Elsevier has created a [Monkeypox Information Center](#) in response to the declared public health emergency of international concern, with free information in English on the monkeypox virus. The Monkeypox Information Center is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its monkeypox related research that is available on the Monkeypox Information Center - including this research content - immediately available in publicly funded repositories, with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the Monkeypox Information Center remains active.
Role of cytokines in poxvirus host tropism and adaptation
Masmudur M Rahman and Grant McFadden

Poxviruses are a diverse family of double-stranded DNA viruses that cause mild-to-severe disease in selective hosts, including humans. Although most poxviruses are restricted to their hosts, some members can leap host species and cause zoonotic diseases and, therefore, are genuine threats to human and animal health. The recent global spread of monkeypox in humans suggests that zoonotic poxviruses can adapt to a new host, spread rapidly in the new host, and evolve to better evade host innate barriers. Unlike many other viruses, poxviruses express an extensive repertoire of self-defense proteins that play a vital role in the evasion of host innate and adaptive immune responses in their newest host species. The function of these viral immune modulators and host-specific cytokine responses can result in different host tropism and poxvirus disease progression. Here, we review the role of different cytokines that control poxvirus host tropism and adaptation.

Address
Center for Immunotherapy, Vaccines and Virotherapy, Biodesign Institute, Arizona State University, USA
Corresponding author: Masmudur M Rahman (Masmudur.rahman@asu.edu)

Introduction
Poxviruses are large double-stranded DNA (dsDNA) viruses infecting insects and various vertebrate species. They belong to the Poxviridae family of viruses and are further classified into two subfamilies: the Entomopoxvirinae, infecting insects, and the Chordopoxvirinae, infecting vertebrates. Poxviruses that infect a wide range of vertebrate species are grouped into 18 genera based originally on their serological reactions, but more recently by their genomic features [1]. Among these poxviruses, members of the genera orthopoxvirus include many of the commonly recognized human pathogens such as variola virus (VARV), the causative agent of smallpox, cowpox virus (CPXV), and monkeypox virus (MPXV). Outside the orthopoxvirus genus, examples of poxviruses with human tropism include molluscum contagiosum virus and tanapox virus (TPV). Most poxviruses have evolved within a small number of host species with which they share co-evolutionary history, however, in lab culture, they can frequently infect cells from different host species. This broader cellular infectivity, compared with more limited host specificity, is mainly due to the lack of requirement for selective receptor proteins on target cells. Unlike most other mammalian viruses, poxviruses rely on relatively ubiquitous cellular surface molecules and exploit multiple host and virus-encoded proteins required for cell binding, fusion, and entry processes [2–4]. At the cellular level, since poxviruses can bind and enter most mammalian cells in vitro, tropism is largely determined by the viruses’ ability to modulate diverse intracellular antiviral pathways activated in response to virus sensing and infection. However, at the host organism level, the innate antiviral pathways activated by different virus-induced cytokines play a major role in determining the poxvirus tropism [5,6]. Here, we specifically discuss the recent progress in understanding how these crucial host cytokines regulate poxvirus tropism and adaptation.

The linear dsDNA genome of poxviruses ranges from 130 to 375 thousand base pairs and encodes between 130 and 300 open-reading frames. The central region of the genome is highly conserved among poxviruses and includes many dozens of essential genes required for transcription, replication, and virion assembly. The two ends of the linear viral genome are much more variable and encode host-interactive genes that control host range, help evade host immune responses, and other functions to control cellular responses. In addition, the function of these viral genes (referred to as host range genes) is closely linked to the successful replication of poxviruses in cultured cells originating from different tissues and hosts. However, the role of many poxvirus-specific host range genes uniquely required for host tropism and evasion of host immune responses is not well characterized from different poxviruses [7].
Antiviral strategies

Figure 1

Myxoma virus (MYXV) species leap from rabbits to hares. MYXV-Lau causes myxomatosis only in European rabbits (Oryctolagus cuniculus). However, during a recombination event, MYXV-Lau acquired a genomic cassette with a C7-like host range gene called M159 from an unknown poxvirus. This new MYXV isolate called MYXV-Tol can now cause myxomatosis-like disease in Iberian hares (Lepus granatensis) and European rabbits.

