Review Article

Weapon Store of Contagious Ecthyma Virus: Accounting for Immune Evasion and Re-Infection Strategies in Target Hosts

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Abstract | Orf otherwise known as contagious ecthyma is a mild, self-limiting, localized skin disease of small ruminant's viz. sheep and goats, ensuring its presence and related economic loss all over the world. The virus is the prototype member of the *Parapoxvirus* genus of the *Poxviridae* family and is known to cause zoonotic affection sporadically. The main attraction to this virus has always been its wide range of virulence factors, known to be responsible for deceiving the host's defense strategies and causing re-infection within a year of infection. From viroceptors like chemokine binding protein to GM-CSF and IL-2 inhibiting factors, to virokine like Interleukin-10, shifting the cell cycle phase (Poxviral anaphase-promoting regulator complex) and enhancing nutrients and oxygen supply (vascular endothelial growth factor), ORFV possesses several unique strategies, to fight against host immune environment. Some of the genes have been acquired from the host and some are flowing through the family and genus evolving with the virus to adapt and efficiently set up an infection in immune-loaded host cells. This review focuses on the important virulence genes of the orf virus and their functions with recent advances and the way they can be manipulated for different benefits to the research community viz candidates for cancer biotherapy, immunomodulators, antivirals, viral vectors, and recombinant vaccines.

Received | March 18, 2022; **Accepted** | August 16, 2022; **Published** | December 26, 2022
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Citation | Karki, M., Kumar, M. and Venkatesan, G., 2022. Weapon store of contagious ecthyma virus: Accounting for immune evasion and re-infection strategies in target hosts. *Hosts and Viruses*, 9: 19-31.
DOI | https://dx.doi.org/10.17582/journal.hv/2022/9.19.31
Keywords: Parapoxviruses, Orf virus, Virulence genes, Immune-evasion, Re-infection

Introduction

Viruses have gained a lot of attraction in the new era because of their ability to mutate fast and emerge into a whole new virus with varying host range and pathogenicity. There has been a long battle between viruses and humans since ages viz. 1918 Spanish flu to 2019 SARS-Cov-2 pandemic. Drastic environmental changes, ecologic and social habits of humans, and economic conditions have been an important factor in the transmission and emergence of various infectious diseases. The emerging and threatening viral diseases to public health put forth the need of "One Health approach" to study every potential virus in detail.

This review is focused on one of the most studied poxviruses after Vaccinia virus. Orf virus (ORFV) is known for its unique properties like immune evasion

and re-infection in the host and has gained the interest of researchers in the present day. Orf is an important disease of small ruminants and also causes mild localized infections in humans [1]. It also affects camels, llamas, and some other wild animal species. Recent reports of ORFV infection in mountain goats, Sitka-black tailed deer, Dall's sheep, muskox, and caribou indicates its host range switch ability [2]. Some reports of malignant lesion which often leads to death of animals are also reported [3]. The virus belongs to the family *Poxviridae* and carries many unique features viz. a number of virulence factors, immune evasion property, and inducing a short-lived immune response and thus re-infecting its host. The disease has been ignored by the small-scale farmers rearing small ruminants due to its self-limiting property and because of this notion, it has caused severe damage to the economy of many countries that have not even been recorded and resulted into spread to wild animals [3]. Although, an increasing number of recent reports on orf outbreak and its consequences, lack of proper attention and vaccines indicates that the virus is emerging to a more fatal form [3]. Different strains and recombination among the variants of virus are reported in one of the studies from Argentina, indicating the need for specific virus determination and specific vaccine [4].

Pathogenomics and virulence factor database for viruses

Pathogenomics is a field well known for bacterial virulence factor study [5] [6]. The study uses high-throughput genome sequencing and extensive bioinformatics for identifying genes encoding resistance or virulence factors [7]. Although a varied pool of virulence genes for different viruses has been already studied, the lacuna is a compilation of the data and a database. This database can help to ease the comparative studies while referring to immune evasion strategies of viruses and help in future challenges.

