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ORIGINAL ARTICLE

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Molluscum Contagiosum Virus Evasion of Immune Surveillance: A Review

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ABSTRACT

Background: Molluscum contagiosum (MC) is an acute infection caused by the molluscum contagiosum virus (MCV) with a worldwide incidence of approximately 8,000 cases per 100,000 individuals annually. Greater than 90% of MC cases occur in the pediatric population, and affected adults are more likely to be younger or immunocompromised. MC has minimal inflammation initially; however, a strong inflammatory response can occur during resolution of the infection, termed the beginning of the end (BOTE). MC infections may last months to years, and it is hypothesized that persistent infections may be due to suppression of immunity by MCV proteins, thus affecting MC's clinical progression.

Objective: We reviewed the current proposed mechanisms of MCV immune evasion and discuss potential therapeutic options for MC treatment.

Methods: A literature search was conducted using electronic databases (Pubmed, Google Scholar, Medline).

Results: We compiled 18 original research articles and identified 11 proteins produced by MCV that are postulated to participate in evasion of host immunity through various molecular pathways. These proteins and/or their downstream pathways may be influenced by MC treatments in phase 3 development, including berdazimer gel 10.3% and VP-102 cantharidin, 0.7%.

Conclusion: MCV is distinctive in evading immune surveillance by inhibiting or dampening several immune pathways via the production of viral proteins. The result is decreasing local inflammatory response which contributes to the prolonged survival of MCV in the epidermis. Persistent MC can be a nuisance for some patients and treatment may be desired. Currently, no treatment has been approved by the US Food and Drug Administration (FDA). Two approaches in the pipeline may affect the immune avoidance mechanisms; nevertheless, their exact mechanisms between the potential therapeutics and viral proteins remain enigmatic.

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INTRODUCTION

Molluscum contagiosum is a highly contagious, benign neoplastic, infectious dermatologic disease.[1] It is commonly seen in children, sexually active young adults, and immunosuppressed patients.[2,3]

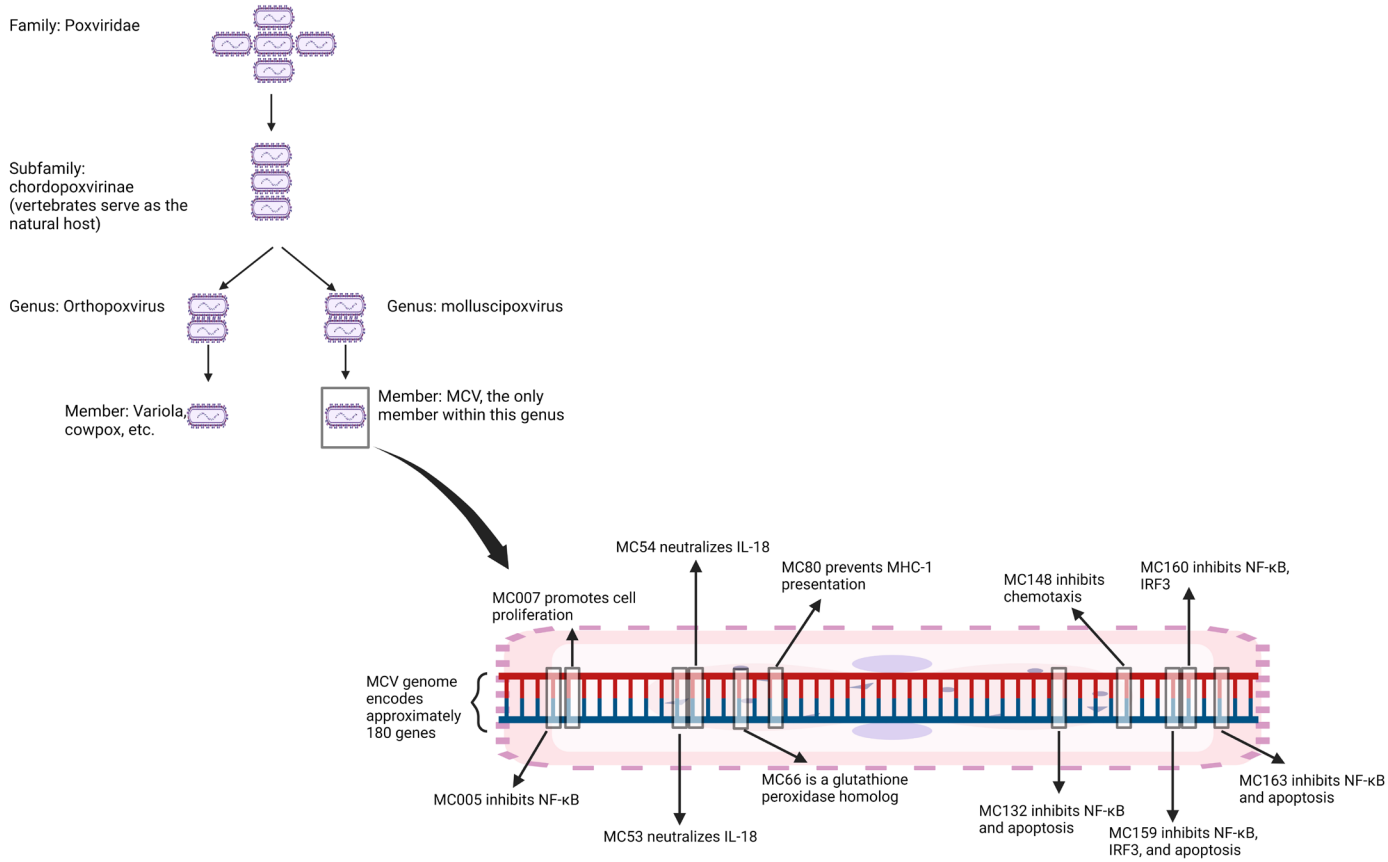
MC is a member of the poxviridae family which includes variola (smallpox), monkeypox, and cowpox. Unlike monkeypox and cowpox (caused by vaccinia virus (VV)), which infect both animals and humans, MCV and VV are unique in that humans are the only host and reservoir for MCV (Figure 1).[2]