![Diagram showing the recombination process between MYXV-Lau and MYXV-Tol](Current Opinion in Virology)

Every vertebrate species can be infected with a selected member of poxviruses, some of which cause disease and some cause only subclinical infections. Genome sequencing of these poxviruses has identified a few viral genes unique to that poxvirus, and functional studies of such genes suggest that they have acquired host-specific functions [8]. For example, recently identified C7L-like host range gene M159 in MYXV-Tol (myxoma virus isolate Toledo), a member of Leporipoxvirus and known to cause disease in European rabbits, is critical for the recent species leap that now causes lethal disease in hares (Figure 1). In culture, the recombinant knockout construct of MYXV-Tol lacking M159 can no longer productively infect neither a hare cell line nor primary hare PBMCs (peripheral blood mononuclear cells) [9••]. On the other hand, MYXV-Lau (myxoma virus isolate Lausanne), which causes myxomatosis in European rabbits and lacks Tol-M159, cannot infect this hare cell line nor primary hare PBMCs. However, the construction of a recombinant MYXV-Lau expressing just the Tol-M159 gene now allowed MYXV-Lau to replicate in both immortalized and primary hare cells. Although the host cell target(s) of M159 are yet to be identified, these results suggest that even the genetic acquisition of a single viral host range protein function can dramatically alter the tropism of recipient poxvirus. Similarly, C7L-like host range proteins from other poxviruses contribute to their host and cellular tropism [10]. Functional and structural studies of these C7-like proteins demonstrated that some of them bind and antagonize host sterile alpha-motif domain-containing 9 protein to overcome type-I IFN-mediated host restriction [11–13•]. Thus, poxvirus-encoded proteins known as host range factors can dictate which cells, tissues, or hosts they can productively infect.

Apart from the virus-encoded proteins, host-specific factors and immune functions critically impact poxvirus tropism. The very well-studied poxvirus for host specificity is ectromelia virus (ECTV), a mouse-specific orthopoxvirus with a very narrow rodent-specific host range in nature. ECTV causes high mortality in susceptible mice strains, including BALB/c, DBA/2, A/J, and C3H, whereas C57BL/6, AKR, and I29 strains are much more resistant to the disease known also as mousepox [14,15]. In ECTV-resistant mice, multiple genetic loci have been identified and are referred to as restriction factors. For example, Ly49H (also called resistance to mousepox-1, Rmp-1) maps to the natural killer gene complex (NKC) and activates NK cells to control early virus replication in C57BL/6 mice, but is lacking in BALB/c mice [16]. Cytokines such as type-I IFN, IL-12, and IL-18 play essential roles in mediating this inherent genetic resistance to mousepox. These studies revealed that host-specific cytokine responses largely contribute to the tropism of poxviruses [17].

Unlike ECTV, some other orthopoxviruses are naturally capable of leaping from their reservoir host species to cause zoonotic diseases, including MPXV, CPXV, vaccinia virus (VACV)-like and Akhmeta virus. These viruses naturally circulate in wild and domestic animals, where they may or may not induce disease, have a broader host range, and often cause disease outbreaks in humans and other animals. For example, MPXV infections have been reported in various rodents, such as mice, rats, rabbits, hamsters, woodchucks, jerboas, porcupines, prairie dogs, hedgehogs, and several nonhuman primate species [18,19]. Although humans are considered accidental hosts, MPXV has now become the major zoonotic poxvirus for humans since the eradication of smallpox [20••]. Similarly, CPXV reservoirs are exclusively rodents in nature, but many wild animals can become accidental hosts, including cats, dogs, elephants, diverse zoo animals, and nonhuman primates from where humans can acquire an infection. Thus, poxviruses that can naturally leap into multiple host species are believed to have the further potential to acquire additional host-adapted mutations or acquired novel host regulatory proteins that can antagonize cytokine responses in diverse hosts. Apart from orthopoxviruses, members of capripoxvirus and parapoxvirus genera that normally infect farm animals can also infect humans after direct contact transmission, suggesting that these viruses encode host range proteins that can modulate human cytokine responses [21].
How cytokine-mediated innate immune responses regulate poxvirus host-specific infections and tropism

