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REVIEW

# Orf virus infection

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## Summary

Orf virus (ORFV) is an important pathogen responsible for a highly contagious zoonotic viral infection that threatens those who handle sheep and goats. Orf virus is the prototype of the *Parapoxvirus* genus, and its resilience in the environment and ability to reinfect its host has contributed to the spread and maintenance of the infection in many species. In healthy humans, the disease usually resolves spontaneously within 3 to 6 weeks. There is no specific treatment and many different approaches such as use of imiquimod, cidofovir, curettage, shave excision, cryotherapy, and electrocautery have all been reported to be successful, without supporting evidence from controlled clinical trials. Throughout its interaction with the different hosts, ORFV has evolved a strategy for immune evasion via the development of an array of virulence factors. The interaction of ORFV with the immune system has been the subject of research for decades. Whole inactivated ORFV has been used as a type of immunomodulating drug; a so called paramunity inducer proposed as both a preventative and a therapeutic immunomodulator across various species. Additional research on the remarkable strategies underlying ORFV infection could lead to improved understanding of skin immunity.

**KEYWORDS**

ecthyma contagiosa, immunity, orf, poxvirus, virology, virulence factor

## 1 | INTRODUCTION

Orf virus (ORFV) is an important pathogen responsible for a highly contagious zoonotic viral infection that threatens those who handle sheep and goats.[1,2] Orf virus is the prototype of the *Parapoxvirus* genus and its resilience in the environment and ability to reinfect its host has contributed to the spread and maintenance of the infection in many species.[1,2] It can be transmitted to humans by direct or indirect contact.[1,2] It is commonly reported after the Islamic Eid El Adha (the feast of sacrifice) in which sheep are handled with bare hands for slaughter.[1,2] In sheep and goats, it is more commonly known as sore mouth disease or scabby mouth disease. Among dermatologists, orf is known as contagious pustular dermatitis, infectious pustular dermatitis, or ecthyma contagiosa.[1-4] In ungulates, the infection is usually acute; however, chronic infections have been reported.[1-4] Infections are localized to the skin and oral cavity. Shedding of the virus-rich scab helps seeding the environmental pool.[1-4]

Host immunity plays a major role in limiting the severity of the disease. An important aspect of ORFV is that it can repeatedly infect previously exposed hosts despite a prominent inflammatory host immune response. Reinfection usually leads to decreased lesion size and quicker time to resolution.[1,2,4] Throughout its interaction with hosts, ORFV has evolved a strategy for immune evasion via the development of an array of virulence factors. The interaction of ORFV with the immune system has been a subject of research for decades and whole inactivated ORFV has been used as an immunomodulating drug, so called paramunity inducer, in both prevention and therapy across various species.[5]

In this review, we aim to provide an update on clinical findings, histopathological features, major virulence factors, immune evasion strategy as well as on the novel immunomodulatory properties of inactivated ORFV and its potential use in human medicine.

**Abbreviations:** APC, antigen presenting cell; ARP, AR containing proteins; CBP, chemokine binding protein; DC, dendritic cell; GIF, granulocyte/macrophage colony-stimulating factor inhibitory factor; GM-CSF, granulocyte/macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MCP-1, monocyte chemotactic protein-1; MHC-II, major histocompatibility complex II; MIP-1a, macrophage inflammatory protein-1a; ORFV, orf virus; OVIFNR, orf virus interferon resistance protein; RANTES, regulated upon activation, normal T-cell expressed and secreted; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; vIL-10, ORFV interleukin-10

## 2 | ETYMOLOGY

The origin of the word orf is unclear. Some sources suggest that it is derived from the Old Norse hrūfa which means scab.[6,7] Another source suggests it is derived from the Old English word orfcwealm

which means "murrain, any infectious disease of lifestock" (orf infection of the hand, sheep to human transmission).[6] A third source suggests that it is derived from the Old English word hwyorf which indicated bovine species.[7]

## 3 | EPIDEMIOLOGY

Orf virus mostly affects lambs and kids; however, adults may also be afflicted.[1,2] The infection spreads rapidly in a flock by contact and up to 90% may be affected; however, mortality is usually low in adults.[1,2] It was reported that, in 1 outbreak, mortality in lambs was 10% and reached 93% in kids.[2] Young animals usually succumb because of oral lesions that impede suckling, secondary bacterial and fungal infection, or maggot infestation.[2] In view of these numbers, it is not surprising that orf has a considerable economic impact on the farming sector.[2] There is increasing evidence of the ability of orf to cross-infect other species of animals other than sheep and goats such as camels, gazelles, reindeers, musk ox, and Japanese serows.[2,8]

Orf is an occupational hazard and the population at risk includes shepherds, butchers, farmers, wool shearers, abattoir workers, and veterinarians.[1,2,9,10] In the United Kingdom, around 30% of sheep workers report previous infection with orf.[11] Orf infection usually occurs in spring and summer months[10] and is usually transmitted to humans either by direct or indirect contact. Humans who are in contact with infected animals, meat, and carcasses can get infected with orf by direct inoculation through abrasions or breaks in the skin.[10,12] Orf virus is hardy; it is resistant to drying and freezing and remains viable on the ground and farm material for months to years.[10,13] This explains why humans can acquire the infection from fomites previously contaminated by infected animals such as farm buildings, fences, feeding troughs, contaminated equipment, wool, pastures, buckets, knives, and ear tags.[9,13,14]

