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Review

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# Modulation of NF-κB transcription factor activation by Molluscum contagiosum virus proteins*

## Modulacja aktywacji czynnika transkrypcyjnego NF-κB przez białka wirusa mięczaka zakaźnego

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## Summary

*Molluscum contagiosum virus* is a human and animal dermatotropic pathogen, which causes a severe disease in immunocompromised individuals. MCV belongs to the *Poxviridae* family whose members exert immunomodulatory effects on the host antiviral response. Poxviruses interfere with cell signaling pathways that lead to the activation of nuclear factor κB, a pleiotropic transcription factor which is crucial for regulation of the immune response, the cell cycle and apoptosis. In resting cells, NF-κB is present in the cytoplasm, where it is associated with inhibitor κB. Upon stimulation by activators, such as proinflammatory cytokines and bacterial or viral products, the inhibitory protein undergoes phosphorylation and proteasomal degradation. NF-κB, in turn, translocates to the nucleus, where it regulates the transcription of various genes that are essential for processes mentioned above. Since poxviruses replicate exclusively in the cell cytoplasm, NF-κB became a good target for poxviral immunomodulation. MCV encodes various proteins which interfere with the signaling pathways that lead to the activation of NF-κB. Ligand inhibitor encoded by MCV, MC54, binds interleukin-18 and inhibits interferon-γ production. Other MCV proteins, MC159 and MC160, belong to intracellular inhibitors of NF-κB and are members of viral FLICE-inhibitory proteins (vFLIPs). MC159 protein encoded by MCV was shown to inhibit apoptosis of virus-infected cells. Such interactions serve immune evasion and are responsible for the persistence of MCV.

**Key words:** **molluscum contagiosum virus • transcription factor • NF-κB**

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**Abbreviations:** **CCL2/MCP-1** – C-C chemokine ligand 2/monocyte chemoattractant protein-1; **c-FLIP** – cellular FLIP; **DD** – death domain; **DED** – death effector domain; **DISC** – death-inducing signaling complex; **FADD** – Fas-associated death domain; **FLICE** – Fas-associated death domain-like IL-1β converting enzyme; **hIL-18** – human IL-18; **hIL-18BP** – human IL-18BP; **Hsp90** – heat shock protein 90; **IFN-γ** – interferon-γ; **IKK** – IκB kinase; **IL-18** – interleukin-18; **IL-18BP** – IL-18 binding protein; **IL-1β** – interleukin-1β; **IκB** – inhibitor κB; **LPS** – lipopolysaccharide; **MCV** – molluscum contagiosum virus; **MHCI** – major histocompatibility complex class I; **NEMO** – NF-κB essential modulator; **NF-κB** – nuclear factor κB; **NIK** – NF-κB-inducing kinase; **NK** – natural killer; **ORF** – open reading frame; **PKR** – protein kinase R; **RIP1** – receptor-interacting protein 1; **TLR4** – Toll-like receptor 4; **TNFR-1** – TNF receptor 1; **TNF-α** – tumor necrosis factor-α; **TRADD** – TNFR1-associated death domain protein; **TRAF2** – TNF receptor-associated factor 2; **vFLIP** – viral FLICE inhibitory protein.

## Introduction

*Molluscum contagiosum virus* (MCV) is a dermatotropic pathogen that causes a skin disorder which is common in children and sexually active adults. The disease, called molluscum contagiosum, persists in individuals with a weakened immune system and is known for its coexistence with AIDS. MCV spreads by both direct and indirect skin contact as well as during sexual activity [22,31]. Although MCV infection is not sexually transmitted *per se*, it is regarded as a marker for sexually transmitted diseases [11,37]. Moreover, cases of vertical transmission of molluscum infections have been reported [19]. MCV also infects animals, such as chickens, pigeons, sparrows, horses and dogs. The lesions which the virus evokes in humans and animals can be seen as small and waxy papules occurring mainly on the face and trunk, as well as in the oral cavity and genital region. They are small and discrete with central umbilication; however, in HIV-positive patients atypical large or nonumbilicated lesions can be observed [6,8,34].