Cytokines and interferons (IFNs) are extracellular signaling molecules that play a key role in mediating an early immune response against invading pathogens, including viruses, and are essential components of host defense. In most cases, cytokine(s) activate protective responses that can provide complete clearance of viral infection. These cytokines, which can be either anti-inflammatory or pro-inflammatory, eventually clear the virus-infected cells by activating diverse mechanisms, including inflammation. These critical cytokines include IFNs, tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-12, IL-18, as well as multiple chemokines. Furthermore, these cytokines alone or in combination with each other, can further activate a network of downstream signaling pathways and stimulated genes such as interferon-stimulated genes (ISGs) and TNF-stimulated genes (TSGs).

Apart from host cytokines, poxviruses also encode diverse immune modulatory factors that can counteract the anti-viral responses activated by different cytokines, including ISGs and TSGs, to determine the host-specific tropism and disease caused by different poxviruses. For example, VACV has been shown to be relatively resistant to IFN responses in cells from different species and also can confer resistance to IFN to other viruses such as vesicular stomatitis virus [22,23]. On the other hand, MYXV-Lau, a leporipoxvirus, exhibits resistance to IFN only in rabbit cells, but the virus is relatively sensitive to the IFN-induced antiviral state in human or mouse cells [24]. This species-specific anti-IFN function is mainly because MYXV-Lau host range factors such as dsRNA-binding vaccinia E3-like protein M029 have specialized in inhibiting restriction factors present in rabbits but not in other species that are yet to be identified [25]. For most of the cytokines that function to protect against viruses, poxviruses have co-evolved encoded proteins that dampen their functions at a different level. They encode self-defense proteins that can directly target the cytokine and prevent it from receptor binding or other interactions, proteins that function as a decoy receptor that also directly binds cytokines and thus competes with the natural receptor, and proteins that can inhibit or modulate the downstream intracellular signaling networks activated by different cytokines [7]. In most cases, whether these virus-encoded proteins targeting different cytokines and their network subsequently determine the tropism of poxviruses is yet to be studied in greater detail [24]. Several reviews have focused on this topic of how viruses counteract different cytokines, and it is beyond the scope of this mini-review [23,26–31].

i) Interferons:
IFNs are the key cytokines that are rapidly produced and released from the cells in response to virus infection or by sensing virus-induced ligands such as pathogen-associated molecular patterns or damage-associated molecular patterns. Subsequently, the released IFNs bind to IFN receptors on the surface of target cells to trigger signaling pathways that activate the expression of hundreds of inducible genes known as ISGs [32,33]. There are three types of IFNs, namely type-I, type-II, and type-III IFNs, which have many subtypes. Some ISGs can be up-regulated by all IFNs, while others are upregulated by selective IFNs. For example, Interferon Regulatory Factor 1 (IRF1) is upregulated preferentially by IFN-alpha and not by IFN-gamma [34]. This type of selective IFN-induced response is vital for cell, tissue, or host-specific innate immune responses and generation of an antiviral state within responsive cells, thereby controlling selective virus infection and spread [35,36]. Thus, one can predict that the orchestration of the expression of host-specific ISGs can alter the cellular or host tropism of different viruses, including poxviruses. Poxvirus-related functions of some of the key ISGs, such as ISG15, protein kinase R, and 2’,5’-oligoadenylate synthetases, are well characterized [37–39]. However, many more remain to be studied in greater detail. As mentioned before, in the case of poxviruses, most of our knowledge about the role of IFNs in tropism has come from studies on ECTV using different strains of mice and genetic knockouts of C57BL/6 mice [14]. In ECTV-resistant C57BL/6 mice, apart from different genetic loci, potent NK, cytotoxic T lymphocytes (CTLs), and IFNγ responses are generated against ECTV infection at higher levels than in ECTV-susceptible BALB/c mice [15]. Further studies in C57BL/6 mice with genetic deficiencies in innate immune pathways such as TLR9–MyD88–IRF7 and STING–IRF7/NF-kB confirmed that inefficient production of type-I IFNs will increase mortality in C57BL/6 mice [40]. Crosstalk between IFN-I and NF-kB pathways also confers resistance to lethal poxvirus infection [41]. A recent study demonstrated that IFN-I response is required in a cell-type-specific manner: C57BL/6 mice lacking IFNR in NK cells and monocytes become sensitive to disease caused by ECTV [42••]. In addition, at the cellular level, different DNA sensing pathways such as cyclic GMP-AMP synthase (cGAS) and stimulator of interferon genes (STING) can trigger the production of type-I IFNs in selected cell types and thus regulate poxvirus cellular tropism [23,43–45]. Using ECTV, it was shown that bone marrow-derived cells play a major role in cGAS-dependent IFN production and protection against ECTV [45]. However, ECTV-encoded protein Schlafen (vSlfn) has been identified as the primary inhibitor of the cGAS–STING pathway, without which the virus is severely attenuated [44•].
Antiviral strategies

