbe* **7**, 440-451 (2010).
- 259 Williams, R. B. A compartmentalised model for the estimation of the cost of coccidiosis to the world's chicken production industry. *International Journal for Parasitology* **29**, 1209-1229, doi:[http://dx.doi.org/10.1016/S0020-7519\(99\)00086-7](http://dx.doi.org/10.1016/S0020-7519(99)00086-7) (1999).
- 260 Terregino, C. *et al.* Pathogenicity of a QX strain of infectious bronchitis virus in specific pathogen free and commercial broiler chickens, and evaluation of protection induced by a vaccination programme based on the Ma5 and 4/91 serotypes. *Avian Pathol* **37**, 487-493 (2008).
- 261 John, S. P. *et al.* The CD225 Domain of IFITM3 is Required for both IFITM Protein Association and Inhibition of Influenza A Virus and Dengue Virus Replication. *J Virol* **8**, 8-9 (2013).
- 262 Weston, S. *et al.* A Membrane Topology Model for Human Interferon Inducible Transmembrane Protein 1. *PLoS ONE* **9**, e104341, doi:10.1371/journal.pone.0104341 (2014).
- 263 Gough, P. M. & Jorgenson, R. D. Rabies antibodies in sera of wild birds. *J Wildl Dis* **12**, 392-395 (1976).
- 264 Hach, J. C., McMichael, T., Chesarino, N. M. & Yount, J. S. Palmitoylation on conserved and non-conserved cysteines of murine IFITM1 regulates its stability and anti-influenza A virus activity. *J Virol* **26**, 26 (2013).

- 265 De Meneghi, D. Wildlife, environment and (re)-emerging zoonoses, with special reference to sylvatic tick-borne zoonoses in North-Western Italy. *Ann Ist Super Sanita* **42**, 405-409 (2006).
- 266 Johnson, N. et al. Human rabies due to lyssavirus infection of bat origin. *Vet Microbiol* **142**, 151-159 (2010).
- 267 Peiris, J. S., de Jong, M. D. & Guan, Y. Avian influenza virus (H5N1): a threat to human health. *Clin Microbiol Rev* **20**, 243-267 (2007).
- 268 Galloway, S. E., Reed, M. L., Russell, C. J. & Steinhauer, D. A. Influenza HA Subtypes Demonstrate Divergent Phenotypes for Cleavage Activation and pH of Fusion: Implications for Host Range and Adaptation. *PLoS Pathog* **9**, e1003151, doi:10.1371/journal.ppat.1003151 (2013).
- 269 Klymiuk, I. et al. In Vivo Functional Requirement of the Mouse *Ifitm1*Gene for Germ Cell Development, Interferon Mediated Immune Response and Somitogenesis. *Plos One* **7**, e44609, doi:10.1371/journal.pone.0044609 (2012).
- 270 Hedges, S. B., Parker, P. H., Sibley, C. G. & Kumar, S. Continental breakup and the ordinal diversification of birds and mammals. *Nature* **381**, 226-229 (1996).
- 271 Goodbourn, S., Didcock, L. & Randall, R. E. Interferons: cell signalling, immune modulation, antiviral response and virus countermeasures. *J Gen Virol* **81**, 2341-2364 (2000).
- 272 Randall, R. E. & Goodbourn, S. Interferons and viruses: an interplay between induction, signalling, antiviral responses and virus countermeasures. *Journal of General Virology* **89**, 1-47, doi:10.1099/vir.0.83391-0 (2008).
- 273 Seth, R. B., Sun, L., Ea, C. K. & Chen, Z. J. Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF-kappaB and IRF 3. *Cell* **122**, 669-682 (2005).
- 274 Kawai, T. & Akira, S. Signaling to NF-kappaB by Toll-like receptors. *Trends in molecular medicine* **13**, 460-469, doi:10.1016/j.molmed.2007.09.002 (2007).
- 275 Versteeg, G. A. et al. The E3-ligase TRIM family of proteins regulates signaling pathways triggered by innate immune pattern-recognition receptors. *Immunity* **38**, 384-398, doi:10.1016/j.jimmuni.2012.11.013 (2013).
- 276 Wang, X. et al. Influenza A virus NS1 protein prevents activation of NF-kappaB and induction of alpha/beta interferon. *J Virol* **74**, 11566-11573 (2000).
- 277 Mibayashi, M. et al. Inhibition of retinoic acid-inducible gene I-mediated induction of beta interferon by the NS1 protein of influenza A virus. *J Virol* **81**, 514-524, doi:10.1128/jvi.01265-06 (2007).

- 278 de Bouteiller, O. et al. Recognition of double-stranded RNA by human toll-like receptor 3 and downstream receptor signaling requires multimerization and an acidic pH. *J Biol Chem* **280**, 38133-38145, doi:10.1074/jbc.M507163200 (2005).
- 279 Galao, R. P., Pickering, S., Curnock, R. & Neil, S. J. Retroviral retention activates a Syk-dependent HemITAM in human tetherin. *Cell Host Microbe* **16**, 291-303, doi:10.1016/j.chom.2014.08.005 (2014).
- 280 Zhu, X. et al. IFITM3-containing exosome as a novel mediator for anti-viral response in dengue virus infection. *Cellular Microbiology* **17**, 105-118, doi:10.1111/cmi.12339 (2015).
- 281 Rajesh, D. et al. Human lymphoblastoid B-cell lines reprogrammed to EBV-free induced pluripotent stem cells. *Blood* **118**, 1797-1800 (2011).
- 282 Firth, A. L. et al. Generation of multiciliated cells in functional airway epithelia from human induced pluripotent stem cells. *Proceedings of the National Academy of Sciences*, doi:10.1073/pnas.1403470111 (2014).
- 283 Degner, J. F. et al. DNase I sensitivity QTLs are a major determinant of human expression variation. *Nature* **482**, 390-394 (2012).
- 284 Buenrostro, J. D., Giresi, P. G., Zaba, L. C., Chang, H. Y. & Greenleaf, W. J. Transposition of native chromatin for fast and sensitive epigenomic profiling of open chromatin, DNA-binding proteins and nucleosome position. *Nat Methods* **10**, 1213-1218 (2013).
- 285 Urnov, F. D., Rebar, E. J., Holmes, M. C., Zhang, H. S. & Gregory, P. D. Genome editing with engineered zinc finger nucleases. *Nat Rev Genet* **11**, 636-646 (2010).
- 286 Mali, P. et al. RNA-guided human genome engineering via Cas9. *Science* **339**, 823-826 (2013).
- 287 Eid, J. et al. Real-time DNA sequencing from single polymerase molecules. *Science* **323**, 133-138 (2009).