Virulence factors or genes of ORFV

Parapoxviruses are known to encode several virulence factors from the ends of the genome. Taken from the ancestral Poxviral genome or its host genome, these virulence genes have co-evolved with the virus to adapt it to host cell environments. A schematic of the location of different virulent genes or factors in the ORFV genome is presented in this review (Figure 1). These genes are not essential for viral replication in cell culture, but support the survival of virus in-vivo by helping the virus to replicate and survive in the specific immune environment [8]. Some of the unique PPV's virulence genes are responsible for determining host range, pathogenesis, and virulence [9]. Some of the virulence genes are "captured" from the host during evolution like dUTPase, vIL-10, VEGF, Poxviral anaphase-promoting complex analog, and anti-apoptotic factors as indicated by their similarity to their cellular counterparts and absence from other Poxviral genomes [9]. This adaptation is probably because of the intricate relationship between host and virus. While CBP and GIF genes are believed to be the descendants of ancestral poxviral genes, NF-kB inhibitors genes found in PPVs are different from that of other poxviruses, without any similarity or homology. The review focuses on the on virulence genes of ORFV, as they hold potential for various uses like in the development of antiviral agent, immunomodulators, bio-therapeutics, and viral vectors [10]. List of potential virulent genes or factors of ORFV genome and their characteristics is depicted in Table 1.

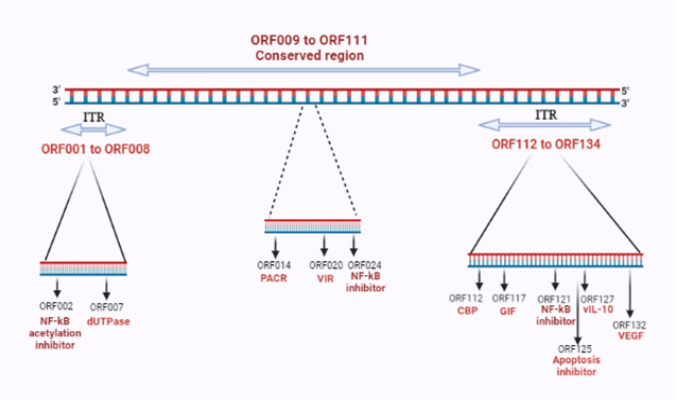

Figure 1: *Schematic representation of different immunomodulatory proteins encoded by virulent genes of orf virus genome, their location and functions.*

VEGF (Vascular endothelial growth factor)

ORFV is the first among the viruses to report the presence of VEGF homologue VEGF-E. All the PPVs are known to encode the ORF132 (VEGF) gene from the 3' terminal of the genome [9]. The VEGF glycoprotein binds the tyrosine kinase receptors, designated as VEGFRs present in the host cell and functions to enhance the oxygen and nutrient supply in infected cells to support virus survival and replication [11]. The gene is reported to be grouped as two different categories viz. VEGF-NZ7 and VEGF-NZ2 are based on differentiating inter-isolate variation [12]. Following this study, molecular epidemiology was done recently revealing the circulation of the VEGF-NZ7 gene containing isolates in India, and some from

Table 1: *Compiling the key functions, ORF length in genome, their homologues if present in VACV and gene length of virulence genes*

Virulence genes	ORF & VACV homologue	Key functions	Gene length
dUTPase	ORF007 (F2L)	Enhancing infection in non-dividing cells	506 bp
NF-kB acetylation inhibitor	ORF002	Inhibitor of NF-kB activation	344bp
NF-kB inhibitor	ORF024; ORF121	Inhibitor of NF-kB activation	875bp; 905bp
VEGF	ORF132	enhance the oxygen and nutrient supply in infected cells	446bp
GIF	ORF117 (A41L)	Manipulate chemokine response	794bp
Apoptosis inhibitor	ORF125	inhibits the mitochondrial downstream pathway of apoptosis	518bp
VIR	ORF020 (E3L)	Suppress antiviral activity by inactivating dsRNA induced interferons	548bp
vIL-10	ORF127	Suppress other defensive cytokines	551bp
CBP	ORF112 (C23L)	Bind and inactivate the cytokines and chemokines in infected cell	863bp
PACR/ Ring H2 protein	ORF014	Maintain infected cells in G0/G1 phase providing cells in sufficient supply	278bp

