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LETTER TO THE EDITOR

Roles of neddylation against viral infections

Kun Han and Jiyan Zhang

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The ubiquitin-dependent proteasome pathway can be hijacked by certain viruses to maintain viral genome amplification. A key class of ubiquitin-E3s involved in this pathway is Cullin-RING ligases (CRLs), which are activated by an additional ubiquitin-like protein NEDD8.[1] The process by which the ubiquitin-like protein NEDD8 is conjugated to its target proteins is officially named 'neddylation'. Consequently, neddylation inhibition, through the use of the pharmacological inhibitor MLN4924, might prevent viral genome amplification.[2,3] Herpesviruses, adenovirus, and influenza virus are MLN4924 susceptible, whereas vaccinia virus and vesicular stomatitis virus are not.[2,3] Neddylation might also promote viral replication independent of CRLs.[4] For example, hepatitis B virus-encoded X protein can act as an NEDD8 substrate and its neddylation by E3 ligase HDM2 enhances its stability and function in viral replication and hepatocarcinogenesis.[4] On the other hand, blockade of neddylation prevents the degradation of host restriction factors and thereby restores the restriction of human immunodeficiency virus by APOBEC3G and SAMHD1,[5,6] lentivirus by SAMHD1,[7] or Rift Valley fever virus by protein kinase R.[8] Both CRLs-dependent and CRLs-independent mechanisms have been suggested in this regard.[9]

Department of Molecular Immunology, Institute of Basic Medical Sciences, 27 Taiping Road, Beijing 100850, China
Correspondence: Dr J Zhang, PhD, MD, Department of Molecular Immunology, Institute of Basic Medical Sciences, 27 Taiping Road, Beijing, PA 100850, China
E-mail: zhangjy@nic.bmi.ac.cn
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As for the innate immune response, the involvement of neddylation was suggested as early as the year 2006.[10] The transcription of type I interferon genes is controlled by nuclear factor-κB (NF-κB) and interferon regulatory factor (IRF) family members including IRF3. Many viruses execute immune-evasive activities by targeting the type I interferon signaling pathway. RNA viruses such as Sendi virus (SeV), vesicular stomatitis virus, and rotavirus induce the degradation of IRF3.[10–12] However, a herpesvirus family member, herpes simplex virus type I (HSV-1), a DNA virus, has no such effect.[13] Even though the degradation of IRF3 upon infection with rotavirus has been demonstrated to be independent of CRLs,[11,12] a Cullin-based ubiquitin ligase pathway was reported to be involved in SeV-induced IRF3 degradation in 2006.[10] Therefore, neddylation promotes IRF3 degradation upon SeV infection.[10] Theoretically, neddylation should promote IRF3-mediated transcription of type I interferon genes.

In addition to IRF family members, NF-κB also plays a key role in mediating the transcription of type I interferon genes. It is demonstrated that neddylation contributes to NF-κB activity by promoting the ubiquitination and subsequent degradation of IκB proteins since the ubiquitination of IκB proteins is carried out by certain CRLs members. Therefore, we speculated that neddylation should promote the HSV-1-induced production of type I interferons, and this hypothesis was confirmed in our study, which was recently published in *Cellular & Molecular Immunology* (Figure 1).[14] With primary macrophages deficient of the catalytic subunit of neddylation E1, we have provided the first evidence that neddylation indeed plays a role in type I interferon production. Interestingly, neddylation blockade only delays but does not completely abrogate HSV-1-induced p65 nuclear translocation.[14] Consequently, the early phase type I interferon production in HSV-1 infection is much more impaired than the late phase.[14] Recently, the notion that the host also exploits the neddylation pathway to fight against virus infection has been supported by additional evidence. Zhang T *et al.* reported that the polymerase basic protein 2 of influenza A virus can be covalently modified by NEDD8, which reduces its stability and blocks the replication of influenza A virus.[15]

Another group later reported that NEDD8 knockdown showed no effect on type I interferon production triggered by lipopolysaccharide (LPS), poly (I:C), or SeV.[16] Since poly (I:C) and SeV induce IRF3 degradation, whereas HSV-1 does not,[10] perhaps the interplay between the NF-κB pathway and IRF pathway determines the outcome. Intriguingly, MLN4924 significantly inhibited type I interferon production triggered by LPS, poly (I:C), or SeV,[16] which has been

