Review



# Role of ZIP-10 in the Regulation of innate Immunity in *Caenorhabditis elegans* During Pathogenic Infection

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# Role of ZIP-10 in the Regulation of Innate Immunity in *Caenorhabditis elegans* During Pathogenic Infection

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**Abstract:** b-ZIP transcription factor ZIP-10 has emerged as a key regulator of innate immunity in *Caenorhabditis elegans* (*C. elegans)*. ZIP-10 as a regulatory protein has multifarious roles in development, stress response, metabolism, and immune modulation triggered by pathogenic infection. Since most of the immune signaling pathways are conserved across species, future studies are envisioned to provide new tools for hypothesis generation/testing aimed at deciphering fundamental defense mechanisms relevant to infectious disease(s). This review outlines recent findings regarding the unfolding novel mechanisms of positive and negative regulation of innate immunity by ZIP-10, speculated to have its role in maintaining immune homeostasis. However, the research evidence of a precise mechanism of its upstream signaling kinase and downstream effectors is limited. Furthermore, this review provides a brief insight into the complex dynamics of host-pathogen interaction, where the pathogens exploit host factors to establish themselves within the system. Therefore, leveraging the high throughput screening potential of this model organism can lead to the identification of novel therapeutic strategies associated with immune dysregulation, significantly relevant for translation to complex system(s).

**Keywords:** *C. elegans*; ZIP-10; innate immunity; stress response; host-pathogen interaction

## Introduction

*C. elegans* belongs to the trophic group of bacterivorous nematodes. Being a natural host of bacteria, it has emerged as an outstanding model to study host-pathogen interactions [1–4]. Successive studies have attempted to understand how it distinguishes pathogenic bacteria from non-pathogenic bacteria and empowers a defense against them. First and foremost, this optically transparent roundworm is endowed with a thick cuticle made of collagen and chitin that acts as a physical barrier to pathogens. Subsequently, the worm captures feed through the pharynx (pharyngeal muscle), a neuromuscular organ that connects the worm's mouth directly to the intestine. The presence of a strong pharyngeal grinder destroys some of the ingested pathogenic bacteria, as demonstrated by studies showing that worm mutants lacking a functional pharynx are more vulnerable to pathogenic infections compared to wild-type worms [5,6]. Nonetheless, the pathogen capable of evading this barrier causes intestinal infections in the worm.

One of the most notable features of the *C. elegans'* immune system is the lack of specialized immune cells and an adaptive immune response. Consequently, the worm exclusively relies on the innate immune response to combat the pathogens. Interestingly, studies have shown that *C. elegans* uses distinct molecular mechanisms to combat the diverse array of pathogens, including fungi, bacterial toxins, and Gram-positive and Gram-negative bacteria [7–10]. More importantly, several studies have revealed a remarkably strong conservation in molecular and cellular pathways between worms and mammals. Studies drawn from the full genome analysis confirm that a majority of human disease genes and pathways are present in *C. elegans* [11]. The unique immune response mechanisms in *C. elegans*, compared to other animals, highlight its ability to mount pathogen-specific defenses without relying on Nuclear Factor kappa B (NF-kB) or Toll-like Receptor (TLR) signaling pathways. This is a remarkable feature of these pathways, as canonically TLR-mediated NF-kB activation is

central to immune responses in complex organism(s). TLRs are pattern recognition receptors (PRRs). These PRRs recognize microbial components known as Microbe-Associated Molecular Patterns (MAMPs) or Pathogen-Associated Molecular Patterns (PAMPs) such as bacterial lipopolysaccharides, viral RNA, and microbial DNA [12].

Intriguingly, *C. elegans* has only one single TLR protein, TLR/TOL-1, associated with the behavioral avoidance of some pathogenic bacteria [13]. The cytoplasmic ligand of TLR is the Toll-Interleukin-1 receptor domain adaptor protein (TIR-1), which is orthologous to mammalian SARM. TIR-1 initiates PMK-1 signaling in innate immunity, comprising TIR-I-NSY-I-SEK-I-PMK-I signaling cascade. Each TLR detects specific PAMPs, allowing responses to be tailored to different pathogens [14]. When TLR binds with PAMPs, it initiates a signal cascade that leads to activation of the NF-kB transcription factor, which ensures a rapid and robust immune response against pathogens.

The site of innate immune defense in this nematode is the intestine, functioning both as a physical barrier as well as an active immune organ. Interestingly, *C. elegans* is a pseudocoelomate; the intestine consists of a single layer of large, polarized epithelial cells that form a hollow tube running from the pharynx to the rectum. This gut tube is composed of 20 non-renewable cells that form nine rings spanning the length of the intestine. These cells are assigned to function in various processes, including digestion, energy storage, and secretion of immune effectors during pathogenic onset. The intestinal cells identify and respond to the pathogens by triggering either constitutive or inducible mechanisms to produce effector molecules to combat the infection [15,16].