The prevalence of active infection in children vs adults occurs at a 9:1 ratio. This is due to a variety of factors, such as childhood exposure to high-risk environments like daycares, the higher prevalence of atopic dermatitis in childhood, and increased immunity in adults due to prior exposure. Immunity to MCV varies significantly in different geographic regions; but adults tend to have a higher seroprevalence of anti-MCV antibodies than children, ranging from 6% to 30%.[4] This higher seroprevalence may confer increased immunity and help explain the lower incidence of MC in adults. However, the Centers for Disease Control and Prevention (CDC) stated that recovery from MCV does not prevent future infection.[5]

MC is caused by a double stranded DNA virus with a brick-shaped morphology known as the molluscum contagiosum virus (MCV).[1,6] There are 4 subtypes of MCV: MCV-1, MCV-2, MCV-3, and MVC-4. MCV-1 is most frequently encountered overall (75-96%) and it is also commonly seen in pediatric patients. MCV-2 is typically identified in individuals with human immunodeficiency virus (HIV).[1,2] MCV-3 and MCV-4 infections are extremely rare and predominate in Asia and Australia.[3]

The characteristic presentation of MC is smooth, skin-colored papules with central umbilication.[6] In pediatric age groups, MC lesions are usually found on the trunk, face, and extremities, and rarely on the palms and soles. For

FIGURE 1. Poxviridae family and molluscum contagiosum virus protein functions.[8,49] "Created with BioRender.com".