Figure 2: *Severe proliferative type of orf lesions present around mouth region of young lamb from a field outbreak.*

China and the rest known isolates possess VEGF-NZ2 type [13]. Mutational analyses suggested that the expression of VEGF in wild-type isolates leads to the formation of rete ridges with extensive epidermal proliferation and scab formation, which was not found in the recombinants [14]. Hence, peculiar finger-like projections of the lesions and involvement of VEGF in severe scab formation (Figure 2) can be correlated with the expression of VEGF [15]. The two types of VEGF genes can be a responsible factor for two types of lesions reported viz. severe and mild, which needs to be experimentally proved using both types of isolates. Even having the marked variation in the sequence, both the types possess conserved homodimeric structure and cysteine knot motif responsible for its activity [9, 15-16]. VEGF is specifically encoded by PPVs, whereas in other poxviruses, it is epidermal growth factor (EGF) only. For the same reason, the highly vascularized lesions of orf can be differentiated from the proliferative lesions of other poxviruses [9]. VEGF-E gene of the Vero cell-adapted attenuated ORFV D1701-V strain is found to be the most suitable target for insertion and expression of foreign genes and using it as an effective viral vector [17].

VIR (viral interferon resistance)

VIR is encoded by the ORF020 gene situated at the left end of the genome and utilizes the strategy providing the resistance to virus against interferon (Figure 1). VIR protein binds the interferon-induced dsRNA-dependent kinases, suppressing JAK-STAT

signaling and subsequently their antiviral activity [9, 18]. VACV E3L gene is the only homolog shared by other poxviruses. ORF020 gene product can complement its homolog gene of VACV E3L *in-vitro*, as it shares 31% amino-acid identity [19]. The gene was found to show species-specific clusters in phylogenetic analysis, which is again an important finding to molecular epidemiology of the disease. The gene is found to be highly conserved among the genus, as well as among the different members of *Poxviridae* suggesting it as a good candidate for broad-spectrum antiviral [20].

PACR (poxvirus anaphase-promoting complex regulator)

ORFV along with its other PPV genus members encodes PACR to modulate the cell cycle in highly specialized immune epidermal cells, unlike most poxviruses that encode nucleotide metabolism enzymes like thymidine kinase and ribonucleotide reductase [9]. ORF014 gene encodes this protein which is similar to the APC11 subunit (RING H2 protein) of APC (Anaphase promoting complex) but lacks its functional ubiquitin ligase activity [21]. Therefore, the competitive binding of PACR to the C-terminal of APC2 subunit (a scaffold protein) in place of APC11 [22, 23] disturbs the functioning of APC and allows the cells to enter S phase [24]. The unbound APC11 subunit undergoes ubiquitination and proteasomal degradation. The unavailability of APC regulates the transition of the G1/S phase i.e., synthetic phase. ORFV-PACR like gene products is also found to be encoded by other poxviruses like MOCV and crocodile poxvirus. PACR gene which is common to all GC rich Chordopoxviruses and their specific targeting of epidermal cells suggest a link between the divergences of poxviruses [9]. Our lab studied that this gene possesses a specific difference in ORF lengths of sheep and goat isolates, reflected in the phylogenetic relationship. For the very first time, we found that the sheep and goat origin isolates can be differentially diagnosed through multiplex PCR (Unpublished data).