Orf can also occur in a nonoccupational setting. Farmer's children and housewives, zoological garden visitors, and people who practice farming as a hobby as well as people who slaughter lambs and sheep for traditional rituals are also at risk.[10,15,16] Orf virus has also been reported in a 53-year-old woman after being scratched by a stray kitten.[17] A yearly outbreak occurs in countries in which there is a Muslim population such as Turkey, Jordan, Iran, France, Belgium, United States, Kingdom of Saudi Arabia, because of increased animal slaughter for the feast of sacrifice (Eid el Adha).[6,14,18-23] In the nonprofessional setting, safe practices are difficult to implement, so cuts in the skin can ensue from handling animals thereby facilitating orf inoculation.[10] Professionals rarely seek medical attention as they are aware of the benign nature of the infection and that it resolves spontaneously within weeks.[7,18]

## 4 | CLINICAL FEATURES

Orf is an epitheliotropic virus that causes a highly contagious vesiculoulcerative pustular infection of both keratinized skin and mucosal surfaces.[1,24] The most important predisposing factor is loss of epithelial barrier integrity.[2] It affects damaged skin as it requires abrasions and breaks in the skin for infection.[1,2] It replicates in regenerating epidermal keratinocytes.[4] In ungulates the lesions are proliferative, typically form pustules (due to large polymorphonuclear infiltration) and scabs.[1,4] It is self-limited, usually affecting the oral mucosa, lips, muzzle, mucocutaneous junctions, nostrils, and gums of sheep and goats and resolves in 6 to 8 weeks.[1,2,4] The lesion starts as erythema and evolves to vesicle, pustule then scab.[1,4] There is no systemic spread.[4] Orf can reinfect its ungulate host; however, later lesions are smaller and resolve in 3 weeks.[4]

### 4.1 | Clinical presentation in humans

Orf usually occurs on the dorsal aspect of hands and fingers (Figure 1), but unusual locations have occasionally been described including the face,[14,25] nose,[26] axilla,[27] scalp,[28] buttocks, genitals,[29,30] perianal,[31] urethral,[14] pericanthal eyelid skin, and conjunctiva.[2]

Immunocompetent patients usually have a single lesion that passes through 6 clinical stages.[1,7] It starts 3 to 7 days after inoculation with the maculopapular stage (days 1-7) with erythematous macule or papule; then the target stage (days 7-14) with necrotic center and red outer halo; in the acute stage (days 14-21), the nodule begins to weep; in the regenerative stage (days 21-28), the nodule becomes dry; in the papilloma stage (days 28-35), the lesion has become papilloma-like and forms a dry crust; finally, the regression stage (after 35 days) where the skin returns to its normal appearance often without residual scar.[1,7] The course of infection takes an average of 6 to 8 weeks.

Constitutional symptoms such as fever, malaise, and lymphadenopathy may rarely occur.[7] Giant orf can occasionally occur in an otherwise healthy individual.[9,16] Orf can be complicated by secondary bacterial infection, erysipelas, lymphadenopathy, lymphangitis, giant recurring lesions, and erythema multiforme. It is estimated that around 7% to 18% of orf patients develop erythema multiforme, which usually develops 2 to 4 weeks after onset of primary orf lesion. It usually involves the hands and forearms.[30] It varies in severity but is self-limited and usually resolve in 1 to 4 weeks.[11] Other secondary immunological reactions reported to occur after orf are widespread papulovesicular eruption,[32-34] Stevens-Johnson syndrome,[35] and antibody mediated hypersensitivity reactions such as blistering disorders.[11]

In immunocompromised patients with T cell dysfunction, the clinical picture changes. Whether inherited or acquired, T cell dysfunction leads to the growth of atypical persistent giant multiple orf.[36,37] Very few cases have been described in transplant patients.[38-41] No cases of orf in the setting of HIV have been reported.

Autoinoculation[13,14,31] and human to human transmission are rare.[25] Interestingly, an outbreak of nosocomial orf infection in a burn unit in Turkey occurred in 2012.[42] In parallel with the predisposition of atopic dermatitis patients to certain viral diseases such as molluscum contagiosum, 3 cases of orf affecting atopic dermatitis patients were described,[15,30,43] in whom lesions were multiple, diffuse, and in atypical areas. They were managed conservatively and regressed on their own.

Clinical differential diagnosis of orf is broad and includes: milker's nodules and atypical mycobacterial infection such as *Mycobacterium marinum*, giant molluscum contagiosum, paronychia, cutaneous leishmaniasis, furuncle, herpetic whitlow, anthrax, tularemia, keratoacanthoma, and vascular lesions such as pyogenic