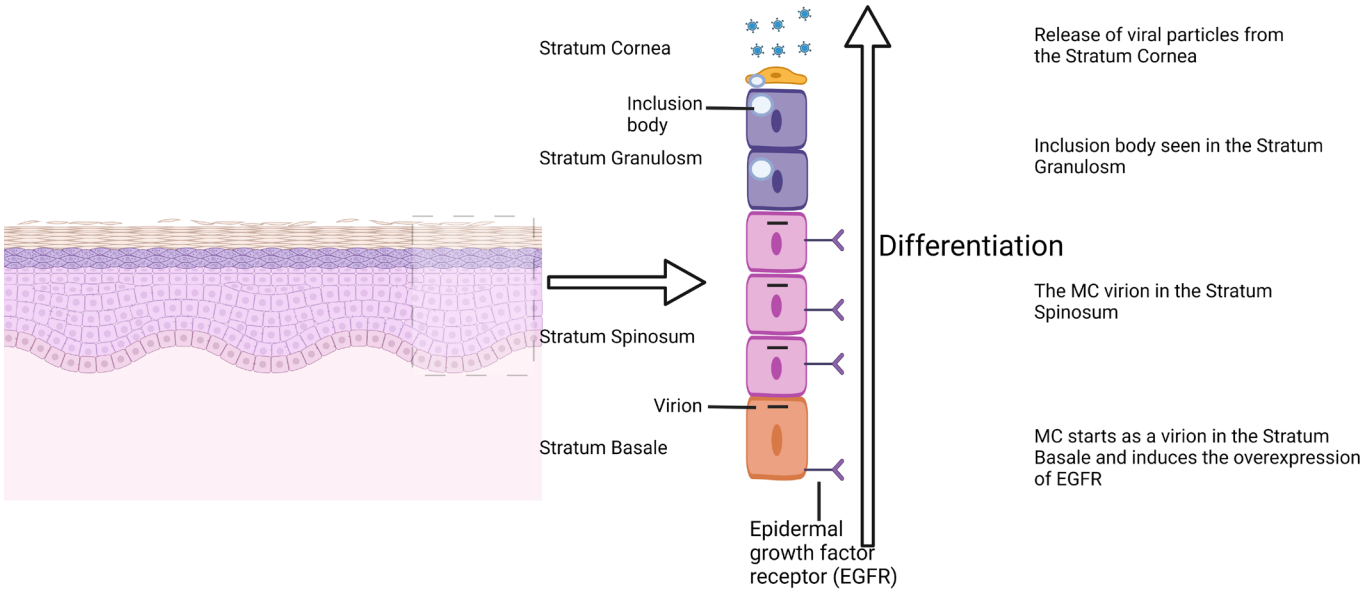
immunosuppressed patients, MC lesions are classically located on the genitalia, abdomen, and thighs, and the lesions can be more widespread.[17] Diagnosis is made via clinical course.[1] The methods of transmitting MCV include autoinoculation, direct contact, and fomites.[6] Individuals with skin barrier dysfunction, such as in atopic dermatitis, are more susceptible to MC.[7] The infection and replication of MC is confined to the epidermal layer and does not permeate the basement membrane.[7,8] Consequently, MCV doesn't disseminate systemically, nor does it stay dormant in human body to inflict latent infection.5 This might be the main reason why recurrence is rarely observed clinically. Microscopically, MC is confirmed by the presence of molluscum bodies or Henderson-Paterson bodies – eosinophilic inclusion bodies in the cytoplasm of the epidermal cells.[2] During infection, the virion can be identified in the stratum basale.[7] As the keratinocytes differentiate from the stratum basale to the stratum corneum, the virus replicates and forms an inclusion body within the cytoplasm. The virus is released from the stratum corneum layer (Figure 2).[7] MCV upregulates epidermal growth factor receptors (EGFR) and augments cell division.[7]

There are no FDA-approved treatments for MC; however, cryotherapy, curettage, pulsed dye laser, cantharidin, benzoyl peroxide, salicylic acid, interferon alpha, and imiquimod have been used.[6] Currently, there is no vaccine for MCV, although there are anecdotal reports of MCV being treated successfully with intralesional measles, mumps, and rubella (MMR) vaccine.[9]

Lending to the failure of effective MCV therapeutics is the fact that MCV does not grow in cell culture or outside a human host, thus most of research of MC must be conducted by immunohistochemical analysis of infected tissues or through surrogate investigations of the VV.[1,8,10,11] Even though MCV is serologically distinct from VV, the sequencing of MCV has shown several homologues of the VV for signaling proteins, an RNA polymerase subunit, and structural proteins.[12] Hence, VV can be used as a surrogate to study MC proteins in vivo.[11]

The genome of the MCV type I was decoded in 1997.[10] The genetics of MCV consists of 180 proteins with 105 traceable to other orthopoxvirus counterparts.[13] However, MCV encodes 50 distinct proteins not found in other poxviruses including major histocompatibility complex class I (MHC-I), chemokine, and glutathione peroxidase homologs.[14,15] The duration of symptoms is variable in the literature. Molluscum lesions are usually present for weeks to months but may persist up

FIGURE 2. Lifecycle of molluscum contagiosum virus.[7] "Created with BioRender.com".



to 5 years; this variation of duration depends on the host immunity as lesions tend to be more widespread, larger in size, found in atypical areas, and refractory to treatment in immunosuppressed individuals.[3,8,16–18,19]

Variola virus promotes a robust immune response, potentially causing multi-systemic reactions with a high risk of mortality. Cowpox virus triggers focal cutaneous changes without systemic involvement.[20] MCV survives within human skin for a prolonged period without significant immune reaction despite high viral load.[13] Partial explanation is that MCV forms a lesion surrounded by keratinocytes that is undetectable by the immune system.[13] Additionally, it is hypothesized that MCV evolved complex mechanisms to evade host immune monitoring, thus allowing lesions to persist. We conducted a comprehensive literature review in an effort to better understand the mechanisms underlying MC persistence and immune evasion characteristics of the MCV. This information is essential to understanding the pathogenesis of MC and sparking future investigation of effective treatment options.