There are at least three subtypes of MCV and two of them, MCV1 and MCV2, cause similar symptoms in humans [8, 18]. In healthy individuals, molluscum contagiosum is a self-limiting viral skin infection that can be resolved within months, whereas in patients with atopic dermatitis or AIDS and in other immunocompromised persons the disease is more severe and prolonged [16,39]. Furthermore, the disorder may cause complications, such as persistence and spread of lesions that can be recurrent. Additionally, it may be associated with secondary bacterial infections occurring in skin. The lesions can be removed surgically and various medications are used in order to eliminate warts. However, these methods may cause scarring or blistering [22]. Since treatments mentioned above rely on tissue destruction and result in infections and scarring, new therapeutic methods are being developed [20].

MCV is the only member of the *Molluscipoxvirus* genus of the *Poxviridae* family consisting of large dsDNA viruses, whose virions are brick-shaped or oval structures that can be seen under a light microscope. Poxviruses contain more than 130 genes in their genomes whose central part includes conserved genes, which are mostly responsible for virus replication. In the terminal regions, in turn, unique genes involved in interactions between virus and host are present [4,7,18,40]. The non-conserved genes within the poxvirus genome are responsible for host range, pathogenesis and immunomodulation [33]. Although MCV lacks most of the immunomodulatory proteins that are encoded by other members of the *Poxviridae* family, its 190 kbp genome contains genes that are likely to encode 163 proteins, such as MC80 (major histocompatibility complex class I (MHCI) homolog), MC148 (chemokine antagonist), and MC66 (glutathione peroxidase homolog), which can be linked with coexistence with the host [23,35].

MCV replicates *in vivo* in human keratinocytes and is not able to replicate *in vitro* in cell or tissue cultures; however, it may induce a typical cytopathogenic effect in human primary fibroblast MRC5 and HEPM cells, but cannot be obtained in permanent human or simian-derived cell lines [3]. MCV replicates in the stratum spinosum, where virus-specific changes, such as viroplasm and virus particles, can be detected. Molluscum bodies formed by virions and non-membrane vacuoles are likely to expand due to the migration of the infected cell into the granular layer. The central core of the lesion, rich in virus, is formed by a disintegrated large inclusion body produced by the infected cell on the gate to the horny layer. The basement membrane, which separates the dermis from the epidermal basal layer, remains intact throughout infection, which may explain little or no inflammatory response and reinfection of the host [4].

## NF-κB as a target for viral immunomodulatory proteins

Poxviruses are well known for their immunomodulatory abilities that enable them to complete their replication cycle and spread within cells effectively. In order to control the host antiviral response, MCV and other members of the *Poxviridae* family exploit different strategies that are based on inhibition of host regulatory proteins, such as nuclear factor κB (NF-κB) transcription factor. The poxvirus replication cycle occurs in the cytoplasm only; thus NF-κB, which is activated within the cytosol, is a good target for various poxvirus inhibitors: ligand inhibitors, intracellular inhibitors of NF-κB, ankyrin repeat and PYRIN domain NF-κB inhibitors [21].

The mammalian NF-κB transcription factor family consists of five proteins – c-Rel, RelA (p65), RelB, NF-κB1 (p50) and NF-κB2 (p52) – which form homo- and heterodimers that are able to activate or inhibit transcription. The most abun-

