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The two faces of oligoadenylate synthetase-like: effective antiviral protein and negative regulator of innate immunity

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The type I interferon response is critical for controlling viral infection and triggers the production of downstream-target genes, termed interferon-stimulated genes (ISGs). While ISGs have a plethora of ways to restrict viruses at different stages of their replication cycle, they are also important to dampen immune responses to avoid tissue damage in the case of exuberant effects. However, this counter regulation of the immune response comes with the downside that it can open a door for viruses to get a foothold in their host. One key family of ISGs is the oligoadenylate synthetase (OAS) family, consisting of the DNA sensor cGAS and the RNA-sensing OAS and oligoadenylate synthetase-like (OASL) proteins. OASL proteins are of particular interest since they are structurally unique and act like a double-edged sword during immune responses to viral infection: they act antiviral, primarily against RNA viruses, whereas most DNA viruses benefit from OASL expression. Here, we put this balancing act of OASL proteins from different species into the spotlight and portray their different faces to viral infections.

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Introduction

The host immune system and viruses are players in a continuous arms race, where both parties thrive to gain the upper hand [1,2]. Understanding the intricate relationship between cellular restriction factors and viral countermeasures provides important insights into host-pathogen interactions and opens up opportunities to combat viral infections. The first hurdle viruses need to overcome upon entry into their host is the innate immune response mediated by pattern recognition receptors (PRR). The PRR family is composed of cell surface and endosomal Toll-like receptors (TLRs), cytosolic retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), as well as nuclear and cytosolic DNA sensors, which induce expression of type I interferons (IFN) and proinflammatory cytokines upon recognition of viral or aberrantly localized nucleic acids [3,4]. Secreted type I IFNs exert their activity in an autocrine and paracrine manner by activation of the type I interferon α/β receptor, subsequently inducing the production of interferon-stimulated genes (ISGs), with many of them acting in an antiviral fashion, while others may play involuntarily into the invader's hands [5]. More than 300 ISGs have been described, but for many we have a lack of knowledge about their exact mechanism of action, which may also vary with respect to the specific viral infection they respond to, the cell type and the species [6].

The ISG oligoadenylate synthetase-like (OASL) protein is highly induced after PRR signaling in many different cell types after infection with viruses from various families. OASL proteins from different species act antiviral against a broad range of emerging viruses with zoonotic potential such as Dengue virus (DENV) [7], Tembusu virus (TMUV) [8], Newcastle disease virus (NDV) [9], vesicular stomatitis virus (VSV) [7], and avian influenza A virus (IAV) [9]. However, a different side of OASL has emerged, revealing a proviral effect upon infection with the DNA viruses Kaposi-Sarcoma-associated herpesvirus (KSHV) [10], herpes simplex virus type 1 (HSV-1), Vaccinia virus (VV), Adenovirus (AdV) [11], as well as the RNA viruses encephalomyocarditis virus (EMCV) [12]. Interestingly, OASL proteins also seem to promote chronic viral infections as shown for

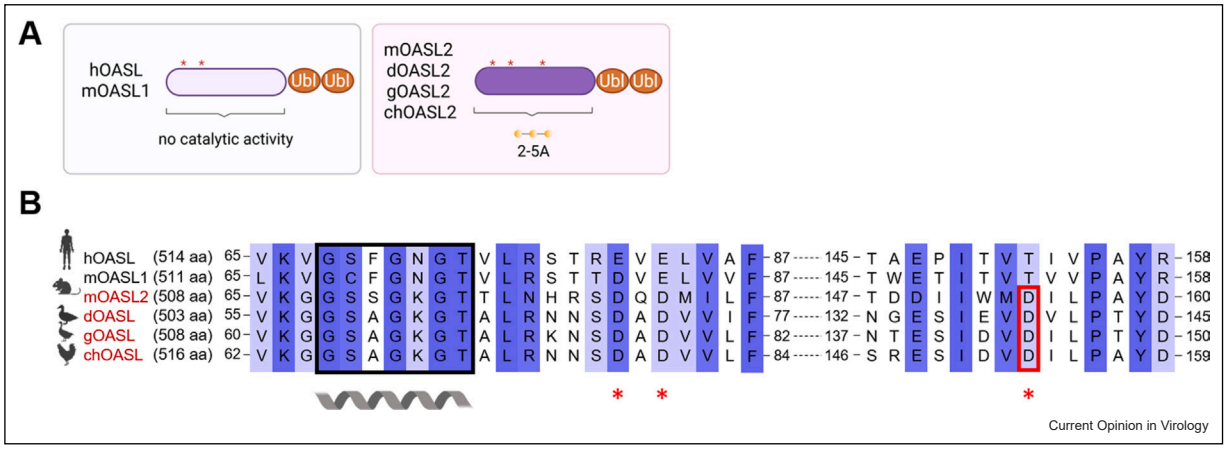
lymphocytic choriomeningitis virus (LCMV) [42] and Hepatitis C Virus [13]. Hence, OASL cannot be pigeonholed as a solely pro- or antiviral protein, and we will summarize in this review the current knowledge about OASL proteins in humans and mice and give a brief insight into avian OASL.

