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Regulation of RNA-induced silencing complex by *Leishmania*: Targeting of host Argonaute-interactome

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Abstract

Intracellular parasites of the genus *Leishmania* have coevolved to regulate host macrophage cell biology, enabling them to survive. It has become clear that small noncoding RNAs are involved in shaping innate and acquired immunity against pathogens. In most situations, small noncoding RNAs exert their functions via RNA interference (RNAi) pathway. It is known that proteins of the Argonaute (AGO) family play a critical role in RNAi as a part of the RNA-induced silencing complex. It is unsurprising that pathogens, including *Leishmania* regulate the RNAi pathway. Herein, we review evidence supporting the potential regulation of host macrophage RNAi machinery by *Leishmania* via targeting AGO proteins and associated proteins to create a pro-parasitic environment. A model is emerging that *Leishmania* performs *de-facto* cross-kingdom RNAi to regulate host gene expression and create a pro-parasitic climate leading to the development of chronic infection.

Keywords: *Leishmania,* Argonaute proteins, pathogenesis, host-pathogen interactions

Introduction

Leishmaniasis is a spectrum of neglected tropical/sub-tropical diseases greatly affecting human health. Despite the devastating effects of leishmaniasis on human health, these diseases are on the rise due to drug resistance, lack of prophylactic vaccine against human leishmaniasis, increase in tourism and global warming. An intracellular pathogen of the genus *Leishmania* is responsible for causing leishmaniasis in humans. Macrophages are the primary resident host cells for *Leishmania*. Paradoxically, macrophages also are the main cells responsible for the destruction of *Leishmania*. Despite tough macrophage microbicidal arsenals and restrictive barriers, *Leishmania* has evolved strategies to evade host macrophage defense to establish infection successfully [1-3]. Regardless of the significant research progress in the area of *Leishmania*-macrophage interactions, this subject is not fully understood. A detailed understanding of *Leishmania*-macrophage coevolving interaction will greatly help control and treat these devastating human diseases. In this context, several accumulating studies have implicated small noncoding RNAs (sncRNAs) in microbial infections, including protozoan parasites [4]. In most situations, sncRNAs perform their gene regulatory functions with the help of the Argonaute (AGO) family of proteins [5].

Role of sncRNAs during *Leishmania* infection

Noncoding RNAs (ncRNAs):

Recent studies have clearly shown over 90% of the eukaryotic genome is

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transcribed, but only a small percentage (1-2%) of the genome is transcribed to code for proteins. It is now abundantly clear that this non protein-coding portion of the genome is involved in a diverse array of biological processes such as proliferation, differentiation and apoptosis [6-7]. With the advancement in sequencing technology, bioinformatics, and high throughput analysis, a large number of ncRNA species have been discovered. Broadly, ncRNAs are classified based on their size into small ncRNAs, less than 200 nt (including microRNAs (miRNAs), small interfering RNAs (siRNAs), PIWI RNAs and small RNAs derived from tRNAs), and large ncRNAs over 200 nt (such as long ncRNAs and circular RNAs) [8]. MiRNAs are the best characterized small noncoding RNAs (sncRNAs) [9].

sncRNAs in macrophage-*Leishmania* interaction:

It has come to light that miRNAs have role to play in macrophage infection biology such as macrophage activation, cytokine polarization, and resolution of inflammation [10]. Thus, it is unsurprising that *Leishmania* regulates host macrophage miRNAs to survive. Various reports have shown modulation of macrophage sncRNAs in infection biology [11-13]. A recent review has highlighted the modulation of miRNAs in both *Leishmania* and infected host, focusing on their roles in parasite survival and infection [14]. Regulation of host miRNAs by *Leishmania* is now considered very important in the *Leishmania* infection process.

In the context of the potential role of sncRNAs other than miRNAs in leishmaniasis, Lambertz et al. have shown the enrichment of sncRNAs derived from tRNAs and rRNAs in exosomes isolated from both old and new-world *Leishmania* [15]. In a previous study from the same group, Silverman et al. showed *Leishmania* exosomes mediated modulation of host innate and adaptive immune response via their effects on human monocytes and dendritic cells [16]. Together, the emerging role of sncRNAs during *Leishmania* infection seems to represent a novel virulence paradigm that invites further examination.