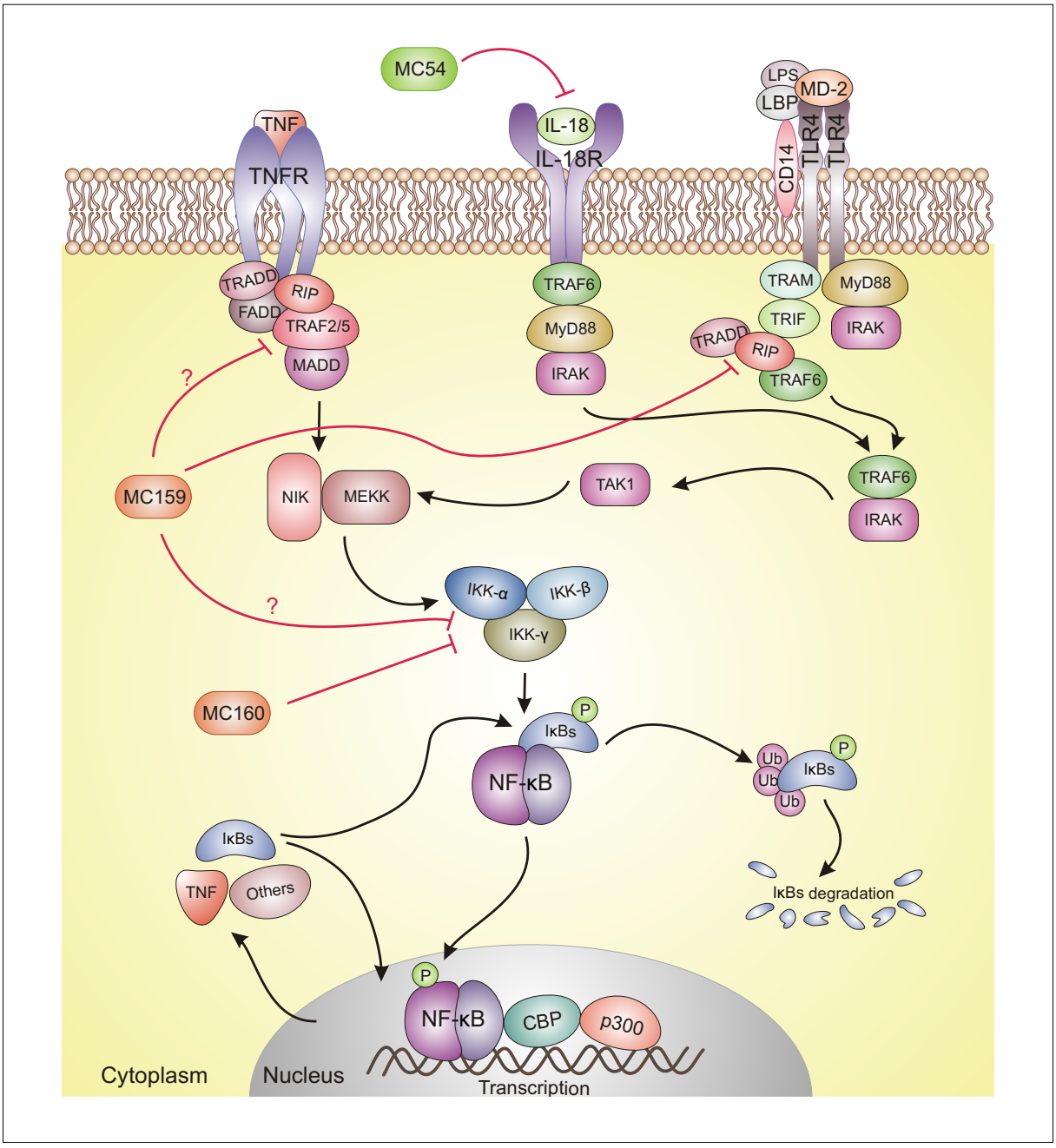


**Fig. 1.** NF-κB signaling pathways and their inhibition by MCV proteins. TNF, IL-18 and lipopolysaccharide (LPS) ligate to TNFR, IL-18R and TLR4, respectively. Ligation-induced activation of various receptors promote the recruitment of receptor proximal adaptor proteins and signaling to the IKK complex, composed of two catalytic subunits (IKKα and IKKβ). Signaling to IKK proceeds through TRAF/RIP complexes, generally in conjunction with TAK1, leading to canonical NF-κB signaling. Signaling to IKK may also proceed through TRAFs and NIK leading to the noncanonical NF-κB pathway. Activation of IKK results in IκB phosphorylation and degradation in the canonical pathway and consequently, nuclear translocation of phosphorylated NF-κB dimers. Those NF-κB dimers bind to DNA and regulate gene expression. Inhibition of NF-κB signaling pathways by viral MC54, MC159 and MC160 is indicated by red blunt arrows

dant form of NF-κB that can be found in mammalian cells is p65/p50 heterodimer associated with its inhibitor, called inhibitor κB (IκB) [30]. The IκB proteins IκBα, IκBβ, and IκBε, or p100 and p105 precursor proteins, maintain NF-κB dimers in the cytoplasm in an inactive state [12]. NF-κB activation is triggered by proinflammatory cytokines, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), viral or bacterial products, and other stimuli that induce IκB phosphorylation by IκB kinase (IKK) complex consisting of IKKα (IKK1) and IKKβ (IKK2) catalytic subunits and IKKγ (NF-κB essential modulator; NEMO) regulatory subunit. Upon activation, NF-κB dimer translocates to the nucleus and regulates transcription of target genes, which are crucial for the cell cycle, apoptosis, inflammatory response and