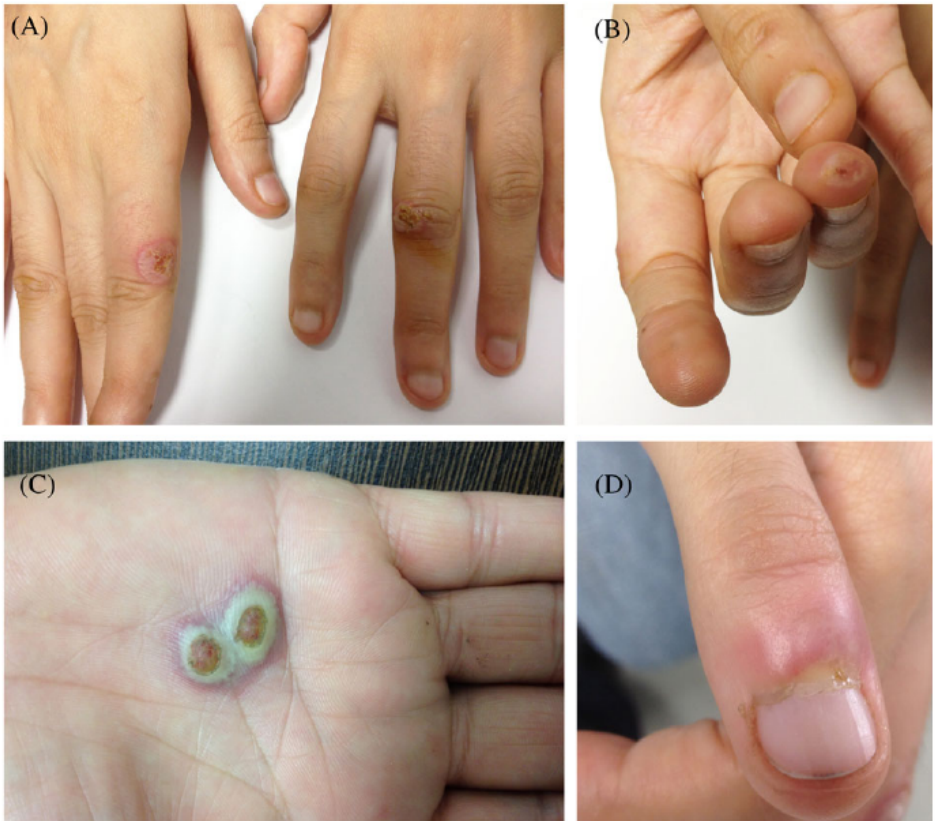


**FIGURE 1** Clinical pictures of orf. A, Multiple inflamed papules with necrotic centers on both hands of a 33-year-old patient. B, Inflamed pustular lesion on the fingertip in same patient. C, "Kissing" inflamed targetoid lesions on the palm of a 70-year-old patient. D, Early inflamed lesion mimicking paronychia in a young adult patient

granuloma.[1,7,21] Orf is chiefly a clinical diagnosis. The clinical appearance of the lesion along with the history of contact with an infected animal is enough to reach a diagnosis. Further investigations are performed only when the diagnosis is doubtful,[2,7] although public health authorities in the United States recommend obtaining lab-confirmed diagnosis and determination of parapoxvirus species.

## 5 | LABORATORY TESTING

The histopathology varies according to the clinical stage. Characteristic histological features include: parakeratotic crust, hyperkeratosis, epidermal hyperplasia, intraepidermal vesiculation, ballooning and degeneration of keratinocytes, increased dermal vascularity, and cytoplasmic and nuclear vacuolation as well as a dense mixed inflammatory infiltrate composed of lymphocytes, histiocytes, neutrophils, and eosinophils (Figure 2).[2,44]

Both real-time PCR and standard PCR are now available.[4,45] In one study, TaqMan real PCR had a sensitivity of 100% and specificity of 93%.[45] Other methods include cell culture isolation, enzyme-linked immunosorbent assay (ELISA), western blotting, restriction fragment length polymorphism, and electron microscopy; however, the use of these methods is not widespread as is the case of PCR.[2]

In veterinary medicine, extensive research is underway to improve methods of diagnosis. A loop-mediated isothermal amplification (amplifies DNA sequences under isothermal conditions) has been developed[46] and is simple, rapid, and cheap compared to other nucleic acid-based tests. In India, a multiplex PCR for simultaneous detection and differentiation of sheeppox, goatpox, and ORFVs in a single tube reaction has been developed. This rapid detection and differentiation is important as both the ORFV and the *Capripoxviruses* can incur severe economic threat. Orf can cause high morbidity in adults and high mortality in lambs and kids (up to 90%), while Capripoxviruses can cause high mortality and morbidity.[47] A digital droplet PCR detection of ORFV, pseudocowpox virus (PCPV), and bovine papular stomatitis virus (BPSV) using RNA polymerase gene sequences has also been developed.[24]

## 6 | TREATMENT

In healthy patients, conservative management is warranted as the disease usually resolves spontaneously within 6 to 8 weeks. Local antiseptics may be used to prevent secondary bacterial infections. Giant lesions are more problematic. Anecdotal reports have reported efficacy of different therapeutic modalities including shave excision, cryotherapy, electrocautery, curettage, imiquimod, or cidofovir; all have been reported to be successful without supporting evidence from randomized controlled.[7,37,48] When medical therapy fails to treat giant orf lesions, wide excision and skin grafting is warranted although recurrence at the skin resection margin is common.[7]

For prevention, wearing nonporous (rubber or latex) gloves when handling sheep or goats is effective as a preventive measure, as well