In most cases, sncRNAs, including miRNAs carry out their function of gene regulation by RNA interference (RNAi). RNAi is a phenomenon by which gene expression is regulated by either degrading target mRNA or blocking its translation. The core of RNAi is RNA induced silencing complex (RISC) which comprises of AGO proteins loaded with sncRNAs like miRNA, siRNA, etc. To perform RNAi, one of the strands of mature double stranded miRNA (guide RNA) is loaded onto a member of the AGO protein family to form RISC, which participates in gene silencing by multiple mechanisms [17]. The following section briefly introduces AGO proteins and their functions.

Argonaute (AGO) proteins:

AGO proteins, specialized RNA binding proteins, are key effector proteins in RNAi. These proteins are found in almost all archaea, bacteria and eukaryotes [18]. Humans have four highly conserved AGO family members (AGO1, AGO2, AGO3 and AGO4). All four AGO proteins share signature domains N, MID, PAZ and PIWI [19]. In humans, only AGO2 seems to have slicer endonuclease activity [20]. Additionally, recent accumulating evidence has shown a close association of AGO proteins with diverse human diseases, including cancer [21-23]. In addition to AGO proteins, some other proteins also form part of RISC by direct or indirect binding, including GW182/TNRC6 protein, heat shock protein70/90 (HSP70/90), etc. [24-26]. After binding to sncRNA, AGO protein serves as a scaffold for glycine/tryptophan (GW) repeats containing 182 protein (GW182) and CCR4-NOT deadenylase complex that facilitate mRNA degradation [27]. Recent studies have shown that loading of sncRNAs onto AGO protein requires HSP70, HSP90 and co-chaperones [28-31]. These proteins seem to use the energy of ATP hydrolysis to induce conformational change in AGO protein so that free AGO protein loads sncRNAs. The emerging role of AGO proteins in human cell pathology has been highlighted in a recent review article [32]. These findings are expanding our understanding of the role of AGO proteins beyond gene silencing.

Regulation of macrophage AGO1 protein during *Leishmania* infection:

In light of the close association of AGO proteins in various human diseases, it is reasonable to ask whether macrophage AGO proteins are associated with *Leishmania* infection. Recently, our group explored this possibility by investigating the potential role of AGO proteins in *Leishmania* pathogenesis [33]. This investigation showed a clear increase in the level of AGO1 protein compared to AGO2 in *Leishmania*-infected macrophages. Strikingly, this increase in abundance of AGO1 positively correlated with higher levels of AGO1 as a part of active AGO- complexes, suggesting *Leishmania's* preference for AGO1 protein in RNAi machinery in infected cells. Dysregulation of AGO1 protein is not uniquely associated with *Leishmania* infection. For example, increased expression of AGO1 protein has been reported in bumblebees in response to slow bee paralysis virus [34].

The preferential use of AGO1 protein during *Leishmania* infection is striking. In this context, it has been shown that in Epstein-Barr virus-infected mammalian cells, sncRNAs other than miRNAs were loaded on AGO1 protein, but not AGO2 [35]. Indeed, differences in the affinity of sncRNAs for members of AGO protein family have been observed in both lower organisms and mammals [36-39]. In another study, based on RNA sequencing of sncRNAs associated with AGO1, AGO2, and AGO3, some biasness towards particular AGO proteins were revealed [40]. Taken together, perfectly

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matched sncRNA duplexes seem to be loaded onto AGO2 protein, whereas non-perfectly matched sncRNAs are loaded onto AGO1 protein. The biological relevance of AGO1 protein was investigated by assessing intracellular survival of *Leishmania donovani* in infected cells, where AGO1 was downregulated using AGO1 mRNA targeting siRNAs. The results presented in this study strongly suggested that AGO1 confers a pathogen survival advantage, suggesting AGO1 role in pathogenesis and could be a novel and essential virulence factor by proxy that promotes pathogen survival [33].