Apoptosis inhibitor

ORFV-125 gene encodes an anti-apoptotic product, a defensive phenomenon of the virus to prevent dying of host cells contain the spread of infection [25]. Sequence analysis of the ORF125 gene shows similarity in its C-terminal motif with Bcl-2-family members, but no homology to the VACV anti-apoptotic F1L gene and other poxviruses [26]. ORF125 protein binds and inactivates the BH3-range proteins, the pro-apoptotic members [27]. ORF125 shows 60-70% identity at the nucleotide level among ORFV isolates and PPVs but doesn't show homology to any other viruses [9]. In contrast to the ORF125 gene, ORFV also encodes an apoptosis-inducing protein (ORF119) functioning by down-regulating the anti-apoptotic proteins Bcl-2 and cIAP-2 [28]. Transcriptome analysis of ORFV infected cells suggested that there is coordinated up and down-regulation of apoptosis-related genes and hence, links the viral interference in apoptosis [29].

dUTPase (dUTP pyrophosphatase)

An essential enzyme for nucleotide metabolism is encoded by ORF007 as an early protein, dUTPase [30]. Unlike other virulence genes, ORF007 is not essential for *the in-vitro* growth of ORFV, but *in vivo*, it enhances the replication of the virus in non-dividing cells [31]. The basic function of dUTPase is to hydrolyze the dUTP to dUMP and pyrophosphate (PPi). This limits the intracellular pool of dUTP and simultaneously provides the precursor (dUMP) for the synthesis of thymine maintaining the ratio of dUTP/dTTP. The increased concentration of dUTP in cells leads to the incorporation of uracil into DNA and other mutational changes [32]. Functional activity of dUTPase is found to be mainly regulated by five conserved amino acids "dUTPase motifs" acting as the active site of the enzyme [33-35]. The enzyme functions in a trimeric state and have the three active sites in which the tyrosine residue was found to be the active catalytic component as the functional loss of enzyme was demonstrated by its modifications (nitration and acetylation) [36]. This motif is reported to be found in all the dUTPase of viruses till now described viz. different retroviruses [37-41]. Therefore, its active site can be targeted for attenuation of the gene. Also, it has been described as a potential target for chemotherapeutic drugs [42]. The activity of dUTPase is found to be over the pH range of 6-9 and a temperature of 25-37°C [43]. This enzyme can be inhibited with an increased concentration of EDTA. Divalent cations like Mg+, MN+ act as co-factor to enhance its activity. ORFV dUTPase is more similar to mammalian dUTPase enzyme than other poxviruses, which suggests that it is acquired by the horizontal transfer from the host cell genome [44].

NF-κB inhibitors

NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex responsible

for the regulation of immune response in infection. It is present in the cytosol of all cell types in an inactive state, bounded with IkB protein (inhibitor of kB). In response to any stimuli like infection, stress, etc., IKK (IkB kinase) is activated which destroys IkB [45]. Activated NF-kB is translocated to the nucleus, where it binds the DNA and helps it to transcribe the sequence, modulate its function accordingly to combat the change in the cell, and establish innate immune response. Hence, NF-kB inhibitors disrupt this process of immunity development. PPVs encoded NF-kB inhibitors are different from those encoded by other poxviruses like leporipoxvirus, molluscipoxvirus, yatapoxvirus, and orthopoxvirus suggesting the evolutionary deviations [46].

ORFV encodes three NF-kB inhibitory factors viz. ORF002, ORF024, and ORF121 [47-49]. The three factors have different functions but, eventually to inactivate the NF-kB signaling. Within the genus also, marked differences in homology have been reported [9]. ORF002 is an early-late protein of 117 amino acids, encoded from the left terminal region of the genome of PPV [50]. Among the three NF-κB inhibitors, the ORF002 is the first nuclear inhibitor having no homologs in other genera of the *Chordopoxvirinae* subfamily except equine molluscum contagiosum virus [51, 52]. Deletion mutants of ORF002 recommended the non-essential role of the gene in replication and virulence [48]. ORF002 and E1A protein of Adenovirus shares some conserved domains, therefore based on the comparative analysis, it was suggested that N-terminal amino acids of the ORF002 protein are responsible for blocking of phosphorylation of serine residue at 256 positions and thereby, inhibition of acetylation of NF-kB-p65 in the nucleus [53]. Notably, it was found that only the deletion of ORF121 has a significant change in virulence and pathogenesis [9]. ORF121 gene is conserved among its ORFV sheep and goat isolates and encoded early in the infection [47]. ORF121 binds NF-kB-p65 and inhibits its phosphorylation and nuclear translocation. Likewise, ORF024 inhibits the phosphorylation of IkB kinases and thereby inhibiting the activation of the IKK complex [49]. Despite tending to compact the genome, why the poxviruses encode several NF-kB inhibitors is a big question to the researchers [54].