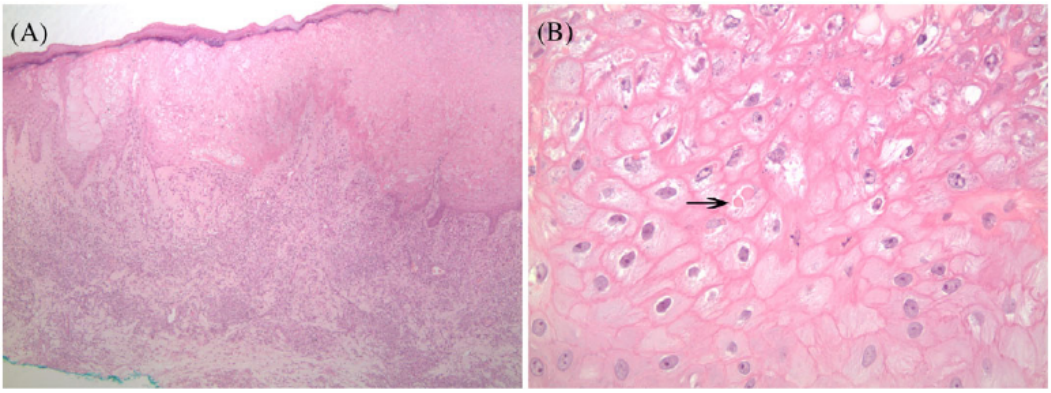


**FIGURE 2** Histology of orf. A, Section of a lesion exhibiting superficial epidermal necrosis, acanthosis with ballooning degeneration, vacuolization of upper epidermal layers, spongiosis, increased dermal vascularity, and an underlying dense inflammatory infiltrate (5× magnification, stained with haematoxylin and eosin). B, Close up view of the characteristic eosinophilic, intracytoplasmic viral inclusions (40× magnification, stained with haematoxylin and eosin)

as practicing good hygiene by washing with warm water and soap for at least 20 seconds after contact with infected animals.[49]

## 7 | VIROLOGY

Orf virus is the prototype species of the *Parapoxvirus* genus of the Poxviridae family that includes PCPV, BPSV, and the parapoxviruses of red deer.[1-4] Tentative species of the parapoxvirus include seal poxvirus, chamois contagious ecthyma, and Auzdyk disease virus. Several of the parapoxviruses including ORFV, BPSV, and PCPV are zoonotic pathogens. Virions of parapoxviruses have a distinctive ovoid structure, 260 nm in length on the long axis and 160 nm on the short axis.[1-4] ORFV contains a linear double-stranded DNA genome.

Genetic studies of the parapoxviruses started in late 1980s and early 1990s.[50-60] The genome was sequenced over a decade ago.[50] It is approximately 138 kb in length.[1-4,50-60] In contrast to other poxviruses, parapoxviruses are G+C rich and ORFV consists of 63% G+C content.[1,2,50] It is covalently closed at the termini (cross-linked ends) and each end forms an inverted terminal repeat.[1,2,4] It contains 132 predicted open reading frames, 88 of which are conserved in other chordopoxviruses. The arrangement of the open-reading frames in ORFV genome is similar to that in vaccinia virus genome, which implies a common evolutionary origin. Even greater similarity exists between the genomes of ORFV and *Molluscum contagiosum* virus as both have high G+C content. Despite having one of the smallest genomes in the poxvirus family, the parapoxviruses share over 70% of their genes with the most virulent viruses.[50-60] While DNA/DNA hybridization revealed strong interspecies homology between central core regions, lack of cross-hybridization between terminal fragments suggested significant differences within this region between the parapoxviruses.[50-60]

Orf virus replicates in the host cell cytoplasm and hence encodes its own machinery for DNA transcription and replication. The genome consists of a central core where genes are highly conserved as they encode the transcription and replication machinery. Outside the core region at both ends are located genes dispensable for growth. Some of these genes are genus specific and encode factors associated with virulence, immune modulation, pathogenesis, and host range.[49] Different ORFV strains exhibit diverse restriction fragment profiles and high degree of interspecies genetic variation. Orf virus has at least 2 infectious particles that allow it to spread from cell to cell: the mature virion, which has an outer membrane derived from endoplasmic reticulum, and extracellular virion, which is produced from the wrapped virion form.

## 8 | VIRULENCE AND PATHOGENESIS

Virulence factors are molecules that enable a pathogen to replicate and disseminate within a host by subverting or eluding host defenses. Orf virus encodes a variety of such proteins (Table 1).[49] Virulence genes are mainly located in the terminal regions; areas of high research interest that contains the genes involved in host specificity and pathogenesis.[61] These genes show remarkable high intraspecies variability, and some of these genes are orthologues of known mammalian genes.[2]

Among the virulence factors, ORFV has several proteins that have mainly an anti-inflammatory function including viral vascular endothelial growth factor (VEGF), ORFV interleukin-10 (vIL-10), ovine interferon resistance protein (OVIFNR), granulocyte/macrophage colony-stimulating factor (GM-CSF) inhibitory factor (GIF), and chemokine binding protein (CBP) (Figure 3).