This study further investigated the role of AGO1 protein during *Leishmania* infection. For this investigation, a whole quantitative proteomic analysis was performed on *Leishmania*-infected macrophages in normal and AGO1-downregulated conditions. Of the 1778 high-confidence human proteins identified, 331 were significantly altered by *Leishmania*. Out of 331 modulated proteins, 212 were downregulated, while 119 were upregulated in infected cells. Most interestingly, out of the 71 *Leishmania*-modulated AGO1-dependent proteins, 20 have previously been implicated in *Leishmania* infection-related studies [33]. Together, this study suggested that *Leishmania*-mediated upregulation of AGO1 protein is a clever strategy to regulate host cell RNAi-mediated gene expression to promote its survival. It is known that unloaded AGO proteins are unstable and degraded by proteosome [41]. Thus, it is reasonable to presume that an increased abundance of functional AGO1 protein is complemented by increased loading of sncRNAs into AGO1. Based on these findings, it hypothesized that *Leishmania* uses selective AGO sorting mechanism that directs distinct sncRNAs loading onto specific AGO-containing RISCs, and that AGO1 seems to be a preferred AGO for the loading of non-perfectly matching sncRNAs, including sncRNAs from the pathogen.

The following section review the evidence suggesting regulation of host RISC by modulating proteome of AGO-associated complex.

Characterization of proteome of AGO-complexes from *Leishmania*-infected macrophages:

As described above, AGO proteins are a central component of RISC, an ultimate component of RNAi machinery. Our recent result discussed above showed significant upregulation of AGO1 protein in *Leishmania*-infected cells [33]. This result led to the assumption that *Leishmania* also affects host RNAi effector RISC complexes components other than AGO proteins to promote its survival. This attractive hypothesis was investigated in a more recent study [42]. For this study, AGO-associated proteins were isolated to characterize their proteome using mass spectrometry. The following section reviews characterization of AGO interactome in non-infected and *Leishmania*-infected macrophages [42].

Comprehensive capture of AGO-interactomes of *Leishmania*-infected and non-infected macrophages:

It is known that the majority of RNAi, independent of AGO-mediated RNA slicing, involves the GW182/TNRC6 family of proteins [27]. These proteins act as scaffold proteins and interact with the AGO proteins once they are loaded with the guide RNA strand. In addition, GW182 also recruits essential components of repressor complexes responsible for decapping, deadenylation and ultimately degradation of target mRNA [43-44]. It has been shown that the GW (glycine-tryptophan) repeats on GW182 protein's N-terminal domain are involved in AGO protein binding [25, 45-46]. A recent structure-function study identified a short peptide (T6B) in the AGO binding domain of TNRC6B that is sufficient to bind all human AGO proteins efficiently [25,47]. Interestingly, T6B peptide binds all four AGO proteins with equal affinity [48]. Based on the affinity of T6B for all the AGO proteins, Huptmann, J et al. developed a protocol to quantitatively isolate AGO proteins from many different cell types, tissues and species [48]. This T6B peptide-based affinity purification of AGO proteins is termed "AGO protein Affinity Purification by Peptide" (AGO-APP) [48]. This procedure offers three major advantages compared to other AGO isolating procedures, such as immunoprecipitation. First, this method isolates all human AGO proteins simultaneously. Second, isolated AGO proteins are functional. Third, it specifically isolates AGO and interacting proteins involved in the process of RNAi, reducing chances of isolating AGO interacting proteins with other potential functions. This procedure will also exclude proteins interacting with other domains of GW182 protein like silencing domain. Additionally, this procedure can also be used to isolate AGO-associated sncRNAs. Thus, AGO-APP has potential to isolate mature active AGO proteins and their interactome.