The oligoadenylate synthetase family

Oligoadenylate synthetases (OASs) are a prominent family of ISGs, which consists of OAS1, OAS2, OAS3, OASL [14,15], and the DNA-sensing PRR cyclic GMP-AMP synthase (cGAS). cGAS joined the OAS family only recently after the identification of its conserved nucleotidyl transferase (NTase) core domain, which is a hallmark of all OAS proteins [16]. The OAS1–3 proteins have significant homology to each other, and contain one, two, or three NTase domains, respectively. The OAS1–3 proteins were originally discovered as dsRNA-induced inhibitors of protein synthesis [17,18]. More precisely, after binding to dsRNA within their NTase domain, OAS1–3 produce the second messenger 2′–5′-linked oligoadenylates (2–5A), which binds to and thereby activates the enzyme RNase L with subsequent degradation of viral and cellular RNA [19]. OASL is an exotic member of the OAS family: in contrast to OAS1–3, it contains two ubiquitin-like (Ubl) domains at its C-terminal end [20,21] (Figure 1). Human OASL (hOASL) exhibits structural similarity with the active, dsRNA-bound form of OAS1 regarding an intrinsic αN4 helix in its NTase domain and utilizes a positively charged groove within its structure around the αN4 helix to bind dsRNA [22,23]. However, hOASL is not enzymatically active as it harbors only two of the three aspartic or glutamic acids in its NTase domain (Figure 1) [20,21]. So, while hOASL is capable of binding dsRNA, it does not seem to feed into the RNase L pathway. On a side note, the OASL gene produces three splice isoforms named hOASLa, hOASLb and hOASLd [20,21,24,25], and most studies so far have only analyzed the role of the full-length isoform hOASLa.

While humans have one OASL gene, mice encode two OASL genes, *mOASL1* and *mOASL2* [24]. Other well-studied OASL proteins are avian OASL, including duck (dOASL), goose (gOASL), and chicken (chOASL) OASL. All proteins share a conserved αN4 helix and the Ubl domain at the C-terminal end of the protein (Figure 1). However, like hOASL, mOASL1 lacks the capability to synthesize 2–5A due to a threonine in place of the aspartic acid in the catalytic triad, while mOASL2, dOASL, gOASL, and chOASL can synthesize 2–5A (Figure 1). Hence, mOASL2 and the avian OASL proteins seem to be an intermediate between the OAS and OASL proteins, since they harbor the catalytic triad and therefore produce 2–5A upon sensing dsRNA, and are equipped with the Ubl domain [9,24,26].