other processes. Therefore, NF-κB is commonly regarded as a pleiotropic factor [41]. Because many NF-κB target genes, including cytokines and growth factors, influence the host cell cycle, viruses have evolved strategies of interference with NF-κB activation. Additionally, NF-κB activation can be altered in order to evade the mechanisms that kill infected cells and limit viral replication. On the other hand, viruses are able to trigger apoptosis to increase virus spread [13]. Many studies have shown the modulation of apoptosis by MCV via MC159 protein belonging to intracellular inhibitors of NF-κB. Another intracellular NF-κB inhibitor encoded by MCV, MC160, interferes with its activation induced by TNF-α. Interleukin-18 (IL-18)-mediated signaling and interferon-γ (IFN-γ) production, in turn, are altered by an MCV-encoded ligand inhibitor, MC54 protein. MC54 binds IL-18, and was therefore named IL-18 binding protein (IL-18BP) [21].

## Modulation of IL-18 and TNF-α signaling by MCV

Expression of the molecules that are able to bind cytokines and block host cell pathways is a well-known immunomodulatory strategy developed by viruses. Poxviral cytokine binding proteins, such as IL-18BPs, belong to the group of ligand inhibitors that intercept the interactions between cellular ligands and receptors and block the signaling pathways that may activate NF-κB [21]. IL-18, the target for IL-18BPs, is a potent antiviral agent that induces IFN-γ production from T cells and macrophages, activates natural killer (NK) cells, and regulates Th1 and Th2 responses [25]. IL-18 also activates the NF-κB pathway, which is significant for regulation of the expression of the IFN-γ gene by IL-18. The IL-18-induced NF-κB activation pathway became a target for poxviruses, including MCV (Fig. 1) [14].

Initially, IL-18BPs encoded by MCV, MC51, MC53 and MC54 were characterized. The open reading frames (ORFs) of MC51, MC53 and MC54 share significant similarities in amino acid sequences and the proteins were included in one family. The MC51-53-54 family homologs were found among human and mouse proteins. Moreover, both of the ORFs of MC54 homologs showed 70% amino acid identity as well as the presence of a signal peptide and four N-glycosylation sites [43].

Further studies of Xiang and Moss [44] revealed that recombinant proteins MC53, MC54 and their two homologs encoded in human and mouse genomes are able to bind both human and murine IL-18 with high affinity. The binding of IL-18 resulted in the inhibition of IFN-γ production; moreover, the blockage of IFN-γ production by recombinant proteins in a dose-dependent manner was observed. However, additional research by Xiang and Moss (2001) showed that MC54 and human IL-18BP (hIL-18BP) have similar hIL-18 binding sites, although their overall sequence identity is low. In contrast, two remaining proteins, MC51 and MC53, lack three or more of the critical amino acids, do not bind IL-18, and may interact with other undefined ligands [1,42]. Other studies demonstrated the presence of an additional C-terminal fragment of MC54 that can be cleaved by cellular furin. The C-terminal tail of the full-length protein was found to be able to bind to glycosaminoglycans. Since glycosaminoglycans are present on the cell surface and in the extracellular matrix, the ability of MC54 to bind to the cell surface was also confirmed. This property may serve inactivation of IL-18 by the full-length MC54 in proximity of the site of infection whereas the short form is likely to inactivate IL-18 at distal locations [45]. The activity of MC54 is suspected to be linked to the lack of an inflammatory reaction around the skin lesions [23,36].