MATERIALS AND METHODS

A literature search was conducted at Pubmed, Google Scholar, and Medline, with the keywords of "molluscum contagiosum", "immune evasion", "NF-κB", "chemokines", "viral proteins", and "apoptosis".

RESULTS

Searching "molluscum contagiosum" and various combinations of the search terms above yielded approximately 350 results. Four reviewers participated in the review process and agreed that only articles published in English after 1995 and proposed detailed descriptions of viral proteins and mechanisms of immune invasion were considered. We included 18 original research articles and 4 review articles.

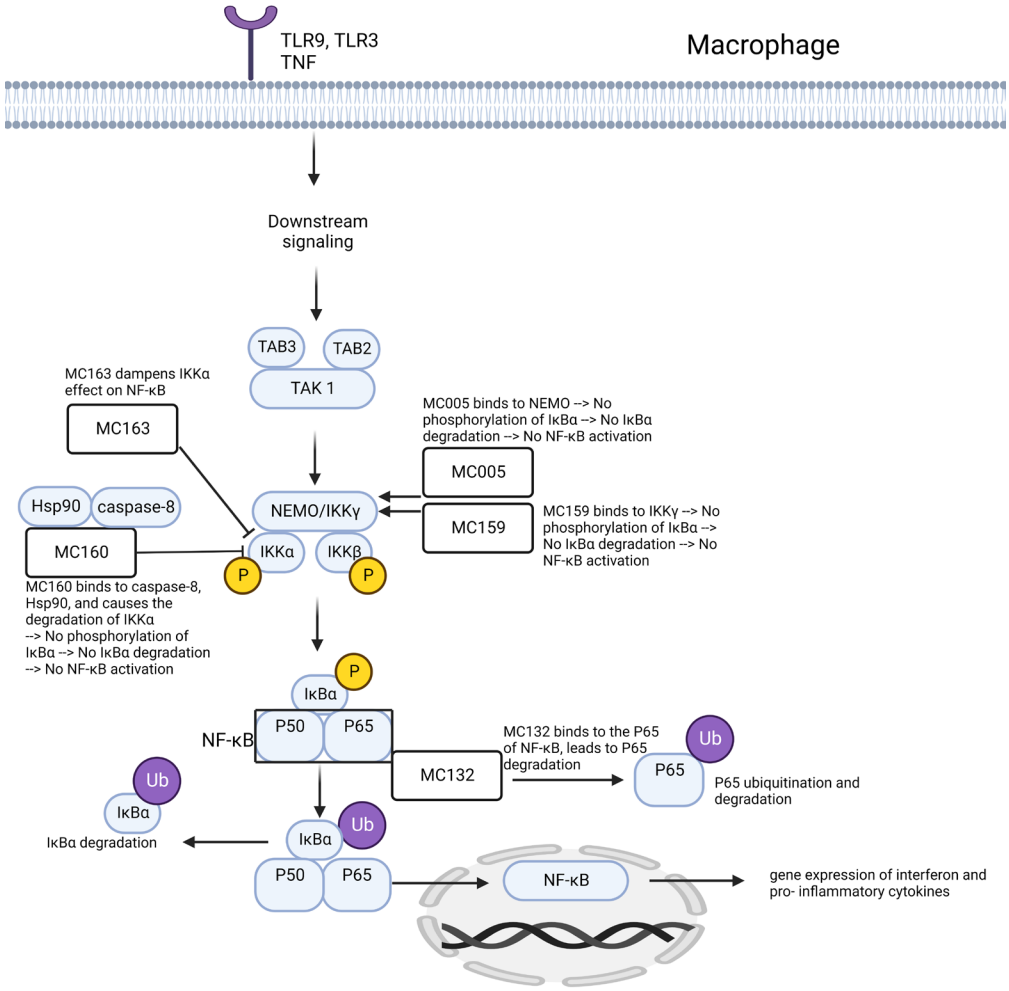
TLR/TNF-induced NF-κB Activation

The human innate and adaptive immune responses coordinate and communicate via various activating and suppressing cytokines and pathways.[21] One of the most studied pathways is the nuclear factor-κB (NF-κB) pathway in macrophages. Innate immune cells, such as macrophages, express a plethora of pattern recognition receptor (PRR) that sense the pathogen-associated molecular patterns (PAMPs) which are the essential components of microorganisms.[22] Toll like receptors (TLRs) are a distinct class of PRRs present on macrophages and dendritic cells. TLRs encompass 10 variants (TLR-1 through TLR-10) in the human immune system.[23]