To test the hypothesis that *Leishmania* targets AGO protein complexes, AGO-APP was used to isolate AGO protein complexes from the cytosolic and nuclear fractions from non-infected and *Leishmania*-infected macrophages. Surprisingly, but interestingly, AGO proteins could not be detected in the nuclear fraction of human macrophages. Contrary to this, in several recent studies, AGO proteins could be detected in the nucleus, suggesting multi-functional role of AGO proteins in the nucleus [49]. From this study, it seems AGO proteins are mainly restricted to the cytoplasm of macrophages. Furthermore, AGO-APP could isolate bound sncRNAs. After confirming the validity of AGO-APP for the isolation of active AGO proteins and presumably associated proteins, cytosolic fractions from non-infected and *Leishmania*-infected macrophages were used to pull down AGO protein complexes followed by their detection using liquid- chromatography-tandem-mass spectrometry (LC-MS/MS). Stable isotope labelling using amino acids in

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cell culture (SILAC) was used for mass spectrometry-based comprehensive quantitation of AGO protein complexes from control and *Leishmania*-infected macrophages. The major advantage of this straightforward procedure of SILAC is that multiple samples can be mixed at the early stages of the procedure, digested simultaneously, and then identified, thus minimizing variations due to technical error and offering the comparison of multiple investigational conditions in a single run. This technology has been extensively used for high-throughput, whole proteome analysis [33, 42, 50, 51].

Proteomic analysis of host AGO-containing complexes:

Proteomic analysis of AGO- interactomes identified 51 proteins. Gene Ontology (GO) analysis of 51 proteins suggested a diverse range of molecular functions associated with AGO-complexes in both non-infected and *Leishmania*-infected macrophages. The majority of identified proteins' molecular functions include catalytic activity, hydrolase activity, RNA binding, ATP-dependent activity, regulator activity, DNA binding, catalytic activity, cytoskeletal protein binding, and protein folding chaperone. Further, this study showed that the level of 17 proteins was differentially expressed between AGO-complexes obtained from non-infected and those from *Leishmania*-infected cells. Amongst these differentially expressed AGO-associated proteins, 11 were downregulated, and 6 were upregulated in *Leishmania*-infected cells compared to non-infected controls. Strikingly, interacting proteins most significantly modulated by *Leishmania* were predominantly heat shock proteins (HSPs), and the majority were downregulated (five out of six HSPs). In addition, macrophage proteins involved in RNAi, protein translation, ATP binding, transferases, oxidases, and host-virus interaction were also found to be altered in response to *Leishmania* infection. The most striking part of this analysis was the identification of ten *L. donovani* proteins as constituents of AGO-complexes in infected cells. Out of these ten *Leishmania* proteins, two were HSP70 and HSP70-related proteins. In this context, it is known that *Leishmania* HSP70 is upregulated in infected macrophages [52]. Moreover, as discussed above, the Hsp70/Hsp90 multi-chaperone systems are involved in the ATP-dependent conformation change of AGO proteins to an open and active state to accommodate the RNA duplex and thus is an integral part of the RISC-loading mechanism [29]. Interestingly, the presence of *Leishmania* HSPs as the constituents of AGO-complex raises the possibility that *Leishmania* HSP70 competes with host HSP70 for binding to the host AGO-complexes. In this context, it is worth noting that sncRNAs and HSPs are enriched in the exosomes of *L. donovani* [15, 53] and can be secreted in the cytosol of infected cell [15, 54]. Taken together, this study hypothesizes that *Leishmania* delivers its HSPs and sncRNAs to the host cell through exosomes, to regulate the host RNAi by loading exogenous sncRNAs onto RISC and alter the host gene expression in favor of parasite survival. Nevertheless, the role of parasite proteins identified in AGO-complexes isolated from infected cells needs to be investigated, as well as their subsequent potential role in *Leishmania* pathogenesis. This study also compared AGO-associated proteome with the results obtained from a previous recent study investigating AGO1-dependent *Leishmania*-modulated proteins [33]. Strikingly, HSPA5, PRDX1, and EEF1G proteins of AGO-complexes that were AGO1-dependent were found to be downregulated in *Leishmania*-infected cells in both studies, thus further emphasizing the importance of the results from the AGO- complexes proteomic study. Although this study indicates that AGO-associated proteins predominantly contribute to the process of RISC in normal and infected cells, there are several limitations—the detailed biological functions and how these identified proteins contribute to RISC biogenesis. Hence, there should be further investigation of potential mechanisms in the future.

