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Review Article

Major Virulence Factors of Orf Virus and Their Mechanism for Immune Evasion

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Abstract

Orf, also called contagious ecthyma or contagious pustular dermatitis, is a zoonotic viral skin disease caused by orf virus (ORFV). ORFV is a species of the *Parapoxvirus* (PPV) genus in the family of *Poxviridae*, with specific characters. ORFV develops various virulence factors that work alone or coordinate with each other assisting the virus in immune evasion and host infection. In this article, major virulence factors of ORFV were reviewed and the mechanism of its immune evasion was investigated.

Keywords: Parapoxviruses; ORFV; Virulence factors; Mechanism of immune evasion

Abbreviations

ORFV: Orf Virus; PPV: Parapoxvirus; ITRs: Inverted Terminal Repeats; vIL-10: IL-10; OVIFNR: ORFV Interferon Resistance Gene; VEGF: Vascular Endothelial Growth Factor; CBP: Chemokine Binding Protein; ANK: Ankyrin; dUTPase: Pyrophosphatase; GM-CSF: Granulocyte-macrophage Colony Stimulating Factor; IFN: Interferon; PKR: Protein Kinase; VACV: Vaccinia Virus; DCs: Dendrite Cells; APCs: Antigen Presenting Cells

Introduction

Orf is an acute zoonotic viral skin disease [1] caused by ORFV, and it is often manifested by proliferative lesions [2]. ORFV is a typical representative of the *Parapoxvirus* (PPV) genus. The ORFV can lead to severe persistent infection or secondary infection through the damages the skin or mucous membranes. Orf is not normally fatal but it is a debilitating disease that can be fatal if lambs and kids are not prevented from secondary bacterial or fungal infections. It has been reported that more than 90% lambs infected with ORFV that aged one week did not survive the secondary or mixed infection of other pathogens [3]. This disease has worldwide distribution and was first reported in human by Newsome and Cross in 1934 [4,5] with the clinical features of erythematous macule, papule, vesicle, pustule and scab formation on the back of the hand, interphalangeal area and anterior arms [6]. Therefore, the breakout and prevalence of such an acute, highly contagious disease could have a serious impact on the development of goat meat industry and people's health.

ORFV belonged to the *Parapoxvirus* (PPV) genus in the family of *Poxviridae*, expresses 35 virus proteins with molecular masses between 10 and 220 KDa on the surface of virus particles. Among these proteins, only those of 65, 39 and 22 KDa proteins could be recognized by the host immune system and stimulate the host to produce relevant antibodies. The viral genome, coding about 132 genes [7], consists of the central region (CORE) and the inverted terminal repeat (ITR) at each end. The conservative central region contains genes that are essential for DNA replication as well as the production of virus particles in the cytoplasm of infected cells. The terminal genes are involved in unessential but yet important functions including: virulence, host range, immune evasion and immunoregulation [8]. Major virulence genes in ITRs included ORFV homologous ovine gene encoding cytokine IL-10 (vIL-10), ORFV interferon resistance gene (OVIFNR), vascular endothelial growth factor (VEGF) the virus encoding chemokine binding protein (vCBP), ankyrin (ANK), dUTP pyrophosphatase (dUTPase), granulocyte-macrophage colony stimulating factor (GM-CSF) inhibiting factor (GIF), apoptosis inducing and inhibiting genes and ORFV121gene that inhibits the host NF-κB pathway [9]. These virulence factors are distributed in terminal at each end ITRs (Figure 1). Studies have reported a highly frequent rearrangement of the terminal sequences through duplication, transposition and deletion, which might provide a mechanism for rapid evolution enabling the virus to adapt to changing circumstances in the host. During the evolution and interaction with the hosts, ORFV develops a set of immune regulation strategy for replication and immune evasion, by taking advantage of various virulence factors. Understanding the various virulence factors and unraveling the mechanism of ORFV immune evasion can be beneficial to develop new and efficient vaccines or medications in order to make a quick and efficient responds to the orf outbreaks and prevalence's. This article presented an up-to-date review on ORFV major virulence factors and its immune evasion mechanism.

Virulence factors in 5' ITR

The dUTPase is an essential enzyme in nucleotide metabolism. It prevents the incorporation of excessive dUTP into the DNA, decreases the mutation frequency and maintains the genetic stability. Similar to herpes virus and type D retrovirus [10], ORFV expresses this enzyme [11]. Phylogenetic analysis has revealed that the dUTPase expressed

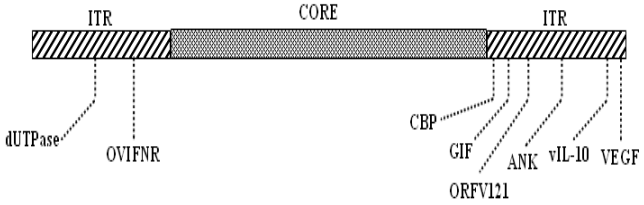

Figure1: Schematic representation of key virulence factors in parapoxvirus.