MCV is usually detected by TLR-3 and TLR-9.[24] A downstream effect of PRR is the activation of the NF-κB pathway. IκBβ-NF-κB resides in the cytoplasm as an inactive complex; upon phosphorylation induced, proteasome mediated degradation of IκBβ, the NF-κB pathway becomes activated with NF-κB, migrating to the nucleus where it serves as a transcription factor. There, it upregulates the production of inflammatory cytokines and chemokines (Figure 3).[22] Tissue necrosis factor (TNF) is also able to trigger NF-κB activation via a similar pathway.[25] Activation of NF-κB is required for virus detection, antiviral signaling, inflammation, and clearance of viral infections.[26]

Although the understanding of MCV is incomplete, several MC proteins have been identified as pivotal host immunomodulators. MC005 protein inhibits NF-κB by binding

FIGURE 3. Effects of molluscum contagiosum proteins on TLR/TNF induced NF-κB activation. MC005 and MC132 inhibit nuclear factor-κB (NF-κB) at the level of NEMO and P65, respectively.13,22,50 MC159 and MC160 prevent the degradation of IKK complex, which again inhibits the activation of NF-κB.28,29 Decreased activation of NF-κB results in an attenuated inflammatory response, and therefore, a lower immune response, allowing MCV to evade detection. "Created with BioRender.com".

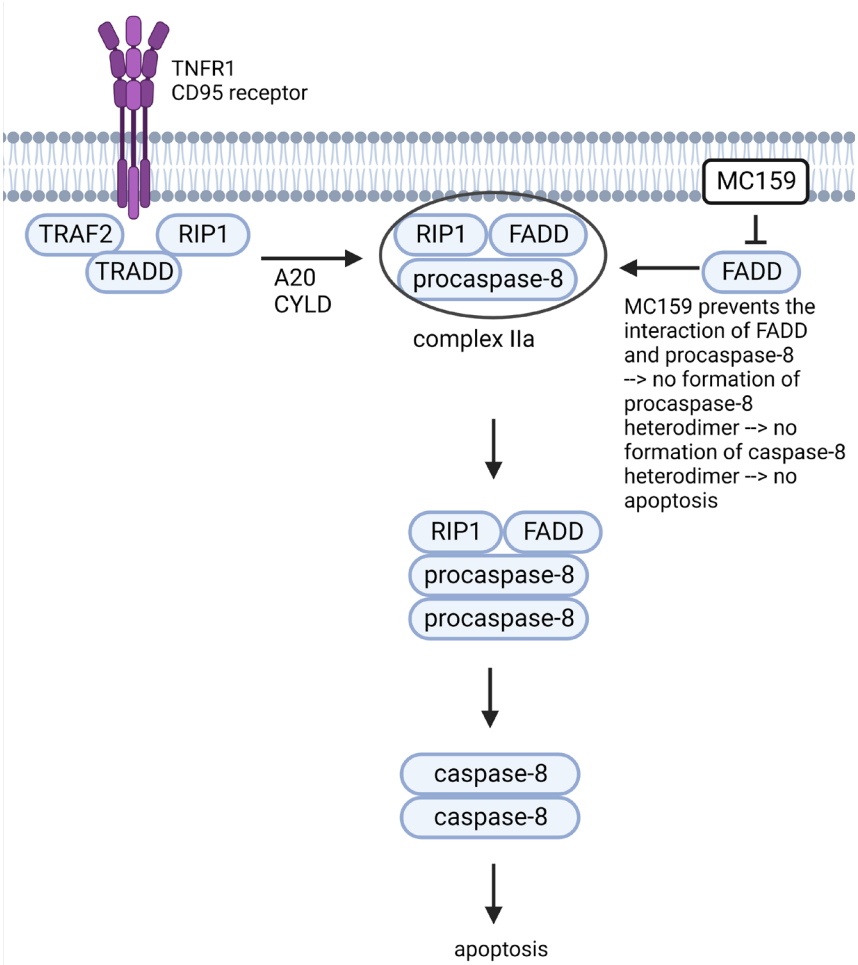


to NF-kappa-B essential modulator (NEMO) and has not been identified in other poxviruses (Figure 3).[13] Interestingly, the molecular structure of MC005 differs slightly in MCV-1 and MCV-2. In MCV-1, it is 89-amino-acids (9-kDa), whereas, it is shorter in MCV-2. It is believed this characteristic may differentiate MCV-1 and MCV-2 in infected populations.[13]