Figure 1



Representation of the domain and sequence structure of the OASL proteins. **(a)** Domain structure of hOASL, murine OASL1 (mOASL1), mOASL2, dOASL, gOASL, and chOASL. hOASL and mOASL1 contain an inactive NTase domain (light purple) with only two of the three aspartic or glutamic acids (red asterisks) needed for catalytic activity. mOASL2, dOASL, gOASL, and chOASL contain an active NTase domain (dark purple) with three aspartic acids (red asterisks) required for production of the second messenger molecule 2–5A. All OASL proteins contain two Ubl at the C-terminus. **(b)** Protein sequence alignments of Homo sapiens hOASL (NP_003724.1), Mus musculus mOASL1 (NP_001346874.1), Mus musculus mOASL2 (NP_035984.2), Anas platyrhynchos dOASL (ARS01326.1), Anser cygnoides gOASL (ANC67974.1), and Gallus gallus chOASL (NP_001384376.1). The αN4 helix (shown in gray) within the NTase domain is important for interacting with dsRNA. Asterisks mark the position of the catalytic triad within the NTase domain important for synthesis of 2–5A. Catalytically active mOASL2, dOASL, gOASL, and chOASL harbor the third aspartic acid (D; red box), which is a threonine (T) in hOASL and mOASL1. Blue shading indicates conservation between the sequences. Alignment was performed with ClustalW and analyzed with Jalview [41,42]. Schemes created with BioRender.com.

Human and murine oligoadenylate synthetase-like — multifaceted proteins in combating or enhancing viral propagation

While several studies highlight an antiviral activity of hOASL against RNA viruses including VSV, respiratory syncytial virus (RSV), Sendai virus (SeV), and DENV [7,23,27], mechanistic insights are still scarce. The Ubl domain of hOASL was shown to enhance RNA sensing by binding to RIG-I and mimicking its polyubiquitination, which is a critical step during RIG-I-mediated signaling, resulting in reduced VSV, RSV, SeV, and DENV infection [7]. Likewise, the Ubl domain of hOASL was also shown to be implicated in its antiviral activity against EMCV [12]. However, the Ubl domain of hOASL may not be the sole critical factor for its antiviral activity. By performing electrophoretic mobility shift assay it was shown that the NTase domain of hOASL is capable of dsRNA binding and that this binding is essential to enhance IFNβ transcription upon SeV infection [23]. This suggests that the dsRNA binding capability of hOASL may also contribute to its amplifying effect on RIG-I signaling.

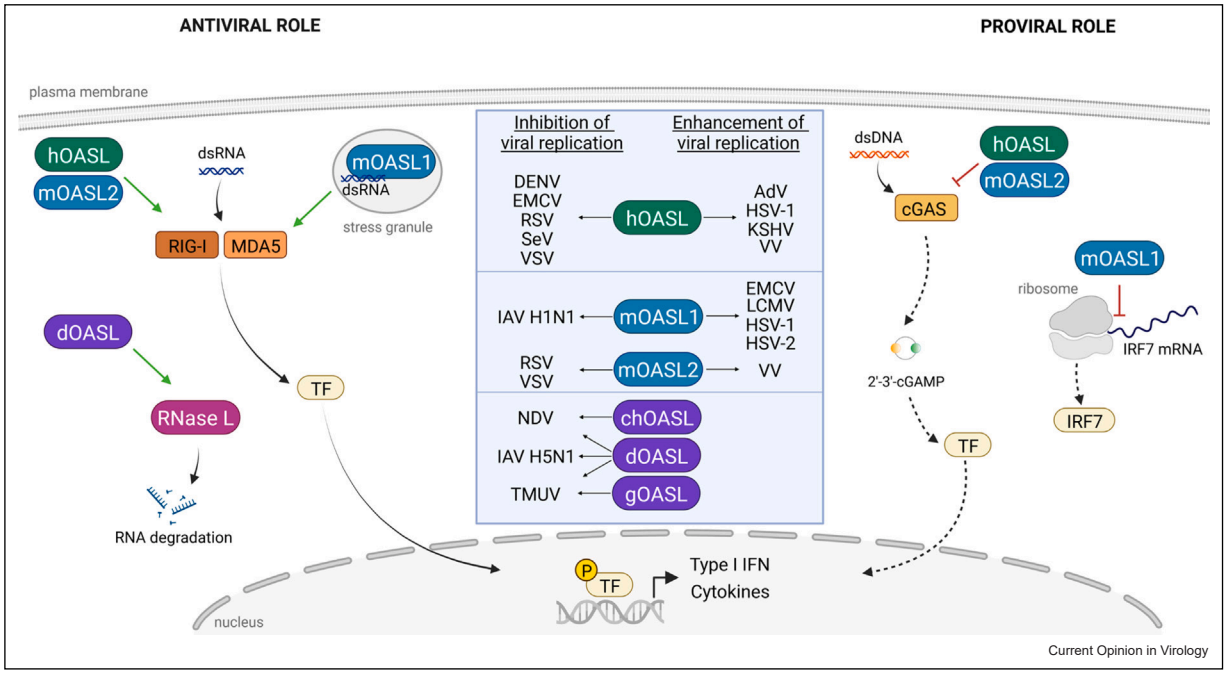
Similar to hOASL, mOASL2 expression was required for protection against VSV infection *in vitro* [7] and *in vivo* [11]. hOASL and mOASL2 also act antiviral in the context of RSV infection in human cells (HEK293 and HCT116) and murine bone marrow-derived macrophages, respectively [27]. Introduction of either wild-type mOASL2 or an enzymatically inactive mOASL2 mutant into murine embryonic fibroblasts led to reduced RSV titers, suggesting that mOASL2 may act independently of its catalytic activity. Whether the Ubl domains or the binding of dsRNA is required for their antiviral activity against RSV still needs to be investigated.