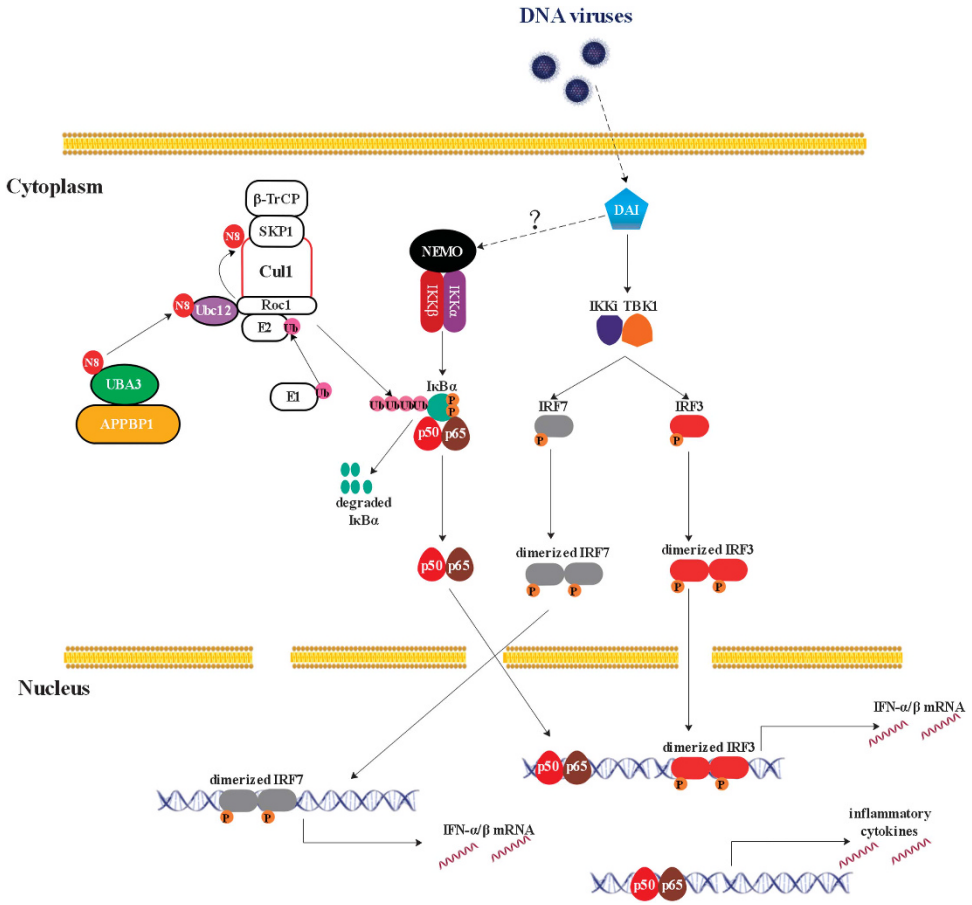

Figure 1 Neddylation contributes to DNA virus-induced production of type I interferons. The transcription of type I interferon genes is controlled by nuclear factor-κB (NF-κB) and interferon regulatory factor (IRF) family members IRF3 and IRF7. DNA virus-induced NF-κB activation depends on the ubiquitination and subsequent degradation of IκB proteins. The ubiquitination of IκB proteins such as IκBα is carried out by a certain member of the Cullin-RING ligases (CRLs), that is, SKP1/Cullin-1/F-box protein β-TrCP/Roc1 complex. As CRLs are activated by the covalent conjugation of an additional ubiquitin-like protein NEDD8 to Cullins, neddylation promotes DNA virus-induced NF-κB activation and thereby promotes DNA virus-induced production of type I interferons.

attributed by the authors to its off-target effects. However, the potential off-target effects of small interfering RNAs and the relatively low efficiency of small RNA interference cannot be excluded. Future studies are required to address this issue.

Together, these 10 years of studies suggest that neddylation might exert distinct roles in the infection of different viruses. Targeting the neddylation pathway against virus infection, though hopeful under certain circumstances, should be cast with caution and requires extensive studies to clarify how neddylation works in each step of virus infection.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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