A novel mechanism for MCV to inhibit human innate immunity and potentially contribute to persistent MC lesions is the effect of MC132 on the NF-κB pathway. NF-κB is inhibited by the MC132 protein which recruits Cullin-5/Elongin B/Elongin C complex, and binds directly to P65, an NF-κB subunit, thus inducing ubiquitination and subsequent degradation of P65 (Figure 3).[26]

MC159 and MC160 prevent the degradation of IκBβ, albeit by a distinct mechanism of action (Figure 3). It is suggested that MC159 inhibits degradation of IκBβ whereas MC160 inhibits degradation of IκBβ, a stronger inhibitor of NF-κB than IκBβ.[27] MC160 inhibits the acute NF-κB pathway during the early stage of infection and MC159 inhibits chronic effects of NF-κB during the chronic infection.[28–30] MC159 also inhibits CD-95 and TNF induced apoptosis via binding to the Fas-associated death domain (FADD) (Figure 4).[8,31] Lastly, MC159 and MC160 have been shown to inhibit interferon regulatory factor (IRF) 3 via direct and indirect inhibition, respectively. IRF3 is an essential transcription factor for the production of interferon (IFN) β, a molecule with potent antiviral effects by inhibiting viral multiplication.[32] Decreased levels of IFN-β contribute to the low immune response in MC. A recent study showed that inserting MC159 and MC160 genes into VV increased infectivity of the

FIGURE 4. Alternate molluscum contagiosum protein pathways. MC159 inhibits TNF and CD95 triggered apoptosis pathways.[8,31] Decreased apoptosis contributes to the formation of neoplastic papules seen in MC and enables the virus to continue to replicate. "Created with BioRender.com".



virus.[11,33] This implicates MC159 and MC160 have potential for applications in medicine and research.

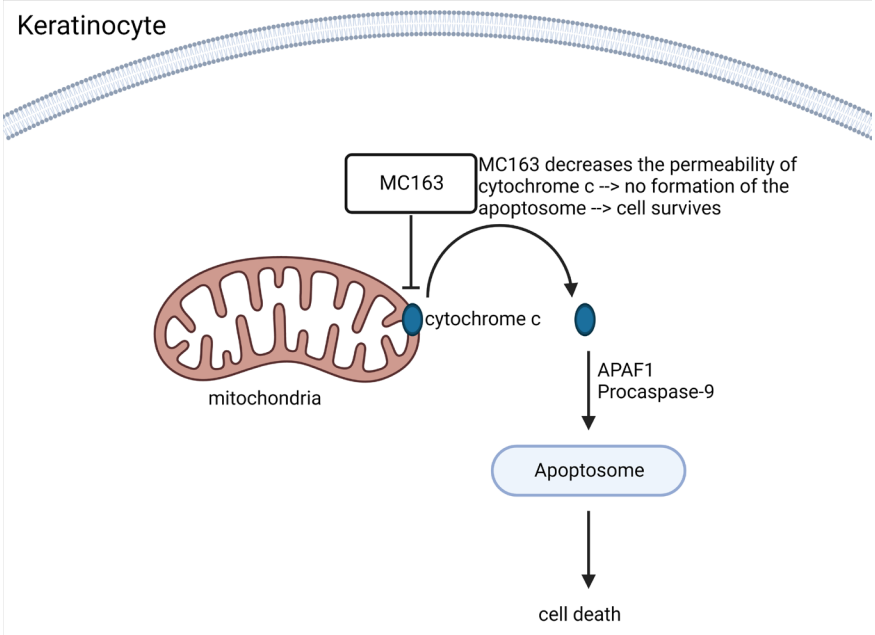
MC163 is another protein that aids in inhibition of the complex NF-κB pathway by inhibiting TNF-α from activating NF-κB, as well as dampening inhibitory-κB kinase (IKK) α and β activation of NF-κB.[34,35] However, MC163 also has a unique mechanism of inhibition of apoptosis. During regular apoptosis, mitochondria normally have increased permeability to cytochrome c that helps in signaling controlled cell death. MC163 binds to the mitochondrial membrane and decreases the permeability of cytochrome c, thus inhibiting apoptosis (Figure 5).[36]