The ability of MC159 and MC160 proteins to interfere with TNF-dependent NF-κB signaling pathways was also studied (Fig. 1). MC159 is also able to inhibit late events of NF-κB activation that are triggered by TNF-α since it prevents IκBβ, but not IκBα degradation and inhibits the expression of NF-κB-regulated late genes, TNF-α and C-C chemokine ligand 2 (CCL2), following TNF-α stimulation. Mutant MC159 does not bind TNF receptor-associated factor 2 (TRAF2), an adaptor protein, which is recruited by TNF receptor 1 (TNFR-1) upon its activation by TNF-α, leading to the activation of NF-κB. Thus, the NF-κB activation mediated by TNF cannot be inhibited. The production of proinflammatory molecules and immunoattractant factors is suppressed in infected cells probably because MC159 prevents them from responding to the TNF-α proinflammatory stimulus [24]. However, recent studies have revealed that MC159 is able to elevate an innate inflammatory reaction. Transgenic mice expressing MC159 showed an increase in monocyte chemoattractant protein-1 (MCP-1) expression. Moreover, MC159 was found to facilitate NF-κB activation induced by TNF-α and Toll-like receptor 4 (TLR4) belonging to innate immune signaling receptors. MC159 was also shown to regulate NF-κB induction via receptor-interacting protein 1 (RIP1) adaptor protein. Like TNFR1-associated death domain protein (TRADD), RIP1 is a crucial mediator in NF-κB activation by TNFR-1 and TLR4 [5]. Recent data suggest the inhibition of NF-κB activation by the interactions between MC159 and IKK proteins, but not between MC159 and TRAF2 [32].

It was shown that MC160 is able to reduce TNF-α-mediated NF-κB activation that involves receptor-interacting proteins, TRAF2 and NF-κB-inducing kinase (NIK), as well as MyD88 adaptor protein. MC160 interferes with IKK activation and reduces its phosphorylation *in vitro*. It may also disrupt IKK1 and IKK2 interactions and its expression was found to correlate with decreased level of IKK1, but not IKK2 [27].

## The role of MCV in apoptosis modulation

MCV ability to modulate apoptosis has been widely discussed in recent years. There are two MCV-encoded proteins, MC159 and MC160, belonging to intracellular NF-κB inhibitors, which interfere with cellular pathways that lead to apoptosis [21] (Fig. 2). Both of them belong to the viral Fas-associated death domain-like IL-1β converting enzyme (FLICE) inhibitory protein (vFLIP) family of viral inhibitors, which are also present in γ-herpesviruses and interfere with death receptor-signaled apoptosis [15,29].

In cells, counterparts of vFLIPs called cellular FLIPs (c-FLIPs) can be found. There are three isoforms of c-FLIPs, which