Cross-kingdom RNAi:

The data from two recent studies discussed in this review strongly point towards cross-kingdom RNAi during *Leishmania* infection. This emerging phenomenon involves the bidirectional trafficking of sncRNAs between the host and corresponding pathogen as shown in multiple studies [4, 55-57]. This evolving trend has been shown as both a host's defence mechanism and a strategy employed by pathogens to target the host RNAi machinery to their advantage [56,58]. The possibility of cross-kingdom RNAi during *Leishmania* infection is presented as a hypothetical model in Fig. 1

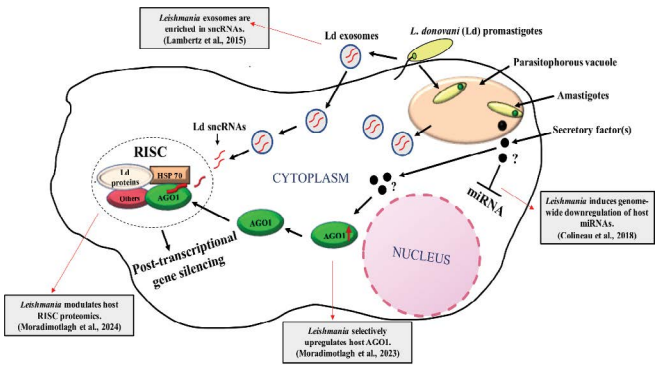

Figure 1: Cross-kingdom RNAi during macrophage-*Leishmania* (Ld) interactions.

Leishmania globally downregulated host miRNAs during infection. It also hijacks macrophage AGO1 to target host transcription. Leishmania secretory exosome-derived sncRNAs compete with host sncRNAs to load on AGO1 to target suf-ficient complementary host transcriptome/transcription. In addition, Leishmania also targets host AGO-interactome by providing its own proteins such as HSP70s. The correspond-ing reference literature for this model is shown in the grey boxes.

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Concluding Remarks

It is well established that *Leishmania* is an expert manipulator of host macrophage cell biology, and it comes with no surprise that it targets AGO proteins and associated protein complexes in infected cells. Since AGO proteins are the central component of RISC, the ultimate effector complex of RNAi, modulation of AGO proteins and associated proteins will have an impact on host RNAi involved in gene regulation. Moreover, based on emerging evidence, it is becoming increasingly clear that targeting host ncRNAs is high on the agenda for pathogens, including *Leishmania*. Two recent published articles [33, 42] and a previous finding showing the presence of sncRNAs in *Leishmania* exosomes [15], provide foundation to explore the role of sncRNAs/ RISC composition in an emerging area of host-pathogen interaction. The striking observation is that *Leishmania* selectively upregulates macrophage AGO1 and recruits its own proteins to AGO-complexes, perhaps manipulating host RISC to regulate gene expression to its advantage. Since AGO1 directly binds sncRNAs, possibly *Leishmania* skews host RNAi by selectively uploading sncRNAs onto AGO1, including its own sncRNAs. Identifying ncRNAs loaded onto infected host RISC has the potential to answer this interesting question. It is evident that all the identified proteins of AGO-complexes in infected cells will not have an impact on *Leishmania* survival; however, it raises an important question as to whether the manipulation of host RISC can be exploited in a general way by *Leishmania* proteins directly or indirectly. A more detailed study of how *Leishmania* achieves manipulation of host AGO- and associated proteins, we will undoubtedly gain knowledge of the regulation of RNAi in infected cells and may unveil new avenues for therapeutic intervention to fight leishmaniasis and may also have implications for other intracellular pathogens. In addition, we note that the prior understanding of the role of RNAi mechanisms in infection is mainly based on plants and insects. The findings discussed in this review provide a foundation for further study of the role of RNAi in *Leishmania* pathogenesis in humans.

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