Viral VEGF, termed VEGF-E, was the first virulence factor to be described with a crucial role in ORFV pathogenesis.[2,4] It bears homology to mammalian VEGF and is transcribed early during infection. Through its exclusive interaction with VEGF receptor-2, VEGF-E induces epidermal and endothelial cell proliferation, increased vascular permeability and dermal angiogenesis. This leads to increased viral growth and replication in newly dividing epidermal cells that are driven by the host's wound healing response with VEGF-E maintaining this regenerative response by directly promoting epidermal regeneration which supplies cellular substrates for viral replication and by indirectly providing the necessary nutrients. VEGF-E also contributes to the formation of scabs rich in viral particles which allows increased survival of the virus formation in the environment for up to a year.[2,4,62] In contrast to VEGF-A, VEGF-E shows negligible tissue inflammation and vascular leakage as it does not bind to VEGFR-1. VEGF-E is also characterized by its ability

**TABLE 1** Summary of main ORFV virulence genes with known protein function

| Viral protein | Gene | Protein function |
|---|---|---|
| Vascular endothelial growth factor | ORF 132 | Induces endothelial cell proliferation, vascular permeability, and angiogenesis in skin |
| Viral IL10 orthologue | ORF 127 | Inhibits the maturation and function of antigen presenting (dendritic cells) hence inhibits the expression of Th1 cell cytokines |
| Interferon resistance | ORFV020 | Binds to the viral dsRNA and inhibits dsRNA activation of both PKR kinase and 2-5 adenylate synthetase allowing orf virus to utilize host cell protein synthesis machinery |
| Chemokine binding protein | ORF 112 | Inhibits chemotaxis and leukocyte recruitment by competitively binding cytokines |
| GM-CSF inhibitory factor | ORF 117 | Prevents the activation of leukocytes and dendritic cells by inhibiting the function of IL-2 and GM-CSF |
| Bcl-2-like inhibitor of apoptosis | ORF 125 | Prevents the apoptosis of the viral infected cells |
| dUTPase | | Inhibits the incorporation of excessive dUTP into the DNA, reduces mutation frequency and preserves the genetic stability |
| Inhibitor of NF-kB signalling pathways | ORF 002, 024 and 121 | Inhibits different processes in the NFKB signal transduction pathway of the host cell, helps ORFV evade the host cell immune response |
| Ankyrin repeat-containing protiens | ORF 008, 123, 126, 128, 129 | Targets the proteasomes of the host cells and uses the ubiquitin-mediated degradation of a wide range of cellular proteins |

Abbreviations: GM-CSF, granulocyte/macrophage colony-stimulating factor; NF-kB (Nuclear Factor- Kappa B); ORFV, orf virus.

to inhibit dendritic cell (DC) development and maturation. Recombinant viruses lacking functional VEGF show remarkably reduced clinical severity.[2,4] VEGF-E also regulates keratinocyte function, enhances epidermal regeneration, and increases matrix metalloproteinase-2 and matrix metalloproteinase-9 expression. This suggests that VEGF-E may potentially promote re-epithelialization of non-healing wounds (such as wounds of diabetic patients).[62]

Mammalian IL-10 has multiple functions including suppression of inflammation, antiviral responses, T-helper type 1 effector function, major histocompatibility complex (MHC) class II antigens and costimulatory molecules on macrophages, as well as enhancement of B cell survival and proliferation. IL-10 can also block nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity and contributes to the regulation of the JAK-STAT signalling pathway. Among the poxviruses, IL-10–like genes have only been found in parapoxviruses including ORFV, BPSV, and PCPV. Orf virus vIL-10 demonstrates considerable homology to IL-10 of ovine (80%), bovine (75%), human (67%), and mouse (64%) origin and has been shown to be functionally indistinguishable[2] from mammalian IL-10. In a murine model, vIL-10 has been shown to play a significant role in immunosuppression by inhibiting cytokine synthesis from macrophages. It also inhibits the maturation and function of antigen presenting cells (APCs), which, in turn, inhibits the expression of Th1 cell cytokines namely IL-2, IL-3, IFN-γ, and GM-CSF. Both ORFV and ovine IL-10 inhibit