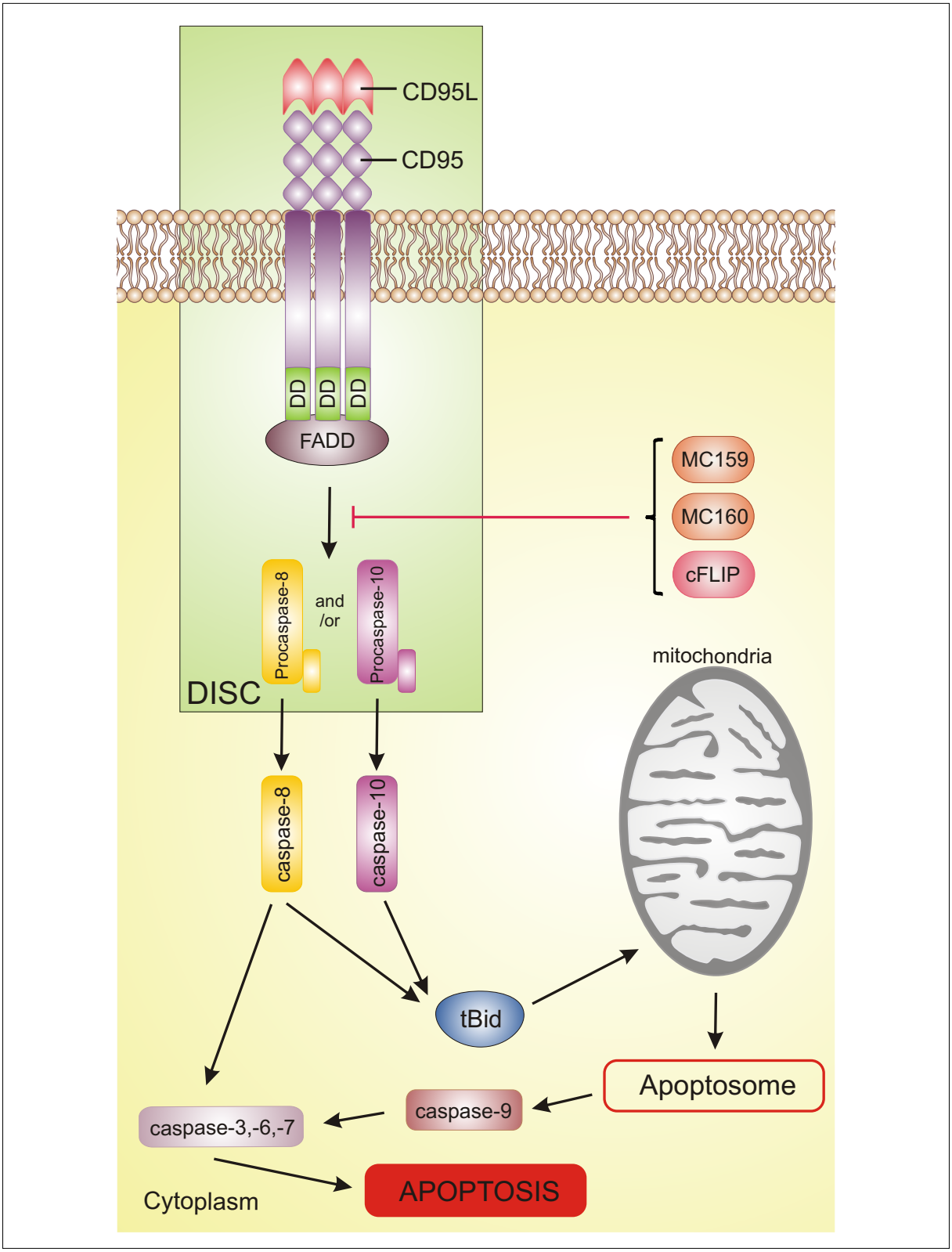


**Fig. 2.** Inhibition of apoptosis by viral MC159 and MC160 (vFLIP). Upon ligation of CD95 (Fas) the adaptor protein FADD is recruited to the Fas death domain (DD). FADD next interacts with procaspase-8 and/or procaspase-10 to form DISC. Activated caspase-8 directly activates executioner caspases (caspase-3, -6 and -7). Moreover, activated caspase-8 and caspase-10 cleave Bid and translocation of truncated Bid (tBid) to the mitochondria promotes apoptosome assembly in the cytosol. Subsequently, active caspase-9 propagates activation of effector caspases that leads to apoptosis. Viral MC159 and MC160 function as cFLIP and interact with FADD what prevents death-receptor-induced apoptosis