Alternate MC Protein Pathways

Besides NF-κB pathway, MC proteins also act on other molecules within the realm of immune activation. Interleukin -18 (IL-18), a potent inducer of T-helper 1 (Th-1) response and Interferon-γ (IFN-γ), is imperative in defending against viral invasion. IL-18 is also known as IFN-γ inducing factor and may be responsible for conditions that involve autoimmunity. Studies have demonstrated that the IL-18 binding protein (IL-18-bp) suppresses the overactive immune system and protects the host.[37] Studies have also shown that MC53 and MC54 in MCV bind to IL-18 and function as an IL-18-bp to neutralize the IL-18.[38,39]

Along with herpesviruses, poxviruses are the only viruses to code for human chemokine and chemokine-binding protein homologs.[10] One such protein encoded by MC, MC148, posits as an inhibitor for chemotaxis of immune cells. The exact mechanism is still elusive. Two models were proposed. One suggests that MC148 binds to chemokines and prevents them from reaching their receptor. The other model suggests that MC148 binds to chemokine receptors directly. MC148 competes with macrophage inflammatory protein (MIP)-1 binding to chemokine receptors 2B and 8 (CCR2B and CCR8).[10] CCR2B is an adhesion molecule utilized by various viral infections, including

FIGURE 5. MC163 decreases the permeability of cytochrome c from the mitochondria of keratinocytes, thus inhibiting programmed cell death.[36,51] This keeps keratinocytes alive for longer and allows MCV to utilize the cellular machinery to continue to replicate. "Created with BioRender.com".



some variants of HIV-1, so MC148 may inhibit the entry of other viruses into human cells. CCR8 receptor antagonism broadly inhibits monocyte function. Taken together, MC148 prevents the recruitment of monocytes, lymphocytes, and neutrophils, and ultimately, the local inflammatory response.[8,40,41] MC148 is expressed early in the life cycle of MCV to aid in immune evasion before subsequent processes take over.

MC infection induces benign growth of keratinocytes, thus viral proteins can control and promote cellular proliferation. MC007 inhibits the retinoblastoma/E2 factor (RB/E2F) complex.[42] Normally, RB is an important regulator for cellular apoptosis and E2F is a family of transcriptional factors.[43] MC007 may contribute to the tumor-like lesions of MCV. In mammals, the selenium-dependent glutathione peroxidase is a protector for programmed cell death.[44,45] MCV also acquires a glutathione peroxidase homolog, MC66, which prevents cell death induced by oxidative stress or ultraviolet radiation.[46,47]

The MC80 protein plays a role in decreasing immune surveillance by inhibiting the acquired immune response. MHC-I plays a crucial role in cellular recognition of viral particles to aid in mourning an immune response. MC80 shares a moderate sequence similarity of MHC-I and binds with components of the MHC-I peptide-loading complex and targets it for destruction in the membrane of the endoplasmic reticulum. This action prevents the viral specific MHC-I-peptide complex from reaching the cell surface to be recognized by immune cells.[48]

DISCUSSION

MC lesions may persist several months to years, perhaps due in part to the immune evasion characteristics unique to the MCV. MC proteins 005 and 132, 159, 160, and 163 subvert host immunity by inhibiting the NF-κB pathway via several effector mechanisms and pathways. Cell death pathways are modulated by MC 007, 66, and 163. MC 148 inhibits immune cell chemotaxis, and MC80 inhibits MHC-1 peptide complex from reaching the cell surface to be recognized by immune cells. Thus, various MC proteins work synergistically through a variety of pathways to evade host immunity, making individual MC proteins a desirable therapeutic target.

Although MC causes persistent infection by evading immune surveillance, a therapeutic goal would be to initiate immune recognition to promote MC resolution by targeting one or more of the MC proteins. MC lesion redness and inflammation, known as the BOTE sign, is a predictor of resolution of MC and indicative of host immunity activation. However, the mechanism by which BOTE inflammation leads to MC resolution is unknown.[19]

Though MC is often a self-limiting condition, treatment may thwart associated complications, such as infection, contagiosity, or aesthetic concerns.[3] There is currently no FDA-approved treatment for MC; however, 2 therapeutics are in phase 3 development.