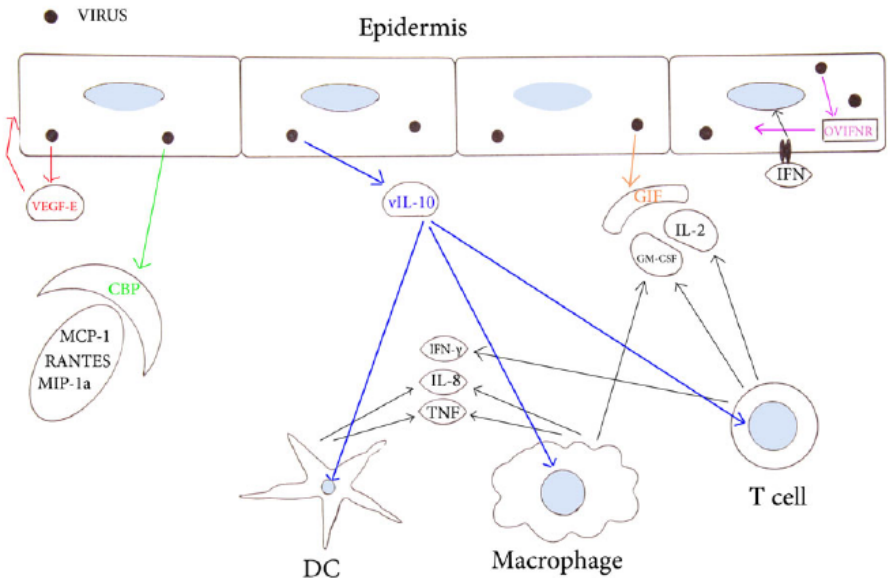


**FIGURE 3** Orf virus main virulence factors. [1] Viral vascular endothelial growth factor (VEGF-E) stimulates angiogenesis and epidermal proliferation providing cellular substrates for viral replication; [2] chemokine binding protein (CBP) suppresses immune cell trafficking by inhibiting many CC-chemokines including monocyte chemotactic protein-1, macrophage inflammatory protein-1a, and regulated upon activation, normal T-cell expressed and secreted (RANTES). [3] Orf virus interleukin-10 (vIL-10) suppresses inflammation and the adaptive responses by inhibiting the transcription of host cytokines including IFN-γ, IL-8, and TNF-α. [4] Granulocyte/macrophage colony-stimulating factor inhibitory factor (GIF) binds to and inhibits host granulocyte/macrophage colony-stimulating factor produced by T cells and macrophages and IL-2 produced by T cells. [5] Ovine interferon resistance protein (OVIFNR) inhibits IFNs with their major antiviral functions. DC, dendritic cell; MCP-1, monocyte chemotactic protein-1; MIP-1, macrophage inflammatory protein-1a

IFN-γ production from activated lymphocytes as well as TNF-α and IL-8 production from macrophages and keratinocytes. Orf virus lacking the IL-10 gene was attenuated in sheep experiments.[2] Orf virus IL-10 decreases inflammation and scar tissue formation and could potentially be used for mediating tissue repair.[63]

Early after infection, ORFV expresses the gene that codes for OVIFNR that halts production of IFN generated by the host cell.[2] This ORFV gene is a homologue of the vaccinia IFN resistance gene E3L. As part of antivirus protection mechanisms, IFN activates both protein kinase R (PKR) and RNAse L. RNA-activated PKR phosphorylates itself and the alpha subunit of the elongation initiation factor (eIF2) which in turn inhibits mRNA translation. Activated RNAse L degrades both cellular and viral RNA.[4,49,61] OVIFNR protein binds to the viral dsRNA. This inhibits dsRNA activation of both PKR kinase and 2-5 adenylate synthetase. Protein kinase R inhibition prevents the downregulation of viral mRNA translation and 2-5 adenylate synthetase inhibition prevents activation of RNAse L. Hence, OVIFNR allows ORFV to use the host cell protein synthesis machinery.[4,49,61]

Another immuno-modulatory protein encoded by ORFV is GIF. GIF is a soluble secreted protein which inhibits GM-CSF and IL-2. It functions as a dimer and binds GM-CSF with a higher affinity than IL-2. It is expressed late in the virus life cycle.[4] GIF protein bears structure-function similarities to the type 1 cytokine receptor superfamily, despite divergent amino acid sequences. Disulphide bonds and the sequence motif (WDPWV) are essential to the GIF activity. The WDPWV motif resembles the WSXWS motif (where X is any amino acid) necessary for the activity of the type 1 cytokine receptors.[61] GM-CSF stimulates the differentiation and activation of macrophages, which in turn results in antigen presentation to T cells. It also supports the recruitment and antigen-presenting function of DCs. By suppressing the function of IL-2 and GM-CSF, GIF prevents the activation of leukocytes and DCs thereby promoting ORFV survival.[49]

ORFV also produces CBP, which functions in inhibiting the antiviral mechanism of immune cells.[64] Chemokine binding protein is structurally and functionally similar to CBP-II proteins of other poxviruses. These bind with high affinity and inhibit many CC-chemokines such as monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1a (MIP-1a), and regulated upon activation, normal T-cell expressed and secreted, which orchestrate monocyte, macrophage and T cell recruitment to infection sites. Chemokine binding protein also binds lymphotactin, a C-chemokine that recruits T cells through the XCR1 receptor.[61] ORFV secretes CBP into the skin epithelium which competitively inhibits chemokine interaction with cognate receptors and thereby inhibits chemotaxis and leukocyte recruitment.[64] This prevents inflammation by inhibiting monocytes and recruitment of DCs. This further suggests that ORFV has been selected to evade specific and nonspecific immune responses. ORFV-CBP can inhibit both DC migration to inflammatory sites and T-cell activation by DC suggests that CBP could have therapeutic potential for treating inflammatory skin diseases.[65]

ORFV has also been shown to encode several proteins that promote the survival of the virus as well as host cell manipulation/exploitation including ORFV-encoded dUTPases, NF-κB modulatory factors, ankyrin repeat proteins (ARPs), and ORFV gene 125 encoded protein.

As an important enzyme in nucleotide metabolism, dUTPase inhibits the incorporation of excessive dUTP into the DNA and hence reduces mutation frequency and preserves genetic stability. This enzyme is also expressed by herpes-viruses and type D retrovirus. Phylogenetic analysis shows that the dUTPase expressed by ORFV is more similar to mammalian dUTPases than to dUTPases from other poxviruses. This suggests probable horizontal transfer of the gene. The process of acquiring host genes from natural hosts is very characteristic of poxvirus evolution, helping the virus adapt to a host system despite active immune response.[2,49]