Virokine, viral interleukin-10 (vIL-10)

vIL-10 was first reported in ORFV found to shares the remarkable functional similarity to ovine IL-10 at its C-terminal [9]. Similarly, virokine IL-10 has a suppressive effect on other cytokines that have inflammatory, antiviral, and other defensive roles [55]. ORF127 encodes the vIL-10 gene early in the infection from the right end of the genome, which plays a vital role in the establishment of virus infection. Both the IL-10R1 and IL-10R2 receptors are necessary for the activity of vIL-10 [56]. Recombinant ORFV having a deletion of ORF127 demonstrated the reduction in virulence and attenuation of the virus [57]. Sequence analysis of the vIL-10 gene from various species has suggested the variation in its amino-terminal, while the carboxy terminus of the gene was found to be conserved and responsible for virulence activity [58]. Low GC content of viral interleukin-10 gene, in contrast to the high GC content of ORFV genome and marked homology at its C-terminal to ovine IL-10 than to other viral IL-10 supports the findings that the gene is acquired from the host [59]. The DNA sequence of ORFV-IL-10 was found to have many synonymous substitutions from its host counterpart, which indicates the horizontal transfer of a gene from the host and evolutionary changes adapted by the ORFV [9]. Alternatively, other members of the genus PPV possess the amino-acid identity to the gene from their host counterparts, not to ORFV, indicating the independent horizontal transfer of the gene from specific hosts [60]. Other poxviruses like Yatapoxvirus and Capripoxvirus possess IL-24 encoding gene, an IL-10 family member [61, 62]. A report from Rajasthan, India stated that vIL-10 from the skin scab of PPV infected camel (Camel contagious ecthyma) resembles more closely to Pseudocowpoxvirus of cattle than ORFV of sheep based on sequence analysis, revealing the transfer of the virus from cattle to camel [58].

Viroceptors of ORFV: GM-CSF and IL-2 inhibitory factor (GIF) and Chemokine binding protein (CBP)

Poxviruses encode several proteins which challenges the chemokine mediated inflammatory response of host cell [63]. ORFV encodes two genes responsible for binding the important chemokines in the infected cells and disrupting their biological function to protect the cells. GIF, is encoded by ORF117 gene of PPVs only and binds two chemokines viz. GM-CSF and IL-2. The two cytokines are completely different in their binding domains [64]. CBP, an early 2.5A° soluble protein is encoded by ORF112 and is also present in other PPVs and members of the family

[65, 66]. Chemokine-binding proteins inhibit host chemokine trafficking, especially of dendritic cells and monocytes to the infected cells and don't possess any similarity to any of the host proteins [67-69]. This is one of the reasons why adaptive immunity doesn't take a full hand in the case of ORFV. The two genes share high homology indicating duplication of the gene during evolution [9]. GIF activity corresponds to the WSXWS-like motif, which is responsible for dimer and tetramer formations, i.e. its functional state [70]. Conserved cysteine residues form disulfide bond important for maintaining tertiary structure of the protein, essential for binding to cytokines [71]. The functional activity of BPSV-ORF117 was found to be deviated from others, indicating more relatedness of ORFV and PCPV than BPSV [72]. The receptors of human and murine GM-CSF and IL-2 have been cloned and characterized, but these don't share any similarity to the ORFV-GIF [73]. The ORFV-GIF binds only the ovine GM-CSF and IL-10, which emphasizes its adaptation to its particular hosts.