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by ORFV has a closer phylogene to the one in mammalian species as compared to the other poxviruses. This could indicate that this gene might be involved in the between-species infections. Therefore, host gene capture [12] could be another ORFV mechanism in order to adapt to the host immune response.

Interferon (IFN) plays an important role in the anti-virus protection process [13]. The ORFV develops a protein against the host IFN response that is encoded by the ORFV interferon resistance gene (OVIFNR). This protein binds to the viral double-stranded (ds) DNA, inhibits the dsDNA-dependent activation of IFN-inducible protein kinase (PKR) and prevents the down-regulation of viral mRNA transcription [14]. It has been reported that when vaccinia virus (VACV) interferon resistance gene (E3L) is replaced by OVIFNR, VACV replication is not affected while its pathogenicity is severely decreased [15]. The OVIFNR decreases the host anti-virus activity through inhibition of the IFN response, which could facilitate ORFV immune evasion.

Virulence factors in 3' ITR

Inflammation is a part of natural host immune response [16], which limits and eliminates the damage factors, helps in the repair of the damaged tissue, dilutes the toxin by liquid seepage and eliminates the necrotic tissue to facilitate further repair and regeneration [17]. In the process of inflammation, dendrite cells (DCs) play an important role as messengers between the innate and adaptive immunity. After stimulation, these cells secrete various cytokines to enhance nonspecific immune response. As one of the most powerful APCs, DCs have the ability to catch wild rang of antigens and present them to other immune cells [18-21] . ORFV can synthesize vCBP, a 2.5 Å protein with hexagonal crystal structure [22], that binds the receptors as competitive inhibitors of homogenous cytokines [23] and inhibits inflammation by preventing monocytes and DCs from transferring into the skin inflammatory lesions or peripheral lymph nodes [24,25]. By inhibiting the function of inflammation and DCs, vCBPs help ORFV to evade specific and nonspecific immune responses.

GM-CSF has well-documented stimulatory effects on the functions of monocytes and macrophages. The most important effects include macrophage differentiation and activation, which results in endocytosis, pathogen elimination and antigen presentation to T cells [26]. IL-2 is one of the Th1 cytokines, which plays a critical role in the immune response against intracellular pathogens [27-29]. GM-CSF and IL-2, as cytokine immune regulator, induce host protective immune response. The GIF with a WSXWS motif, encoded by ORFV [30], can specifically inhibit the biological activity of IL-2 and GM-CSF [31]. The GIF further suppresses the function of IL-2 and GM-CSF in order to promote the ORFV survival.

The NF-kappaB family of transcription factors play a central role in the immune response by regulating several processes ranging from immune regulation, inflammation, stress response and apoptosis [32-34]. Some pathogens can inhibit the transcriptional regulation of NF-kB and promote immune evasion such that the host cannot eliminate them via inflammatory reactions [35,36]. The ORFV121 encodes a novel NF-κB inhibitor that binds to NF-κB and inhibits the phosphorylation and nuclear translocation of NF-kB-p65 thereby inhibiting the translation of the immune-related genes [37]. The ORFV121 is a virulence determinant for ORFV in natural hosts. ORFV uses ORFV121 in order to disturb the host transcription and impair host immune response through inhibiting the NF-κB pathway signal transduction, such that it can successfully evade the host immune system.

The ankyrin repeat (ANK) is a common motif in proteins, which was first identified in yeast in 1987. The F-box-like domains are present in most of the poxvirus ankyrin repeat proteins that can take advantage of the proteasome mechanism of the host cells [38]. ORFV express the 5 ANK proteins that degrade the host's anti-virus factors through the F-box-like domains, thereby promoting the ORFV replication and infection of different species [8, 39].