The substantial feature of this inducible immune response is the implication of multiple signaling cascades that regulate the production of host-encoded immune effectors (AMPs and immune-responsive proteins) having the potential to destroy pathogens in pathogen and tissue-specific ways The classical immune pathways in *C. elegans* subsuming the innate immune response are the p38/MAPK pathway [5], DBL-1/TGF-B pathway [17], insulinJIGF-1 signaling [18], JNK-1like MAPK pathway [9], ERK MAP kinase cascade [19], Program Cell Death [20], GPCR/FSHR-1 signaling [21], intracellular pathogenic response (IPR) [22] and the unfolded protein response (UPR) [23]. Upon infection, *C. elegans* induces a broad transcriptional response in its intestinal cells, leading to the activation of its defense mechanism, including secretion of antimicrobial effector molecules [10]. This review highlights the role of bZIP transcription factor ZIP-10 in innate immunity in *C elegans*, drawing upon a range of studies that illuminate its function and significance.

ZIP-10 is a C2H2-type zinc-finger transcription factor that binds to DNA and modulates the expression of target genes. bZIP is a large superfamily of transcription factors that contains a region rich in basic amino acid residues followed by a leucine zipper domain. ZIP-10, an ortholog of human BATF3, was discovered in 2006, in a microarray analysis performed to understand body size regulation and other developmental processes coordinated by DBL-1/ TGF-B. Canonically, ZIP-10 is regulated by an SMAD protein integrated into the TGF-B pathway. Taken together, this discovery was noteworthy as ZIP-10 established a direct link between the TGF-B signaling cascade and specific gene regulation accountable for diverse developmental processes [24]. Approximately 33 bZIP TFs have been identified in *C. elegans*, which are predominantly expressed in the intestinal tissues and govern various cellular aspects, including metabolism, development, and innate immunity etc.[25,26].

Recent research has highlighted ZIP-10's role in metabolic, stress, and innate immune networks owing to its multifaceted regulatory mechanisms. Future studies hold promising avenues for testing new hypotheses in this genetically tractable nematode, leveraging its relevance with the aim of extrapolating results to complex system(s).

## ZIP-10 is Deployed Under Host-Inducible Immune Response

Innate immunity is the first line of defense in *C elegans* against pathogenic forays. This evolutionarily conserved mechanism consists of two defense mechanisms, viz, constitutive and inducible defense mechanisms. On pathogenic onrush, under typical conditions, the defense mechanism mediated by innate immunity directs an immediate response to pathogens, employing basal expression of immune effector molecules. Whereas the host inducible defense mechanism employs germline-encoded PRRs to recognize microorganisms. These PRRs recognize microbial

components known as MAMPs/PAMPs. It is difficult to modify MAMPs/PAMPs for microorganisms as these molecular signatures are essential for their survival. Canonically, upon pathogen recognition, the PRRs induce a signaling cascade including transcription factors to activate immune-responsive molecules, including antimicrobial peptides, caenopores, lysozymes, lectins, and reactive oxygen species (ROS), etc. [27,28].

As described earlier, the only PRRs encoded in the *C. elegans* genome have been identified as TOL-1. However, it has not been characterized to have a role in PAMPs recognition, although a Damage Associated Molecular Pattern (DAMP)/G protein2q coupled receptor interaction has been reported to have a critical role in response to *Drechmeria* infection [29]. Given that the underlying defense mechanism is governed by the Toll/NF-kB axis, it is not encoded in the *C elegans* genome. For all that, studies have reported distinct immune responses in *C elegans* against diverse pathogens, indicating underlying mechanisms of specific pathogen recognition [28]. Hence, it remains unclear how *C elegans* recognises pathogens and activates its defense through specific MAMPs/PAMPs or more generally through cellular damage and stress caused by pathogens.

ZIP-10's role in immunity has gained increasing attention, and the data drawn from recent studies indicate its role in expediting immune responses by regulating transcriptional networks that modulate pathogen load. However, the exact mechanism by which ZIP-10 initiates pathogen recognition and its downstream target genes, activating immune effectors, remains to be completely classified and warrants further studies.

## Immune Modulation During Microsporidia Infection

ZIP-10 has been studied extensively for its role in killing bacteria, however, emerging evidence suggests it plays a vital role in combating intracellular pathogens like microsporidia. Microsporidia are obligate intracellular parasites belonging to free-living fungi. *C. elegans* is naturally infected by this pathogen, making it an excellent system for studying intracellular immunity [30].