An analysis of the sequence of vCBP shows more similarity to GIF (GM-CSF and IL-2 inhibitory factor) than type-2 CC-chemokine binding protein family, indicating the evolution from the same ancestral gene [74]. The gene is conserved within the genus with a varied percentage of identity but shares low identity with other poxviruses CBP [9]. Recently, infection studies conducted based on the deletion mutants of CBP, wild type (*wt*) ORFV and revertant virus were carried out in sheep to prove its role in virulence, pathogenesis and host response [75]. Hence, the recombinants may prove as good subunit vaccine candidate as significant change in antibody response was observed for knock-out ORFV than *wt* and revertant virus.GIF and CBP are important virulence factors of ORFV, distantly related to the 35kDa protein family. GIF is a highly conserved gene of PPVs and possesses the 'WDPWV' and SUSHI domain. The SUSHI/CCP/SCR domain is basically a conserved protein domain with a structure consisting of a protein loop within another loop. CBP possesses high variations among ORFV as well as other poxviruses. For the first time, the presence of SUSHI domain in GIF gene of ORFV isolates from India has been reported [76].

Orf virus induced immunity in host

ORF011 and ORF059 encoded proteins are immunodominant and responsible for inducing immune response [77]. However, few and weak neutralizing antibodies are found in serum of infected animals. Neutrophils, natural killer cells, dendritic cells are observed to in infected cells after infection and a rush of cytokine has also been observed [78]. Similarly, Th1 response was found to comparatively confer strong cell-mediated immunity.Also, MHC-II+ dendritic cells population was observed in PPOV infected sheep [79]. However, the clear picture of immunity development is not clear till date, and need a specified stage-wise in-vivo experimental study to clear innate as well adaptive immunity phases of the disease. Biggest challenge is escaping the immunity developed and re-infecting the same host. Most probable reason is these virulence factors that help the virus to manipulate the immune environment of host cell. The re-infection is the major problem faced by livestock health sector to control this disease.

Applications of ORFV

Firstly, the Poxviruses have always played an important role as vaccine vectors viz. modified VACV Ankara (MVA), fowlpoxvirus, canarypoxvirus, and now the ORFV [80]. A Vero-cell culture adapted attenuated strain/apathogenic ORFV-D1701-V strain has been proved itself as an efficient immunomodulatory virus vector to develop recombinants via replacing VEGF-E gene with an insert often referred as an inactivated Parapoxvirusovis (iPPVO). VEGF-E is the most important gene in orf virulence and thereby this replacement subsequently reduces the disease pathogenicity.This vector has been used to develop vaccines against many diseases in the last two decades. Pseudorabies virus (PRV) glycoproteins gC and gD based ORFV-D1701 vector vaccine have shown both humoral and cellular immunity against natural infection in mice [81]. Another example of recombinant iPPVO as vector vaccine replacing VEGF-gene by rabies virus G glycoprotein successfully mounted protective immunity against lethal challenge infection in mice [82].

Also, iPPVO expressing PRV-gC and gD is used as booster dose for activation of strong immunity and found to be more efficient than other prime-boost regimens [83, 84]. Also, iPPVO plays a key role as antiviral immunotherapeutic against Herpes simplex virus, Hepatitis B virus, rabbit haemorrhagic disease and etc[85, 86]. This has been used to track the immune response by the host cell against iPPVO. A

complex cytokine response from different immune cells including both Th1-related (IL-12, IL-18, IFN-ɣ) and Th2-regulatory cytokines (IL-4) was demonstrated in Equine, mice, and rats, *in-vivo* [87-90]. Also, the iPPVOinduces the secretion of IFN-α and–β by dendritic cells via TLR-independent pathways [91]. Human peripheral cells have also been showing induction of Th-1 cell and monocyte-related cytokines [92]. Even in non-permissive cells, canine polymorphonuclear cells (*in-vitro*), iPPVO induction demonstrated an enhanced phagocytic activity, MHC-II upregulation, and CD4+ T-cell proliferation, and oxidative burst in monocytes [93]. The immunostimulating effect of this inactivated ORFV expressing H5 has proved to protect against high pathogenic strains of avian influenza H5N1 and H1N1 in mice [94, 95]. Whereas, a study shows iPPVO co-culture with Equine Herpes virus-1 and 4 does not affect the viral proliferation and increased IL-10 mRNA and multi-cytokine expression [96].
Secondly, ORFV has joined the legacy of poxviruses as a potent oncolytic virus candidate for cancer biotherapyand has shown remarkably pronounced effects in murine cancer models [97]. They are widely accepted because of skin tropism, strong induction of innate immunity at the infection site, and no systemic invasion. IFN-ɣ and IL-10 induction by iPPVO directs the study towards its anti-fibrotic therapeutic approach and found to exercise it successfully in pre-established liver fibrosis in rat models [98]. Its widening applications have also touched the acaricidal therapy to treat canine generalized demodicosis via the combination of amitraz and iPPVO and provide faster recovery than amitraz alone [99]. This non-specific immunomodulator is also found to be effective in equine respiratory diseases when used along with *Propionibacterium acnes* [100].