A pivotal phase 3 study of topical berdazimer sodium, a topical nitric oxide (NO) releasing medication has shown promising results for the treatment of MC.[52] The role of NO has been well established in boosting cutaneous innate immunity and providing a wide range of antimicrobial effects.[53] Berdazimer sodium suppresses DNA proliferation of human papillomavirus (HPV) 18 in vitro, and 12% topical application was suggested to be effective and safe for treatment of genital warts.[54] Berdazimer sodium also reduces the activity of various T cell mediated immune pathways in atopic dermatitis patients, suggesting its immune regulatory effect.[16,55]

A phase 3 vehicle-controlled clinical trial with over 800 MC patients demonstrated favorable efficacy and safety of berdazimer gel, 10.3% (Novan, Inc, Durham, North Carolina, USA).[52]The participants have to be at least 6 months old, healthy individuals with 3 to 70 clinically evidence MC lesions. At the end of the study, MC lesion counts were significantly reduced in the berdazimer group vs vehicle after 12 weeks of once daily application. Treatment emergent adverse events (TEAEs) were mainly mild to moderate in severity, with local pain and erythema being the most commonly reported.[52] It is postulated that berdazimer sodium promotes BOTE and, ultimately, resolution of MC lesions.[16]

Another MC treatment option in the pipeline is a shelf-stable formulation of topical cantharidin, 0.7%.[56] Cantharidin is an inhibitor of phosphodiesterase derived from blister beetles and has been used for decades as an off-label treatment option.[3,57] The exact mechanism is still unclear, although it is postulated to involve desmosome destruction and skin shedding.[57]

VP-102 (Verrica Pharmaceuticals Inc, West Chester, PA, USA) is a drug-device designed to deliver precise concentrations of cantharidin to MC lesions. Two randomized trials evaluated VP-102 among 528 patients who were at least 2 years old with clinical diagnosis of MC. Treatment was administered once every 3 weeks until complete lesion clearance was achieved. A maximum of 4 treatment sessions were allowed. VP-102 achieved higher complete clearance rate than vehicle after one treatment as well as at the end of study.[57] Concerning the safety profile, majority of the reported adverse events were mild to moderate, mostly consisting of local skin changes. The most commonly encountered TEAEs were vesicles, pain, pruritus, erythema, and scab on the application site.[57]

Resolution of MC is often characterized by clinical signs of inflammation and redness, or BOTE. BOTE may present with asymptomatic or pruritic scale, erythema, and hemorrhagic crusting that can be mistaken as bacterial superinfection.[16] The mechanism of BOTE has yet to be elucidated.[19] Recognition and diagnosis of BOTE as a herald of the natural resolution of MC could prevent unwarranted additional treatment with corticosteroids or antibiotics.[16,19] The emerging virological and immunological evidence of immune evasion mechanisms unique to MCV may serve as the basis for understanding BOTE in the resolution of infection with MC.

In summary, this review highlights the unique ability of MCV to evade the host immune system through a variety of molecular pathways. How or if these pathways impact the duration or severity of MC infections is unknown. Elucidating the precise mechanisms by which MCV and potential MC treatments affect immune-evasion pathways will remain challenging in the absence of MC cell or animal models.

Limitations

Until the FDA approves a MC treatment, the standard of care will likely continue to be "watch and wait." It is anticipated that if MC treatments are FDA-approved, data regarding immunocompromised or skin of color MC will remain scarce but recent therapeutic advances toward treating MC hold promise.[56]

CONCLUSION

MCV is a unique poxvirus, replicating only in the human epidermis. It results in acute cutaneous infection and resolves when immune system pathways engage and recognize the virus. The infected patient has no risk of systemic viral infection. The unique immune evasion proteins produced by MCV may lend to persistent infections lasting months to years. BOTE, an indicator of host immune activation, is the natural resolution signal; potential therapeutic strategies may influence the initiation of BOTE. However, the impact of current and/or potential therapeutic MC treatments and their ability to promote BOTE via modulation of MC immune evasion proteins and pathways remains elusive and challenging due to research model limitations. Nevertheless, recent studies show 2 topically applied agents in phase 3 development clear MC lesions better than vehicles. Topical berdazimer gel 10.3% may promote BOTE via release of NO, whereas cantharidin is thought to enhance shedding of infected keratinocytes. Recent advances in the understanding and characterization of MC evasion proteins may lead to targeted therapeutics to treat this common and bothersome infectious disease.

DISCLOSURES

HH, CS, and FY have no conflicts of interest to disclose. BB serves as a Novan- consultant.

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