To date, little is known about the antiviral role of mOASL1 during viral infection. During IAV H1N1 infection of NIH-3T3 mouse embryonic fibroblasts, overexpressed mOASL1 associates with the RLR melanoma differentiation-associated protein 5 (MDA5) in stress granules during early stages of viral replication, and this is dependent on its dsRNA binding ability [28]. Stress granules are dynamic RNA-protein complexes composed of stalled translation initiation complexes, host RNA-binding proteins and other proteins [29], and viral infections often induce formation of stress granules, leading to accumulation of viral RNA [30]. Hence, mOASL1 was proposed to possibly bind and trap viral RNAs during early stages of infection in stress granules to promote efficient antiviral signaling [28]. Interestingly, Zhu et al. observed that hOASL relocalized to stress granules in response to SeV infection [7]. Further studies are needed to confirm this proposed mechanism of action of mOASL1 and need to investigate whether hOASL may act in a similar fashion by analyzing stress granule formation upon viral infection, possible colocalization with viral dsRNA, presence of RNA sensors and their signaling adaptors, as well as isolation and purification of stress granules in infected cells to identify their composition.

While an efficient type I IFN response is crucial to control viral infection, negative feedback loops are essential for keeping exuberant immune responses at bay [31]. Hence, dependent on the timing of the viral life cycle, the cellular proteins that are involved in this negative feedback loop may be unwillingly beneficial for the virus. This seems to be the case with mOASL1: In mice lacking mOASL1, elevated IFNα and IFNβ levels were observed and, congruently, EMCV and the alphaherpesviruses HSV-1 and HSV-2 replicated to lower titers [32,33]. To analyze the impact of mOASL1 on the translation of type I IFNs, a polysome analysis revealed that mOASL1 specifically inhibited translation of the transcription factor interferon regulatory factor 7 (IRF7) by binding to the 5′ untranslated region of IRF7 transcripts [32]. IRF7 forms a complex that binds to the promoter regions of antiviral genes to activate their transcription, including type I IFNs [34]. Consistent with these findings, the negative regulation of type I IFN secretion mediated by mOASL1 benefitted chronic infection with LCMV in mice [35]. Mechanistically, mOASL1 leads to a downregulation of type I IFN production at early phases of infection, which suppresses T-cell functions allowing the virus to chronically infect mice [42]. Hence, by downregulating expression of an important amplifier of the type I IFN response, mOASL1 promotes viral infection and thereby may be able to permit viral persistence.