The NF-κB family of transcription factors plays a key role in modulating early immune responses against viral infections. ORFV has evolved 3 gene products ORFV002, ORFV024, and ORFV121 that modulate NF-κB activity by targeting unique parts of the pathway, both at the cytoplasmic and nuclear levels.[66,67] ORFV024 functions in the cell cytoplasm. It inhibits the phosphorylation of IκB kinases IKKα and IKKβ by targeting steps upstream of the IKK complex. ORFV121 functions in the cell cytoplasm, downstream of IκB. It binds to and inhibits the phosphorylation and nuclear translocation of NF-κB-p65. ORFV002 functions in the cell nucleus, it binds to and inhibits the p300-mediated acetylation of NF-κB-p65, possibly by disturbing the association of p300 and NF-κB-p65.[66,67] Mutant ORF with deleted ORFV121 resulted in remarkably reduced disease manifestations in sheep, indicating that ORFV121 is a bone fide virulence factor. This is in contrast to virus strains containing the gene deletions of ORFV002 and ORFV024 which showed no clinical attenuation of the disease in sheep. In view of the NFκB pathway is so complex, involving a multitude of processes that lead to a broad spectrum of cellular responses, it is not surprising that viruses of the *Chordopoxvirinae* subfamily have evolved to target different elements of the pathway. By inhibiting different processes in the NFκB signal transduction pathway of the host cell, ORFV successfully evades the host cell immune response.

In contrast to other poxviruses, most members of the *Chordopoxvirinae* encode several ARPs. Little is known about this family of proteins and ARPs are not commonly found in viruses. Ankyrin repeat proteins play a role in various biological processes (cell-cell signaling, cytoskeleton integrity, protein transport, and inflammatory response). ORFV genome termini contain 5 genes encoding ARP ORFV008 ORFV123, 126, 128, and 129. The ARP contain F-box like domains that are recognized by ubiquitin ligase complexes which allows them to target the proteomes of host cells.[68] By using ubiquitin-mediated degradation of a wide range of cellular proteins, ORFV ARPs can modulate various cellular responses to viral infection.[49,68]

Finally, ORFV gene 125 encodes a protein with anti-apoptotic activity. It acts as an inhibitor of bcl-2 and thus prevents apoptosis of viral infected cells. This is a novel mechanism of immune evasion by parapoxviruses and orthologues have not been found in other viruses.[1,2,49]

## 9 | HOST IMMUNE RESPONSE

The interaction of ORFV with the immune system has been a subject of research for decades.[5] Although both cell-mediated and humoral immune responses have been demonstrated in sheep and humans, cell-mediated immunity plays the major role against ORFV.[1,2]

Antibodies do not seem to confer protective immunity to ORFV although the IgG2 isotype might be important in defense against ORFV. IgG2 is not transported in milk of ruminants which might explain why colostral antibodies are not protective in lambs and kids.[1-3]

Immunohistochemical studies on sheep skin following primary infection and reinfection showed that primary cells accumulating in the lesion were neutrophils, T cells, B cells, and DCs.[1-3] CD4+ cells are found in the papillary dermis whereas CD8+ cells are seen throughout the dermis and B cells are restricted to the reticular dermis.[1,2] Following infection, polymorphonuclear cells are the first to migrate to the site, followed by accumulation of CD4, CD8 T cells, and B cells in the dermis. CD4 T cells are the predominant T cells in the skin in both primary and reinfection.[1-3] CD4+ cells and DCs accumulate faster and to a greater extent than other cell types in both primary and reinfection.[1,2] The immune response to ORFV is primarily a Th1 response.[1,2] Inactivated ORFV also leads to a dominant Th1-type immune response suggesting that the viral particle itself elicits the immune response.[5] The dynamics of the immune response have also been studied by canulation studies of afferent and efferent lymphatic ducts of draining lymph nodes in sheep.[1,4] Following reinfection, there is a biphasic lymph cell response involving CD4+ T cells, CD8+ T cells, B cells, and DCs with CD4 T cells being the most numerous lymphocytes in afferent lymph. The production of GM-CSF, IL 1, IL-8, IL-2, and IFN-γ in lymph cells cultured from afferent lymph follows the same biphasic pattern. There is a rapid production of the inflammatory cytokine IL-1b and the chemokine IL-8 after reinfection and a delayed production of GM-CSF, IL-2, and IFN-γ.[1,4]

Studies with cyclosporin A treated sheep and lymphocyte depletion studies revealed that CD4 T cells and IFN-γ and to a lesser extent CD8 T cells were important for clearance of ORFV. The cell-depletion study suggested a small role of antibody in protection against ORFV and as such the role of CD4+ T cells as helper cells for antibody could also be essential.[1,4]

## 10 | IMMUNE EVASION

Immune evasion can be defined as the strategy used by pathogenic organisms to evade a host's immune response to maximize their chance of being transmitted to a fresh host. An important aspect of ORFV is that it can repeatedly infect a previously exposed host despite a prominent inflammatory host immune response as described above.[1,2] However, the size and severity of the lesions usually diminish with each episode. The ability of orf to evade the immune system has not been explained so far. Proposed mechanisms for immune evasion include suppression of inflammation and the adaptive responses through vIL-10, inhibition of interferon through OVIFNR, inhibition of the NF-κB signalling pathway (ORFV002, ORFV024, and ORFV121), inhibition of immune cell trafficking through CBP, inhibition of GM-CSF and IL-2 through GIF, and increasing cellular substrates for viral replication though VEGF-E (details provided above in Section 8). In addition, ORFV may directly interfere with antigen presentation and APCs and a structural protein of the virus induces the expression of CD95 leading to CD95-mediated apoptosis of antigen presenting monocytes and macrophages thus diminishing the primary T-cell response.[1,2,4,5]