Type-I IFNs also play a major role in controlling the infection of MYXV in cells derived from mice, humans, and likely other vertebrate species. For example, in mouse primary embryonic fibroblasts, virus-mediated induction of type-I IFN through ERK and IRF3 signaling pathway completely inhibits MYXV replication. Mice that are genetically lacking STAT1 and thus defective in IFN signaling became susceptible to lethal MYXV infection after intracranial injection [46]. Thus, the ERK–IFN–STAT1 pathway contributes to the species-specific protection against MYXV infection in host species outside of lagomorphs. However, MYXV has evolved rabbit-specific strategies that can inhibit this highly conserved pathway to cause lethal disease in rabbits. This rabbit-specific specificity is likely related to the evolutionary time, estimated to be at least 10 million years, that MYXV has co-evolved with South American rabbits. It is anticipated that IFN signaling contributes to the selective tropism of most, if not all, chordopoxviruses. Apart from the natural protection against certain poxviruses, the host can also co-evolve with the virus to acquire genetically controlled innate immunity against the selective pressure from poxviruses. This is evident from the genomic sequencing of feral rabbits from Australia and Europe, and it was found that the evolution of resistance in European rabbits to MYXV is associated with enhanced innate antiviral immunity that was acquired in just the 70 years following the first release of MYXV into wild rabbit populations in the early 1950s [47]. MYXV, on the other hand, also evolved to overcome these newly acquired innate host defenses [48,49]. Thus, the ongoing dynamics of the virus-host battle can shape and reshape the host tropism of poxviruses.

iii) Other cytokines:

- IL-18 is a pleiotropic pro-inflammatory cytokine belonging to the IL-1 superfamily. IL-18 plays an important regulatory role in both innate and acquired immune responses against diverse pathogens, including poxviruses [56]. IL-18 signals through membrane-bound IL18Rα and IL18Rβ, which then stimulates the production of IFNγ from T-helper lymphocyte cells (Th1) and macrophages and also enhances the cytotoxicity of NK cells. IL-12 is a member of the heterodimeric cytokines, composed of two chains, IL12A (p35) and IL12B (p40). IL-12 signals through a heterodimeric receptor formed by IL12Rβ1 and IL12Rβ2 to activate NK and T cells to stimulate the production of antiviral cytokines such as IFNγ and TNF [57]. IL-12 and IL-18 are important for the cell-mediated immune response against poxviruses [58]. C57BL/6 mice that are lacking either IL12p40 (IL12p40−/−) or IL-18 (IL-18−/−) or both cytokines (double-knockout IL12p40−/−IL18−/−) are becoming highly susceptible to ECTV infection [58]. In these mice, the Th1 cytokine response was diminished, but the Th2 cytokine response was enhanced. In addition, there were reduced cytotoxic NK cells and CTL responses, resulting in reduced proliferation of virus-specific CD8+ T cells compared with the wild-type mice [58]. Thus, IL12p40 and IL-18 play an important role in the activation of antiviral responses by up-regulation of IFNγ production and cell-mediated immune responses. The role of IL-12 and IL-18 in activating innate and adaptive immune responses against viruses was further tested using recombinant
Conclusions