Similarly, we found a proviral effect of hOASL in the context of infection with KSHV. This proviral function of hOASL was independent of the RNA-binding activity or the Ubl domain but instead dependent on the presence of the KSHV protein open reading frame (ORF) 20 [10]. Both ORF20 and OASL copurify with 40S and 60S ribosomal subunits, and when they were coexpressed, they associated with polysomes. While ORF20 did not have a global effect on translation, we found that ORF20 enhances RIG-I-induced expression of endogenous hOASL. Although our study could not identify the precise mechanism how hOASL exerts a proviral effect during KSHV infection, it provided evidence that KSHV not only tolerates but also reinforces hOASL. A study that may explain this phenomenon was published one year later. Gosh and colleagues showed that hOASL promotes infection of the dsDNA viruses VV, HSV-1, and AdV [11]. Upon expression of full-length hOASL or a mutant lacking the Ubl domain they found that both interacted and colocalized with the cytoplasmic DNA sensor cGAS, thereby inhibiting the catalytic activity of cGAS without affecting its ability to bind DNA. Hence,

Figure 2



Pro- and antiviral roles of human, murine and avian OASL. Green arrows indicate enhancement of downstream signaling, while red blunt-ended arrows indicate inhibition. Viruses affected by OASL expression in a negative (left side) or positive (right side) manner are listed in the blue box. Created with BioRender.com.

similar to mOASL1 which targets IRF7, thereby creating a proviral environment, hOASL disrupts the type I IFN response by inhibiting its family member cGAS. Further, the authors observed a similar proviral function of mOASL2 in mice upon VV infection, suggesting that mOASL2 may also target cGAS. This reinforces the hypothesis that mOASL2 may be the functional murine homologue of hOASL, at least regarding their effect on the cGAS signaling pathway.

Antiviral roles of avian oligoadenylate synthetase-like

While human and murine genomes code for three *OAS* and up to two *OASL* genes, birds primarily express only OASL [36]. Hence, avian OASL may have to fill in for tasks that are otherwise covered by OAS proteins in human and mice. One indication for this hypothesis is that all known avian OASL are enzymatically active (Figure 1) [9]. In the case of chOASL, chicken fibroblasts with a knockdown of chOASL were reported to respond with decreased ISG and increased viral transcript levels upon challenge with the RNA virus NDV [37], suggesting an antiviral role. Interestingly, unlike hOASL and mOASL2, which enhance RIG-I signaling, chicken lack RIG-I expression [38]. Nevertheless, these results indicate a connection between chOASL and the type I IFN response. Antiviral activity against NDV was also observed with dOASL [9] (Figure 2).

As birds are reservoirs for avian IAV, which are viruses with zoonotic potential [39], analyzing the antiviral mechanism of avian OASL proteins is of particular importance. In fact, dOASL was shown to inhibit replication of a highly pathogenic avian IAV H5N1 virus by activating the RNase L pathway in a Ubl-dependent manner [9] (Figure 2). Also, in the context of infection with the RNA virus TMUV, dOASL and gOASL showed antiviral activity [8,40] (Figure 2). However, the authors could exclude that the catalytic activity or the Ubl domains were involved in the observed phenotype, suggesting a novel mechanism independent of RNase L activation and RIG-I that is yet to be discovered. These findings may guide us to previously uncharacterized functions of OASL proteins that may or may not be found in the human and murine system as well.

Conclusion

Many functions of virus-induced ISGs are not completely understood, as shown for the OASL proteins featured in this review. As elaborated here, the actions of hOASL and mOASL2 are two-faced: they can be protective against RNA virus infection by enhancing RIG-I activity, but also beneficial for DNA virus infection by

inhibiting their family member cGAS (Figure 2). Some evidence exists that mOASL1 also has two faces, yet with another focus: It directs viral RNA to stress granules containing PRRs and inhibits IRF7 translation, with anti- and proviral outcomes, respectively (Figure 2). An open question is why the differential activity towards these important signaling pathways exists and how it is spatially and temporarily regulated. Furthermore, since birds primarily express OASL rather than OAS proteins, insights into avian OASL may be translated into the human and mouse system and potentially uncover functions which are otherwise masked by the presence of OAS proteins. Especially considering the impact of avian OASL on several viruses with zoonotic potential, insights into the role of these important antiviral proteins are surely needed in the future and will improve our understanding of the immune responses towards viral infection.

Data Availability

No data was used for the research described in the article.

Declaration of Competing Interest

None.

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- •• of outstanding interest

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