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Review

Poxviruses and the evolution of host range and virulence

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ABSTRACT

Poxviruses as a group can infect a large number of animals. However, at the level of individual viruses, even closely related poxviruses display highly diverse host ranges and virulence. For example, variola virus, the causative agent of smallpox, is human-specific and highly virulent only to humans, whereas related cowpox viruses naturally infect a broad spectrum of animals and only cause relatively mild disease in humans. The successful replication of poxviruses depends on their effective manipulation of the host antiviral responses, at the cellular-, tissue- and species-specific levels, which constitutes a molecular basis for differences in poxvirus host range and virulence. A number of poxvirus genes have been identified that possess host range function in experimental settings, and many of these host range genes target specific antiviral host pathways. Herein, we review the biology of poxviruses with a focus on host range, zoonotic infections, virulence, genomics and host range genes as well as the current knowledge about the function of poxvirus host range factors and how their interaction with the host innate immune system contributes to poxvirus host range and virulence. We further discuss the evolution of host range and virulence in poxviruses as well as host switches and potential poxvirus threats for human and animal health.

Contents

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1. Poxvirus host range factors

Poxviruses are large double-stranded DNA viruses, which exclusively replicate in the cytoplasm of their host cells. The genomes of currently sequenced poxviruses contain between 135 and 360 kb and contain up to 328 predicted open reading frames (ORFs). Poxviruses can be grouped into 2 subfamilies: *chordopoxvirinae*, which infect vertebrates and *entomopoxvirinae*, which infect insects. Among *chordopoxvirinae*, 10 genera are currently recognized: orthopoxviruses, yatapoxviruses, leporipoxviruses, capripoxviruses, cervidpoxviruses, suipoxviruses, parapoxviruses, molluscipoxviruses, crocodylipoxviruses and avipoxviruses. Because yatapoxviruses, leporipoxviruses, capripoxviruses, cervidpoxviruses and suipoxviruses form a sisterclade to orthopoxviruses in phylogenetic analyses, the former can be classified as "clade II" poxviruses (labeled in Fig. 1) (Bratke and McLysaght, 2008; Hughes and Friedman, 2005). Approximately 50 relatively conserved genes are found in all sequenced poxviruses and another 40 genes are present in most chordopoxviruses (Lefkowitz et al., 2006). These genes are important for the general biology of poxviruses such as transcription, RNA processing, replication and virion assembly and are generally found in the central regions of the genomes. Genes that are involved in the interaction with the host map generally towards the terminal regions of the genomes and often exhibit lower sequence identity and lineage-specific distribution. Many but not all of these genes are dispensable for virus replication in cell culture, but viruses that have been engineered to lack them are usually attenuated in infection models. Therefore these genes are referred to as virulence genes, and their protein products as virulence factors. Inverted terminal repeats (ITRs) flank the ends of the genomes, which range in size from approximately 0.1 to 13 kb, and contain identical sequences at both ends (Table 1). In most viruses, the ITRs contain multiple examples of duplicated genes.

A striking feature of chordopoxviruses, is that the range of host species that can be productively infected by a given virus, referred to as host range, can vary drastically even between closely-related species within a single genus (McFadden, 2005). Among orthopoxviruses for example, variola virus, the causative agent of smallpox, was strictly human-specific before its eradication, whereas cowpox- and monkeypox viruses naturally infect a wide variety of mammalian species and therefore possess relatively broad host ranges. Remarkably, most poxviruses can enter a large variety of cells from many different animal species in a fashion that is mostly independent of species-specific receptors and involve virion proteins that are conserved in all poxviruses (Moss, 2006). Virus replication and establishment of permissive infection requires the successful manipulation of the host antiviral immune system, especially, the innate immune responses. Certain poxvirus genes have been identified, which are important for viral replication in a subset of cells or host animals, whereas they are dispensable in others. Genes that are important for poxvirus-specific differences in host range can be referred to as host range genes (McFadden, 2005). Until now, approximately 15 genes have been identified in different poxviruses that possess host range function (reviewed in Werden et al., 2008). Deletion of those genes leads to viral replication defects in a subset of normally permissive cells. Known poxvirus host range genes can be grouped into 12 distinct gene families. Some of these families contain only one member, whereas others contain many members, likely resulting from lineage-specific duplications (Bratke et al., 2013). Interestingly, not a single host range gene has been identified that is present in all poxviruses. On the contrary, the majority of host range genes show evidence for multiple independent lineage-specific inactivation events, which indicates that those genes might have been dispensable for virus replication in their respective hosts. Alternatively, gene inactivations might have provided the virus with a selective advantage by causing its attenuation and making its infected host less sick. This could lead to better host survival and increased mobility, which could in some cases lead to better virus transmission.

The precise molecular mechanisms of how host range genes influence poxvirus host range are only partly understood. Different molecular mechanisms for host range function are possible (Fig. 2). Since host range proteins often antagonize the host cell innate immune system, the mere presence or absence of host range genes can lead to successful replication or replication defects in different animals or their derived cells. Many host range genes have been identified by the analysis of spontaneously arisen mutants and/or targeted gene deletions that resulted in altered growth characteristics and host range, as compared to their progenitors. Examples of this include the spontaneous deletions comprising the serpin gene SPI-1 in rabbitpox virus (RPXV) and K1L in vaccinia virus (VACV) that were subsequently confirmed by targeted deletions (Ali et al., 1994; Gillard et al., 1986). All deletions of host range genes analyzed so far have resulted in the restriction of the virus host range, however theoretically, the deletion of at least certain genes could also result in extended host range, e.g. if a host-derived molecule targeted a viral gene product and thereby mediated the induction of an antiviral response only in cells possessing that factor. Another way to identify host range genes is by the insertion of genes from one virus into the genome of another virus, which has a restricted host range. This method was used in the identification of the ankyrin/F-box protein CP77 (CHOhr/CPXV-BR025), which enabled VACV replication in otherwise non-permissive