Cytokines are the gatekeeper and among the first lines of host defense against invading pathogens, including poxviruses. On the other hand, successful viruses have demonstrated the ability to emerge, re-emerge, or persist in a host in a fashion that is linked to their ability to subvert or evade antiviral cytokine responses. The outcome of such host and virus interactions determines the overall tropism of the virus at the cellular, tissue, and host level. Among the DNA viruses, poxviruses are known to circulate in almost every vertebrate species and can cause disease in host-restricted manner. However, poxviruses are also known to leap species, occasionally re-emerge, and cause zoonotic infections. For example, MPXV was long thought to be a rodent poxvirus in Africa that only occasionally caused disease in humans as a dead-end infection with a secondary human-to-human attack rate of less than 10%. But the current worldwide MPXV epidemic revealed the potential for extended human transmission that is linked to human behavior rather than evolution of new genetic viral variants (which, of course, may still occur). But host species leaping of poxviruses can also be due to either acquiring novel genes or selecting mutations in key immune-evading proteins that allow dampening of the cytokine responses in the newly adapted host [62•,63]. For example, VARV, which caused smallpox and killed millions of people per year for centuries, may have jumped from an unknown precursor host species or reservoir thousands of years ago and then adapted to humans after the original host had gone extinct [64]. During its adaptation in humans, VARV has lost multiple genes from the most recent common ancestor, suggesting that mutation or gene loss can enhance host-specific virulence of poxviruses [65,66••]. After the successful eradication of smallpox by a very successful worldwide vaccination program, newer emerging poxviruses such as MPXV and CPXV are appearing as ‘new’ zoonotic viruses and are becoming a progressively bigger threat to human health. The current MPXV outbreak and spread in many countries in populations that are not vaccinated prove that they are still a global threat. Sequencing of the circulating MPXV clades suggests that the MPXV has acquired mutations in certain genes involved in regulating host responses, compared with the apparent precursor virus from West Africa, but it is unknown if any of these mutations are responsible for the apparent increases in human-to-human transmission [20••,67•,68]. More functional studies can only reveal whether they newly acquired host immune regulatory functions. Understanding the role of cytokines and how poxviruses counteract them also has implications for the development of vaccines, antiviral drugs, use of poxviruses as a vaccine platform, expression vector, and oncolytic viruses for the treatment of cancers.

Funding

This work was supported by National Institutes of Health grant R01 AI080607 and R21 AI163910 to G.M. and M.M.R. The funders had no role in study design, data collection, and interpretation or the decision to submit the work for publication.

Conflict of interest statement

The authors declare no conflict of interest.

Data availability

No data were used for the research described in the article.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Odom MR, Hendrickson RC, Lefkowitz EJ: Poxvirus protein evolution: family wide assessment of possible horizontal gene transfer events. Virus Res 2009, 144:233-249.

2. Moss B: Poxvirus cell entry: how many proteins does it take? Viruses 2012, 4:688-707.

3. Moss B: Membrane fusion during poxvirus entry. Semin Cell Dev Biol 2016, 60:89-96.

4. Schmidt FI, Bleck CK, Mercer J: Poxvirus host cell entry. Curr Opin Virol 2012, 2:20-27.

5. Bartee E, McFadden G: Cytokine synergy: an underappreciated contributor to innate anti-viral immunity. Cytokine 2013, 63:237-240.

6. McFadden G, et al.: Cytokine determinants of viral tropism. Nat Rev Immunol 2009, 9:645-655.

7. Seet BT, et al.: Poxviruses and immune evasion. Annu Rev Immunol 2003, 21:377-423.

8. Bratke KA, Mclysaght A, Rothenburg S: A survey of host range genes in poxvirus genomes. Infect Genet Evol 2013, 14:406-425.