## 11 | IMMUNE MODULATION: ORFV AS PARAMUNITY INDUCER

Immunomodulation refers to the alteration of the immune system or of an immune response by agents that activate or suppress its function. Paramunization with paramunity inducers, which are nonimmunizing biological products, is used to induce an optimal short-term, immediately effective, regulated, activated, antigen-nonspecific defense, or "paramunity".[69] Orf virus paramunity inducer has been produced from purified, attenuated ORFV that was inactivated by g-radiation or chemical means and which mainly contains virus components that are mostly derived from the viral envelope.[69] Attenuation (through several hundred passages in cell cultures) and inactivation of poxviruses results in a decrease in their immunizing properties whereas their paramunizing activities increase. Though not completely clear, the immunomodulating activity of inactivated ORFV is probably related to virus particles.[5]

Indeed, inactivated ORFV induces antiviral activity in different animal models of acute and chronic viral infections and the therapeutic potential of inactivated ORFV has been recognized in multiple relevant human diseases such as chronic viral diseases, liver fibrosis, or diverse forms of cancer.[5] For example, inactivated ORFV showed antifibrotic activity and inhibited human HBV and HCV replication in preclinical models.[70] Orf virus was also found to have antitumor properties: in syngenic mouse, B16-F10 melanoma model treated with intraperitoneal injections of inactivated ORFV resulted in 72% inhibition of tumor growth.[71] Inactivated ORFV strongly impacts cytokine secretion in both mice and human immune cells.[5,72] Inactivated ORFV generates an auto-regulatory cytokine response that starts initially with the upregulation of Th1 cytokines such as IFN-γ, IL-12, IL-18, the inflammatory cytokines TNF-α, IL-8 and IL-6, as well anti-inflammatory cytokines such as IL-10 and IL-1RA, followed by subsequent induction of Th2-related cytokines IL-4 and IL-10 which attenuates the immune response. The Th2 response limits the inflammatory response and prevents tissue destruction and helps reach a physiological balance. IFN-γ is a key mediator of the observed antiviral effect, because applying neutralizing antibodies of IFN-γ abolished this activity.[5]

Studies on bone marrow-derived DCs and human peripheral immune cells in vitro indicated that APCs play a major role.[5,72] ORFV particles are opsonised by complement 3b (C3b), leading to intracellular uptake with ensuing cellular signaling mediated via CD14 and toll-like receptors.[5,72] This, in turn, induces the release of various cytokines by human monocytes/macrophages. IL-12 and IL-18 induce IFN-γ expression by pre-activated T or NK-cells.[5,72] The induction of anti-inflammatory cytokines like IL-4, IL-10, and IL-1RA is likely to avoid an exaggerated inflammatory response.[5,72]

In-vitro studies using mouse bone marrow-derived DCs indicated that inactivated ORFV is able to activate DCs including plasmacytoid DCs (pDCs) which play a significant role in antiviral resistance.[5] Both plasmacytoid and conventional DCs produced IFN-α/β after stimulation with inactivated ORFV, and MHC-II, MHC-I, and CD86 were

expressed mainly on conventional DCs.[5] We have also identified pDCs in the lesions taken from humans following natural infection.[44] However, MxA expression was diminished in orf lesions which is indicative of decreased type I IFNs, of which pDCs are the major source. This has recently been elucidated by showing that the ORFV inhibits IFN stimulated gene expression by modulating the Janus kinase/signal transducer and activation of transcription signalling pathway.[73]

## 12 | VACCINE

In humans, there is no efficient vaccine to prevent ORFV. Individuals vaccinated with smallpox are not protected against orf. In sheep and goats, there is no universally licensed ORFV vaccine.[2] Orf vaccines are produced on the basis of virus propagated in vivo (from scab material) or in culture.[2,4] Although vaccines can limit the severity and duration of the disease, they do not generate solid immunity that is long lasting (4-6 months) and hence vaccinated animals can be re-infected repeatedly.[2,4]

Orf virus has a potential use as a recombinant vaccine vector that expresses foreign genes in permissive and nonpermissive hosts.[2] Orf virus as a vector has several advantages: lesions are limited to the skin and there is no systemic dissemination. Moreover, frequent immunization does not lead to effective neutralizing antibodies against the ORFV particle.[2]

## 13 | CONCLUSIONS

Latest progress in ORFV research provides a new understanding of the novel and essential mechanisms of virus pathogenesis, the evolution of its virulence proteins, its value as an important immunomodulator, and new insight into the nature of skin immunity. While the function of multiple genes involved in replication, immune subversion and angiogenesis has been identified, the function of other ORFV genes is still unknown. Further research shall help uncover the role of these genes and provide us with additional evolutionary insight into this exceptional virus. Additional research into the underlying processes of ORFV immune evasion may also help to develop new therapeutic interventions and efficient vaccines that would reduce orf outbreaks and enable us to respond to them in a quick and efficient manner. Most promising is the potential use of the novel immunomodulatory properties of inactivated ORFV in human medicine as an antitumor agent and an enhancer of resolution of certain viral infections.

### CONFLICT OF INTEREST

The authors have no competing interest.

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