# OASs in Defense of Mycobacterial Infection: Angels or Demons?

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## Abstract

The interaction between pattern-recognition receptors (PRRs) and pathogen-associated molecular patterns (PAMPs) induces type I interferon (IFN) responses. IFNs stimulates hundreds of genes to exert its biological effects. OASs are the members of IFN-stimulate genes (ISGs). Among them, OAS1 activates RNase L to cleave RNA viruses genome, OAS2 activates downstream immune signaling pathways of IFNs, OAS3 induces RNase L to cut the genome of RNA virus and activate IFN I response to enhance the immune effect, and OASL inhibits the survival of RNA viruses by activating RIG-I signaling pathway but promotes the reproduction of DNA viruses by inhibiting the cGAS signaling pathway. However, the role of OASs in mycobacterial infection remains incomprehensible. In this review, we summarized the latest literature regarding the roles of OASs in mycobacterial infection.

## Introduction

*Mycobacterium tuberculosis* (*M. tuberculosis*) is an obligate intracellular pathogen, which is capable of maintaining long-term persistence in host by modulating its innate and adaptive immune response (Toledo Pinto et al., 2018). The mechanisms by which host immune response restricts *M. tuberculosis* replication and transmission are still unknown. *M. tuberculosis* invades and induces large amounts of cytokines secretion by macrophage such as interferon (IFN), IL-1β and TNFα (Leisching et al., 2017b). Although type II IFN has been proved to restrict the proliferation and persistence of *M. tuberculosis*, secretion of type I IFN by host cells in turn benefits its intracellular survival and replication (Ahmed et al., 2016; Leisching et al., 2017b). IFN-stimulating genes (ISGs) are involved in the host's immune responses against bacterial infection such as *M. tuberculosis* (Leisching et al., 2017b). Thus, understanding the role of IFN

signaling pathway is critical to elucidate the pathogenesis of *M. tuberculosis*. 2'-5'-oligoadenylate synthetases (OASs) is IFN-inducible proteins, consist of OAS1, OAS2, OAS3 and 2'-5'-oligoadenylate synthetases-like (OASL) (Hornung et al., 2014). OASs are associated with the secretion of type I IFN and plays completely different immune regulatory role during viral and bacterial infection (Ghosh et al., 2019). Herein, we aim to demonstrate a landscape of OASs regulating mechanisms during infection, which may further clarify the role of OASs in mycobacterial infection.

**Roles of OASs in controlling virus infection**
OAS1, 2, 3 but not OASL have synthetase activity and function in host's defense against viral infection (Zhu et al., 2015). OAS1 recognizes viral double-stranded RNA (dsRNA) by a 3'-single-stranded pyrimidine (3'-ssPy) motif and stimulates the oligomerization of ATP into 2',5'-linked oligoadenylates (2,5A). 2,5A binds to ribonuclease L (RNase L) to cleave RNA resulting in attenuated proliferation of virus (Carey et al., 2019; Sasaki et al., 2002; Vachon et al., 2015). OAS2 inhibits the replication of RNA viruses by enhancing type I IFN activated downstream immune responses (Mengmeng et al., 2017; Sheng et al., 2016). When RNAs of ZIKA virus are recognized by RIG-I and melanoma differentiation-associated gene 5 (MDA5), inducement of type I IFN activates Jak/STAT signaling pathway leading to ISGs transcription to play antiviral and immune regulatory roles (Liao et al., 2020). Moreover, studies have shown that when NOD2 binds to OAS2, the activity of RNase L is enhanced (Dugan et al., 2009). During RNA virus infection, OAS3 induces RNase L to cleave intracellular RNAs, which activates RIG-I and MDA5 *via* downstream signal adaptor Mitochondrial Antiviral Signaling Protein (MAVS) to enhance type I IFN response and inhibits RNA virus replication (Diner et al., 2013; Li et al., 2016; Yoneyama et al., 2004).

OASs are also involved in regulating diverse cellular functions such as the inducement of apoptosis, enhancement of IFN-α and IFN-β signaling responses, immune cell receptor modulation and autophagy (Leisching et al., 2018). In the absence of viral nucleic acids, the activation of OASs can restrict protein synthesis and induce cell apoptosis through RNase L cleavage and degradation of host mRNA (Kristiansen et al., 2010; Li et al., 2016). However, the effect of OAS1, 2, and 3 on DNA virus invasion is still unclear.