9. Águeda-Pinto A, et al.: Identification of a novel myxoma virus C7-like host range factor that enabled a species leap from rabbits to hares. mBio 2022, 13:e0346121.
Making different knock-out and knock-in recombinant viruses, this study demonstrates that the C7L-like host range factor present in the myxoma virus isolate Toledo is responsible for the infection of hare cells and caused myxoma virus species leap from rabbits to hares.

10. Liu J, Rothenburg S, McFadden G: The poxvirus C7L host range factor superfamily. Curr Opin Virol 2012, 2:764-772.

11. Meng X, et al.: Structural basis for antagonizing a host restriction factor by C7 family of poxvirus host-range proteins. Proc Natl Acad Sci USA 2015, 112:14858-14863.

12. Meng X, et al.: C7L family of poxvirus host range genes inhibits antiviral activities induced by type I interferons and interferon regulatory factor 1. J Virol 2012, 86:4538-4547.

13. Conrad SJ, et al.: Myxoma virus lacking the host range determinant M062 stimulates cGAS-dependent type 1 interferon response and unique transcriptomic changes in human monocytes/macrophages. PLoS Pathog 2022, 18:e1010316.

This study demonstrates that the C7L-like host range factor M062 from myxoma virus isolate Lausanne regulates the SAMD-9-dependent DNA sensing pathway.

14. Esteban DJ, Buller RML: Ectromelia virus: the causative agent of mousepox. J Gen Virol 2005, 86:2645-2659.

15. Sigal LJ: The pathogenesis and immunobiology of mousepox. Adv Immunol 2016, 129:251-276.

16. Fang M, et al.: CD94 is essential for NK cell-mediated resistance to a lethal viral disease. Immunity 2011, 34:579-589.

17. Cheng WY, et al.: Comparison of host gene expression profiles in spleen tissues of genetically susceptible and resistant mice during ECTV infection. Biomed Res Int 2017, 2017:645680.

18. Beer EM, Rao VB: A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. PLoS Negl Trop Dis 2019, 13:e0007791.

19. Alakunle E, et al.: Monkeypox virus in Nigeria: infection biology, epidemiology, and evolution. Viruses 2020, 12:11.

20. Isidro J, et al.: Phylogenomic characterization and signs of microevolution in the 2022 multi-country outbreak of monkeypox virus. Nat Med 2022, 28:1569-1572.

21. Silva NIO, et al.: Here, there, and everywhere: the wide host range and geographic distribution of zoonotic orthopoxviruses. Viruses 2020, 13:1.

22. Whitaker-Dowling P, Youngner JS: Vaccinia rescue of VSV from interferon-induced resistance: reversal of translation block and inhibition of protein kinase activity. Virology 1983, 131:128-136.

23. Smith GL, Talbot-Cooper C, Lu Y: How does vaccinia virus interfere with interferon? Adv Vir Res 2018, 100:355-378.

24. McFadden G: Poxvirus tropism. Nat Rev Microbiol 2005, 3:201-213.

25. Rahman MM, McFadden G: Myxoma virus dsRNA binding protein M029 inhibits the Type I IFN-Induced Antiviral State in a Highly Species-Specific Fashion. Viruses 2017, 9:2.

26. Alvarez-de Miranda FJ, et al.: TNF decoy receptors encoded by poxviruses. Pathogens 2021, 10:8.

27. El-Jaar M, Teir M, Maluquer de Matos C: Vaccinia virus activation and antagonism of cytosolic DNA sensing. Front Immunol 2020, 11:568412.

28. Lawler C, Brady G: Poxviral targeting of interferon regulatory factor activation. Viruses 2020, 12:10.

29. Hernaiz B, Alcamí A: Virus-encoded cytokine and chemokine decoy receptors. Curr Opin Immunol 2020, 66:50-56.

The review discusses the current knowledge on how virus-encoded cytokine and chemokine decoy receptors regulate the host antiviral responses mediated by cytokines and chemokines.