The vIL-10 gene of the ORFV is one of the early viral genes, which encodes a 21.7 KDa protein made of 185 amino acids [40]. Its polypeptide sequence shows a high level of amino acid identity to sheep (80%), cattle (75%), human (67%) and mice (64%) IL-10. vLI-10 inhibits the maturation and function of antigen presenting cells (APCs) such as dendrite cells (DCs), which could inhibit the proliferation and transcription of a range of Th1 cell cytokines including IL-2, IL-3, IFN-γ and GM-CSF. Consequently, this could decrease the secretion of TNF-α, IL-8 and IFN-γ from macrophages, CD8+ lymphocytes and keratinocytes [41,42]. It has been reported that vIL-10 inhibited the secretion of IFN-γ and GM-CSF from Concanavalin A- (ConA)-activated peripheral lymphocytes [41]. Furthermore, it is known that vIL-10 has a partial ability to inhibit the proliferation of THP-1 monocytes and the synthesis of some factors [43]. vIL-10 can also induce CD4+ Th1 cells, the major participants of immune response, in order to inhibit the secretion of IFN-γ from NK, CD4+ and CD8+ cells [44]. In other words, vIL-10 inhibits the immune responses and provides suitable environment for the ORFV infection.

Vascular endothelial growth factors (VEGFs) are critical inducers of angiogenesis in normal conditions or in diseases process such as cancer, psoriasis and orf [45,46]. The VEGF genes can extensively vary in terms of amino acid sequence in different strains of ORFV, whereas the structure and function of the VEGF proteins remain conservative [47]. ORFV recombinants with the variant VEGF genes disrupted showed markedly reduced infection symptoms [48,49]. In the process of ORF, VEGFs enhance the proliferation of endothelial cells and increase the vascular permeability which is facilitated by the viral replication and pustule formation [50]. Meanwhile, the virus enrichment at the scab lesions increases its survival opportunities and extends the survival period of ORFV [9]. Therefore, VEGFs are critical in ORFV for the contagious pustular symptoms.

Other factors inducing or inhibiting host cell apoptosis

Previous studies have reported that ORFV induced apoptosis in APCs, epidermis cells and lymph cells, mediated through the CD95 pathway [51,52]. The activated ORFV dsRNA triggers the caspase cascade through caspase-8 activation and apoptosis [53]. This is one of the most important mechanisms with which ORFV eliminates the immune system at lesions and causes repeated infections. Some of the ORFV membrane proteins induce apoptosis in the host APCs and suppress the activation of T cells via CD95/CD95L pathway [51]. Intriguingly, ORFV can inhibit the apoptosis in the infected cells at the same time. It has been shown that the ORFV's 125th gene can take advantage of cytochrome c pathway in order to inhibit apoptosis.

Table 1: The key virulence factors encodes by ORFV , their functions and mechanism for immune evasion.

No.	Protein	Host Targets	Major Function(s)
1	vIL-10	DCs, Th1	inhibits the maturation of DCs, inhibits the proliferation and transcription of a range of Th1 cell cytokines
2	OVIFNR	dsRNA	decreases the host IFNs response with PKR pathway
3	VEGF	vascular endothelial	enhances the vascular permeability which is facilitated by the viral replication and pustule formation
4	CBP	DCs, cytokines	inhibits the function of inflammation and DCs by competitive binding cytokines
5	ANK	Panthenol, proteasome	degrade the host's anti-virus factors through the F-box-like domains
6	dUTPase	Host dUTPase gene	cross-species infection
7	GIF	IL-2, GM-CSF	suppresses the function of IL-2 and GM-CSF
8	ORFV121	NF-kB-p65	inhibitsthe translation of the immune-related genes by NF-kB pathway
9	Other factors	CD95, cytochrome c et al	induces or inhibits host cell apoptosis

Furthermore, the protein encoded by this gene was reported to have a Bcl-2-like inhibitory effect on apoptosis [54]. The novel immune evasion mechanism mediated by this protein encoded by ORFV has not yet been discovered in other viruses.

Future perspectives

The details of the interaction mechanisms between ORFV and the host are still unclear. However, the studies on ORFV virulence factors and the mechanism of immune evasion could provide us with more information to further unravel the mechanisms of pathogenesis (Table 1). It is already known that genes are highly variable at the terminal ends of ORFV genome and genetic recombination occurs between homologous sequences, as well as non-homologous sequences. In the process of viral mutation, sometimes some nonessential genes are deleted while some host genes can be captured and merged into the genome. This process could promote the evolution of some new adaptive subgroups. Under the selective pressure of immune systems, ORFV take advantage of such mutation strategy to get rid of the anti-virus effects induced by the host's Th1 cells. In practice, ORFV can be potentially used as a perfect vector or gene carrier [55-58]. It can be concluded that ORFV takes advantage of many of the host resources to fight back against the host immune system. For instance, ORFV develops a dual inhibitory or inducing mechanism against apoptosis that could be originally a powerful anti-infection tool. Unraveling the ORFV virulence factors and immune evasion mechanism, might contribute to the ORF etiology elucidation, as a new category of study in ORFV. It could potentially create a solid foundation for the development of new vaccines and medications.

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