Human OASL is one of the ISG and its mouse ortholog is 2'-5'-oligoadenylate synthetases-like 1 (OASL1) and 2'-5'-oligoadenylate synthetases-like 2 (OASL2), sharing 70% and 48% amino acid sequence identity with human OASL respectively (Zhu et al., 2015). It has an N-terminal structural domain that is highly conserved among OAS family, but its C-terminal structure is completely different from other members (R, 1998). The C-terminal has a unique structure consists of two ubiquitin-like domains (UBL) and an OAS-like structure dsRNA binding domain that can bind to dsRNA (Diner et al., 2013). Studies on OASL2 are relatively rare, but there are more in-depth studies on OASL1. In the early stages of RNA virus infection (Figure 1), OASL1 capture viral RNAs by stress granules and promoted efficient RIG-I-like Receptor (RLR) signaling (Kang et al., 2018). In addition, OASL1 can rapidly transfer into antiviral stress granules (avSGs) and

interacted with MDA5, a cytosolic viral sensor, within avSGs promoting type I IFN signaling (Kang et al., 2018). While in the late stages of infection, OASL1 interacts with IRF7 transcripts to inhibit its translation and results in decreased IFN expression (Kang et al., 2018). The interaction between OASL and transcriptional repressor methyl CpG binding protein 1 (MBD1) was found to enhance RIG-I signaling (Manzanillo et al., 2012; Watson et al., 2012). OASL binds directly to RIG-I in the cytosol and mimics polyubiquitin, leading to enhancement of antiviral signaling (Zhu et al., 2014). In addition, OASL can directly activate IFN-β promoter, promoting the expression of IFN-β to eliminate RNA virus (Oshiumi et al., 2015; Wang et al., 2018).

During DNA virus infection, OASL initials distinct immune response correspondingly from different RNA virus infection. When invading into host cells (Figure 1), DNA viruses could release DNA which may activate the enzyme activity of nucleotide transferase cGAS (Zevini et al., 2017). The activated cGAS facilitates ATP and GTP for the synthesis of 2'3'-cGAMP, which activates endoplasmic reticulum membrane protein STING (Chen et al., 2016). STING can be activated by subsequently cyclic dinucleotides (CDNs), then STING escorts tank binding kinase 1 (TBK1) to endosomal compartments to associate with and activate IRF3 and IRF7 that resulted in autophagy and type I IFN responses to limit the proliferation and spread of DNA viruses (Barber, 2014; Chen et al., 2016). While, OASL binding to cGAS results in the inhibition of cGAMP production without affecting its DNA-binding abilities, the interaction between OASL and cGAS is independent of the presence of DNA (Ghosh et al., 2019). Briefly, DNA viruses could induce an OASL-mediated type I interferon inhibitory effect by blocking cGAS-STING-TBK1 signaling pathway for its replication (Liu et al., 2017).

**Roles of OASs in controlling mycobacterial infection**
OASs are involved in defense against viral infection, but its function during *M. tuberculosis* infection remains elusive. Interestingly, the upregulation of OAS1, OAS2, and OAS3 expression was observed in both active and latent tuberculosis (Leisching et al., 2019). During active tuberculosis, OAS1 is the top up-regulated gene and its polymorphisms are associated with tuberculosis (Berry et al., 2010; Wu et al., 2018). When interferes the expression of OAS1, the number of viable intracellular *M. tuberculosis* significantly increased, and the expression of TNF-α and IL-1β decreased significantly relative to control (Berry et al., 2010; Kristiansen et al., 2010; Leisching et al., 2019). In addition, OAS1 expression was further detected in peripheral blood leukocytes from leprosy patients (Rego et al., 2018). OAS1 is induced and released to sera during *M. leprae* and *M. tuberculosis* infection (Rego et al., 2018). OAS2 expression is enhanced significantly during *M. tuberculosis* invasion (Mvubu et al., 2016). Similarly, when interferes the expression of OAS2 or OAS3, the number of viable intracellular *M. tuberculosis* significantly increased. The secretion of TNF-α, Monocyte Chemoattractant Protein-1 (MCP-1), and IL-1β were reduced following OAS3 silencing in response to pathogenic mycobacteria infection, but only IL-1β levels were also decreased in the case of non-pathogenic mycobacterial infection (Leisching et al., 2019). Besides, the secretion of OAS1, 2, and IL-10 was not affected after OAS3 was