By modulating the immune response of the host, some of the genes have been used as therapeutic agent for certain important inflammatory diseases. Synthetically produced VEGF using recombinant DNA technology can be used in conditions like hypoxia to restore the oxygen supply to tissues when blood circulation is inadequate and also to provide nutrient supply to regenerate the affected cell [101]. The synergistic effect of ORFV-VEGF and IL-10 immunomodulatory proteins has been studied to treat wounds in a murine model recently, resulting in the expected outcome of enhanced wound closure, re-vascularisation, re-epitheliasation and less wound scarring [102]. Rabies virus G and M protein based VLP containing membrane anchored immunostimulatory molecule, GM-CSF, induces enhanced immunogenicity and 100% protection against wild type virus [103]. MOR103 drug is available to control high levels of GM-CSF found in joints with rheumatoid arthritis [104]. Likewise, pathogenesis behind diseases like psoriasis itching involved, due to over-expression of IL-2 can be controlled. The IL-2 used as therapeutic agent has been also known to determine the severity of the side effects [105], therefore in these cases also GIF can be used effectively.

Conclusions and Recommendations

Earlier, orf virus was known only as an entity causing mild self-limiting disease of sheep and goats. Later, its varied range of virulence factors, re-infection causing ability, and widening host range to wild animals gained the attraction of researchers to study the virus and its genome in more detail. Some of the important virulence factors are known to acquire from their respective hosts via horizontal gene transfer namely VEGF, IL-10, PACR etc for utilizing them against host defense mechanism. Ironically, the same genes can be used by certain manipulations for our benefits. VEGF is the most studied virulence factor of ORFV, followed by GIF, CBP and vIL-10 and they have been proved as potential candidates as biotherapeutics. Other virulence factors like dUTPase, VIR, apoptosis inhibitor, NF-kB inhibitors are still at the primary stage of study after being noticed in the genome of ORFV. The virus has evolved through many adaptations to ensure its presence in the environment and host. In the last decade, various uses of ORFV have been studied extensively as viral vector for other important diseases, bio-therapeutic for medical important diseases like cancer. We need to keep up our ability to fight against these small entities and maintain the balance of ecology.

Acknowledgment

The authors thank the Director, Indian Veterinary Research Institute for providing the necessary facilities to carry out this study. The financial support provided by DBT, India under the North-East Twinning program on DBT-NER on Pox project (BT/385/NE/TBP/2012) is also acknowledged.

Abbreviations

Viral interferon resistance gene (VIR), Vascular endothelial growth factor (VEGF), viral interleukin-10 (vIL-10), GM-CSF and Interleukin-2 inhibitory factor (GIF), Chemokine binding protein (CBP), Poxviral anaphase promoting complex regulator analog (PACR).

Novelty Statement

The MS entitled "Weapon Store of Contagious Ecthyma Virus: Accounting for Immune Evasion and Re-Infection Strategies in Target Hosts" focuses on the important virulence genes of the orf virus and their functions with recent advances and the way they can be manipulated for different benefits to the research community viz candidates for cancer biotherapy, immunomodulators, antivirals, viral vectors, and recombinant vaccines.

Author's Contribution

MK and VG planned, collected the data and prepared the draft. AK and VG edited and revised the review for final submission.

Conflict of interest

The authors have declared no conflict of interest.

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