30. Nelson CA, et al.: Structural conservation and functional diversity of the Poxvirus Immune Evasion (PIE) domain superfamily. Viruses 2015, 7:4878-4898.

31. Smith GL, et al.: Vaccinia virus immune evasion: mechanisms, virulence and immunogenicty. J Gen Virol 2013, 94:2367-2392.

32. Schneider WM, Chevillotte MD, Rice CM: Interferon-stimulated genes: a complex web of host defenses. Annu Rev Immunol 2014, 32:513-545.

33. Schoggins JW, et al.: A diverse range of gene products are effectors of the type I interferon antiviral response. Nature 2011, 472:481-485.

34. Galon J, et al.: IL-12 induces IFN regulating factor-1 (IRF-1) gene expression in human NK and T cells. J Immunol 1999, 162:7256-7262.

35. Wu X, et al.: Intrinsic immunity shapes viral resistance of stem cells. Cell 2018, 172:423-438.e25.

36. Hubel P, et al.: A protein-interaction network of interferon-stimulated genes extends the innate immune system landscape. Nat Immunol 2019, 20:493-502.

37. Burgess HM, Mohr I: Cellular 5'-3' mRNA exonuclease Xrn1 controls double-stranded RNA accumulation and anti-viral responses. Cell Host Microbe 2015, 17:322-334.

38. Liu SW, et al.: Poxvirus decapping enzymes enhance virulence by preventing the accumulation of dsRNA and the induction of innate antiviral responses. Cell Host Microbe 2015, 17:320-331.

39. Edwards-Dorreira B, et al.: ISG15 is counteracted by vaccinia virus E3 protein and controls the proinflammatory response against viral infection. J Virol 2014, 88:2312-2318.

40. Xu RH, et al.: Sequential activation of two pathogen-sensing pathways required for Type I interferon expression and resistance to an acute DNA virus infection. Immunity 2015, 43:1148-1159.

41. Rubio D, et al.: Crosstalk between the type 1 interferon and nuclear factor kappa B pathways confers resistance to a lethal virus infection. Cell Host Microbe 2013, 13:701-710.

42. Melo-Silva CR, et al.: Resistance to lethal ectromelia virus infection requires Type I interferon receptor in natural killer cells and monocytes but not in adaptive immune or parenchymal cells. PLoS Pathog 2021, 17:e1009593.

This study demonstrates the importance of a functional type I interferon signaling pathway in monocytes and natural killer cells to protect against the lethal ectromelia virus infection in C57BL/6 mice.

43. Cheng WY, et al.: The cGas-Sting signaling pathway is required for the innate immune response against ectromelia virus. Front Immunol 2018, 9:1297.

44. Hernández B, et al.: Viral cGAMP nuclease reveals the essential role of DNA sensing in protection against acute lethal viral infection. Sci Adv 2020, 6:38.

This study demonstrates that orthopoxvirus-encoded viral Schlaen vSfN is the primary inhibitor of antiviral innate immune responses activated by the cGAS-STING pathway, and in the absence of this protein, mouse poxvirus pathogenesis is severely reduced.

45. Wong EB, et al.: Resistance to ectromelia virus infection requires cGAS in bone marrow-derived cells which can be bypassed with cGAMP therapy. PLoS Pathog 2019, 15:e1008239.

46. Wang F, et al.: Disruption of Erk-dependent type I interferon induction breaks the myxoma virus species barrier. Nat Immunol 2004, 5:1266-1274.

47. Alves JM, et al.: Parallel adaptation of rabbit populations to myxoma virus. Science 2019, 363:1319-1326.

48. Kerr PJ, et al.: Next step in the ongoing arms race between myxoma virus and wild rabbits in Australia is a novel disease phenotype. Proc Natl Acad Sci USA 2017, 114:9397-9402.