silenced (Leisching et al., 2019). All three OAS *i.e.* 1, 2, and 3 are antagonists of intracellular *M. tuberculosis* replication by regulating cytokine secretion (Leisching et al., 2019).
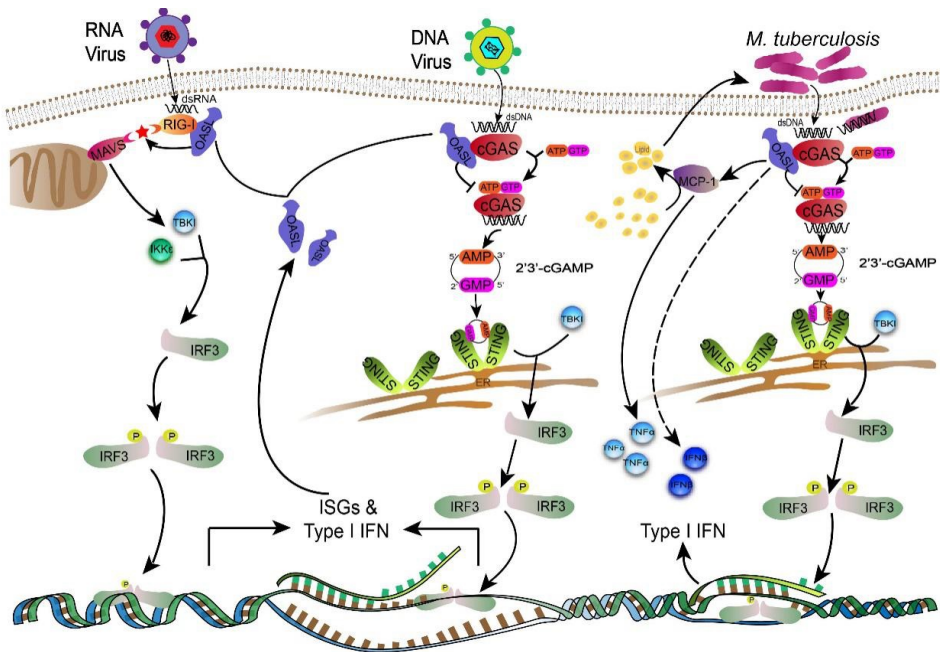


**Figure 1.** OASL initiates various anti-pathogen immune responses. When RNA virus enters the cell, the releasing of dsRNA activates RIG-I, OASL promotes RIG-I recognition of the virus, leads to the recognition of the virus, and activates the MAVS to promote the release of TBK1 and IKK enzymes. TBK1 initiates phosphorylation of IRF3, thus promotes the type 1 IFN response and finally lead to the clearance of the virus. When DNA virus enters the cell and releases dsDNA, which activates DNA sensor cGAS, catalyzes the synthesis of two phosphodiester bonds between GMP and AMP to produce 2'3'-cGAMP. Afterward, STING on the endoplasmic reticulum is activated by 2'3'-cGAMP, the activation of STING stimulates TBK1 and promoting type 1 IFN response and related ISGs. However, OASL inhibits cGAS's utilization of ATP and GTP, leading to virus proliferation and escape from being eliminated by the host immune response. During *M. tuberculosis* infection, the released dsDNA could be sensed by cGAS leading to autophagy induction and type I IFN production through cGAS-STING-TBK1 axis. Moreover, OASL directly activates MCP-1, and the activated MCP-1 will collect and aggregate lipid droplets in the cell, providing proper conditions for the survival of mycobacterium, thus promoting mycobacterium growth.