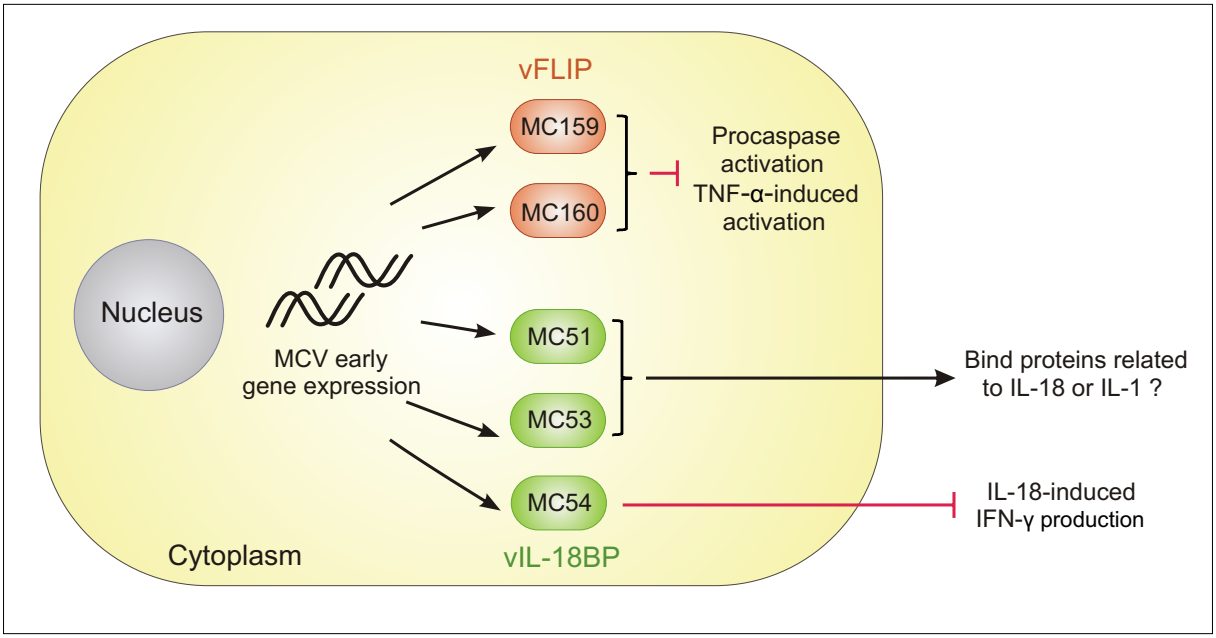


**Fig. 3.** MCV inhibitors of NF-κB. The role of MCV proteins: vFLIP (orange) and vIL-18BP (green) is presented. MC159 and MC160 (vFLIP) inhibits procaspase activation and TNF-α-induced activation. MC51 and MC53 probably bind proteins related to IL-18 and IL-1 whereas MC54 inhibits IL-18-induced production of IFN-γ

contain two tandem death effector domains (DEDs) at the N-terminal end. DEDs are necessary for the recruitment of the death-inducing signaling complex (DISC), consisting of oligomerized receptors, adaptor molecule Fas-associated death domain (FADD), procaspase-8 (FLICE) and -10, and c-FLIP. The formation of DISC results in the activation of procaspase-8 and the subsequent cell death. DEDs play a role in the interactions between FADD, procaspase-8, -10 and c-FLIP, whereas the receptor-FADD interaction is mediated by the death domains (DDs) [reviewed in 28].

vFLIPs, which contain two DEDs, inhibit the recruitment of FLICE by CD95 (Fas), the death receptor, via the interaction of their DEDs with FADD. This interaction protects against death-receptor-induced apoptosis and may serve viral persistence and oncogenesis [38].

It was also shown that DED domains of MC159 protect against death-receptor-induced apoptosis, and studies on the crystal structure of MC159 revealed that the interaction between the surface of MC159 containing the conserved charge triad, Fas and FADD appears to compete with self-association of FADD and disrupts the oligomerization of DISC by interaction with FADD molecules [2,46]. Other studies showed that two tandem DEDs of MC159 strictly associate with each other due to the presence of a conserved hydrophobic interface that can also be found in the tandem DEDs, the components of v-FLIPs, c-FLIPs, caspase-8 and caspase-10. Moreover, significant homology of the packing interactions between the two domains of MC159 and between the Apaf-1 CARD domains and caspase-9 was found [17].

As mentioned above, MCV influences both apoptosis and the activation of NF-κB transcription factor. MC159 prevents apoptosis via inhibition of protein kinase R (PKR), a viral dsRNA-activated serine/threonine kinase that mediates apoptosis in virus-infected cells, as well as in other non-infected cells. PKR-induced apoptosis relies on the FADD/caspase-8 and the mitochondrial caspase-9 pathways. Upon dsRNA treatment, which triggers PKR-mediated apoptosis, NF-κB transcription factor undergoes activation via the induction of IKK [9]. MC159 was found to inhibit PKR-induced NF-κB activation and other downstream events stimulated by PKR without counteracting the antiviral action of PKR in response to poxvirus infection [10].

MC160, which induces IKK1 degradation, is stabilized by cellular heat shock protein 90 (Hsp90), which is required for IKK1 stabilization as well. In MC160-expressing cells, IKK1 levels can be restored by Hsp90 overexpression, which may reverse IKK1 degradation. Thus, MC160 is seemingly able to compete with Hsp90. It was also shown that the N-terminal portion of MC160 contains DED, which interacts with procaspase-8. Such interaction prevents procaspase-8-induced NF-κB activation [26].

## Conclusions

Multiple strategies of MCV interference with the activation of NF-κB transcription factor, a key regulator of antiviral response, are related to the presence of viral proteins, which display anti-inflammatory properties and are linked to the persistence of MCV infections (Fig. 3). The interactions between NF-κB and MCV immunomodulatory proteins are crucial for viral immune evasion and should be studied extensively in order to find a target for an effective anti-MCV therapy.

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