49. Kerr PJ, et al.: Punctuated evolution of myxoma virus: rapid and disjunct evolution of a recent viral lineage in Australia. J Virol 2019, 93:8.
50. Ruby J, Bluthmann H, Peschon JJ: Antiviral activity of tumor necrosis factor (TNF) is mediated via p55 and p75 TNF receptors. J Exp Med 1997, 188:1591-1596.
51. Tuazon Kels MJ, et al.: TNF deficiency dysregulates inflammatory cytokine production, leading to lung pathology and death during respiratory poxvirus infection. Proc Natl Acad Sci USA 2020, 117:15935-15946.

This study demonstrates the importance of a functional TNF signaling pathway, including transmembrane TNF that regulates the production of other proinflammatory cytokines to protect the host against lethal virus infection.

52. Atrasheuskaya AV, et al.: Protective effect of exogenous recombinant mouse interferon-gamma and tumour necrosis factor-alpha on ectromelia virus infection in susceptible BALB/c mice. Clin Exp Immunol 2004, 138:207-214.
53. Chan FK, et al.: A role for tumor necrosis factor receptor-2 and receptor-interacting protein in programmed necrosis and antiviral responses. J Biol Chem 2003, 278:51613-51621.
54. Wang F, et al.: RIG-I mediates the co-induction of tumor necrosis factor and type I interferon elicited by myxoma virus in primary human macrophages. PLoS Pathog 2008, 4:e1000099.
55. Bartee E, et al.: The addition of tumor necrosis factor plus beta interferon induces a novel synergistic antiviral state against poxviruses in primary human fibroblasts. J Virol 2009, 83:498-511.
56. Ihim SA, et al.: Interleukin-18 cytokine in immunity, inflammation, and autoimmunity: Biological role in induction, regulation, and treatment. Front Immunol 2022, 13:919973.
57. Hamza T, Barnett JB, Li B: Interleukin 12 a key immunoregulatory cytokine in infection applications. Int J Mol Sci 2010, 11:789-806.
58. Wang Y, et al.: IL-12p40 and IL-18 play pivotal roles in orchestrating the cell-mediated immune response to a poxvirus infection. J Immunol 2009, 183:3324-3331.
59. Gherardi MM, Ramirez JC, Esteban M: IL-12 and IL-18 act in synergy to clear vaccinia virus infection: involvement of innate and adaptive components of the immune system. J Gen Virol 2003, 84:1961-1972.
60. Verardi PH, et al.: IL-18 expression results in a recombinant vaccinia virus that is highly attenuated and immunogenic. J Interferon Cytokine Res 2014, 34:169-178.
61. Stanford MM, et al.: Myxoma virus expressing human interleukin-12 does not induce myxomatosis in European rabbits. J Virol 2007, 81:12704-12708.
62. Senkevich TG, et al.: Ancient gene capture and recent gene loss shape the evolution of orthopoxvirus-host interaction genes. mBio 2021, 12:e0149521.

Genomic analysis of orthopoxvirus accessory genes responsible for virus-host interactions suggests that most of the accessory genes were captured early in chordopoxvirus evolution in host followed by extensive gene duplication resulting in several paralogous gene families.

63. Hendrickson RC, et al.: Orthopoxvirus genome evolution: the role of gene loss. Viruses 2010, 2:1933-1967.
64. Thèves C, Crubézy E, Biagini P: History of smallpox and its spread in human populations. Microbial Spectr 2016, 4:4.
65. Alcamí A: Was smallpox a widespread mild disease? Science 2020, 369:376-377.
66. Mühlemann B, et al.: Diverse variola virus (smallpox) strains were widespread in northern Europe in the Viking Age. Science 2020, 369:6502.

A significant study demonstrated the presence of variola virus (smallpox) strains during the Viking Age and how the virus evolved to kill millions of people worldwide.
67. Wang L, et al.: Genomic annotation and molecular evolution of monkeypox virus outbreak in 2022. J Med Virol 2022, https://doi.org/10.1002/jmv.28036.

A study demonstrating that the strains of monkeypox virus 2022 outbreak are undergoing mutations from the closely related strain isolated in 2018.
68. Khosravi E, Keikha M: B.1 as a new human monkeypox sublineage that linked with the monkeypox virus (MPXV) 2022 outbreak - Correspondence. Int J Surg 2022, 105:106872.