As the intracellular parasite, *M. tuberculosis* could escape into cytosol and the escaping *M. tuberculosis* is usually accompanied by the release of its DNA (Manzanillo et al., 2012). The extracellular mycobacterial DNA activates the DNA-dependent cytosolic surveillance pathway (Figure 1) (Manzanillo et al., 2012;

Watson et al., 2012). When *M. tuberculosis* escapes into cytosol, cGAS and mycobacterial DNA were co-located and aggregated (Wassermann et al., 2015). This interaction initiates cGAS utilization of GTP and ATP to produce cGAMP, which activates the STING-TBK1-IRF3 signaling axis and induces type I interferon production and autophagy activation (Barber, 2014; Majlessi and Brosch, 2015; Watson et al., 2015). cGAS is participating in intracellular *M. tuberculosis* role in balancing immune-protection and immune-pathogenesis (Majlessi and Brosch, 2015). It has been reported that OASL could bind to cGAS and inhibit IFN-β production (Ghosh et al., 2019). During infection of *M. tuberculosis*, OASL is highly induced in host cells (Etna et al., 2015; Leisching et al., 2017a; Mvubu et al., 2016; Zhang et al., 2019). When OASL expression is suppressed, the number of both pathogenic and non-pathogenic mycobacteria was found increased compared to control, indicating that OASL is able to inhibit mycobacterial intracellular replication (Leisching et al., 2020). In addition, TNF-α and IL-1β secretion were significantly reduced along with decreasing MCP-1 production when interfering with OASL expression in macrophages (Leisching et al., 2020; Nancy et al., 2014). Decreased MCP-1 and TNF-α in turn lead to unrestricted growth and dissemination of mycobacteria (Hasan et al., 2006). MCP-1 provides an environment conducive to mycobacterium survival by ingesting and collecting lipid droplets (Figure 1) (Chetan et al., 2015; Koul et al., 2004). OASL can be detected in serum from active tuberculosis patients and with higher expression levels relative to latent tuberculosis patients (Sambarey et al., 2017). And the expression level significantly decreased after six months of IFN treatment, indicating that type I interferon induced OASL involved in controlling the growth of *M. tuberculosis* (Sambarey et al., 2017).

Similarly, *M. leprae* infection induced a high level of OASL in primary human Schwann cells, macrophages, and monocytes. The expression of OASL could be induced by mycobacterial genomic DNA in a STING dependent manner and inhibits autophagy for bacterial survival (de Toledo-Pinto et al., 2016). When OASL expression is inhibited, the viability of *M. leprae* was decreased. OASL can also affect the release of MCP-1 in the *M. leprae* that MCP-1 expression increases after silencing OASL expression (Rego et al., 2018). However, the expression of OASL decreased after BCG treatment and in response, the expression of MCP-1 increased (Rego et al., 2018). The study indicated that OASL actually promotes the survival of *M. Leprae*. *M. leprae* usually alters the host immune system by boosting lipid metabolism or suppressing pro-inflammatory cytokines, which are very similar to the host colonization mechanisms of *M. tuberculosis* (Guerreiro et al., 2013; Toledo Pinto et al., 2018). *M. leprae* suppress host antimicrobial responses are achieved through type I IFN induced IL-10 response, by causing binding of IL-27 with IFN-β, which leads to the inducement of IL-10 production (Teles et al., 2015). IL-10 exerts profound inhibition on innate and adaptive immunity, contributing to the chronic progressive diseases with bacterial infections and enabling *M. leprae* to maintain long-term persistence in the host (Teles et al., 2015). This finding suggests that OASL may no longer be associated solely with antiviral responses, but also involved in the antimycobacterial responses and host defense mechanisms in the macrophage.

Altogether, it is possible that OASL manipulates mycobacterium replication in dissimilar ways.

## Conclusion

Type I IFN signaling pathway serves as a positive role in regulation of *M. tuberculosis* intracellular survival. So far, it is known that OAS1, 2, 3 inhibit the survival and replication of *M. tuberculosis* by regulating the secretion of cytokines. It is noteworthy that the antagonistic effect of OASL in the treatment of *M. tuberculosis* but promotes the survival of *M. leprae* that may through inhibiting the cGAS pathway, and the more detailed mechanism remains to be studied.

## Acknowledgement

## Competing interests

The authors declare that they have no competing interests.

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