In a recent study, researchers have discovered an interesting phenomenon in the development of the microsporidian pathogen *Nematocida parisii.* The high-throughput RNAi screen provided insight into the host transcription crucial in the regulation of *N. parisii* development. The study revealed that ZIP-10 coordinates with other transcription factors, associated with intracellular pathogen response (IPR): a defense mechanism specifically tailored to intracellular invaders. The epistasis analysis revealed that ZIP-10 acts in conjunction with MDL-I and PHA-4 in a canonical pathway to promote sporulation in *N. parisii.* The study proposes an investigation of upstream signaling that regulates these transcription factors, as well as downstream effectors of MDL-1 and ZIP-10 that contribute to promoting intracellular pathogen development [31].

It has been speculated that ZIP-10 interacts with chromatin-modifying complexes, altering the accessibility of immune gene promoters to facilitate their prompt activation during the onrush of pathogens. The precise mechanism by which ZIP-10 directs these responses awaits future studies, which can yield a comprehensive understanding for ongoing research.

This line of research motivates the question of whether pathogens can exploit host machinery in favor of their development inside the host. The response from follow-up research is affirmative. As demonstrated by a recent study that delineates the role of the antimicrobial protein AAIM-I, secreted by the intestine of *C. elegans*. AAIM-I facilitates microsporidia invasion in *C. elegans,* while concurrently thwarting colonization of certain pathogenic bacteria, like *P. aeruginosa.* Altogether, this study confirms the evolutionary trade-off where *C. elegans* may prioritise defense against a prevalent microsporidium over bacterial resistance [32].

Immune pathways often crosstalk with metabolic regulators, as established by a study where perturbation in purine metabolism activates IPR [33]. It will be worth exploring if ZIP-10 senses metabolic changes and contributes to IPR activation. It will be interesting to study whether ZIP-10 mutants show altered responses to purine disruption or microsporidia infection. Altogether, this makes it an emerging area for researchers to explore: How this interplay between ZIP-10, purine metabolism, and the IPR pathway holds potential implications for understanding ZIP-10's transcriptional regulation governing resistance against intracellular pathogens.

This intricacy of metabolic pathways with immune response redirects the necessity for *C. elegans* to adapt its immune system to outstrip the varying strategies imposed by the pathogens. Future studies aiming to investigate oxidative stress and metabolic shifts in balancing defense against bacteria and microsporidia can explore whether this intersection is associated with ZIP-10. Although ZIP-10 has not been shown to be directly linked to IPR, there could be a potential link between them because both ZIP-10 and IPR are activated in response to stress.

Studies have shown that ZIP-10 senses metabolic changes and serves as an intriguing intersection of immune and metabolic responses. Understanding how ZIP-10 modulates metabolic reflexes within cells while employing a context-dependent mode holds the key to fascinating answers for ongoing research.

## Energy Landscape of Cell During ZIP-10-Governed Immune Modulation: Signaling Network

Immune signaling pathways rely on ligand-receptor interactions, phosphorylation, and activation of certain transcription factors towards thermodynamically favorable orchestration of each step. Being a regulatory protein, ZIP-10 could alter the threshold for immune activation or suppression based on the energy landscape of a cell. The ongoing research is very focused on the multifaceted role of ZIP-10 in innate immunity. The immune modulation operates in a context-dependent mode to achieve immune balance because immune responses demand high energy. Consequently, ZIP-10 influences cellular metabolic pathways affecting the energetic cost of mounting an immune defense.

During infection, *C. elegans* needs to redirect resources to immune responses. This involves a tradeoff between growth, reproduction, and survival. Recent studies have indicated how ZIP-10 modulates energy dynamics or regulatory mechanisms of immune responses when the nematode is under attack by pathogens like microsporidia. Consequently, this impacts metabolic reflexes within the system as illustrated by purine metabolism [33].

The efficient use of energy resources, possibly regulated by ZIP-10, would allow the immune system to function more efficiently under stress. To maintain the overall cellular homeostasis, ZIP-10 works in conjunction with other signaling pathways. The most well-characterized pathway suggests that ZIP-10 acts downstream of the p38/MAPK pathway, which is crucial for immune signaling. Moreover, its interaction with insulin-like growth factor-1 (IGF-1) signaling may fine-tune the immune response based on the metabolic status of an organism. This integration of immune and metabolic pathways highlights the complexity of its role in regulating the balance between immunity and metabolic homeostasis. The immune response in *C. elegans* involves cross-talk between multiple signaling pathways, including p38 MAPK, insulin/IGF-1 signaling (IIS), and DBL-1/TGF-B pathways, etc. [8,28].

Perturbations in cellular stress pathways, including oxidative or metabolic may converge with immune response pathways to integrate multiple signals for a coordinated defense. ZIP-10 interacts with the IIS pathway to regulate immunosenescence. It serves as a part of the feedback loop within the IIS pathway, which influences longevity and immune responses. The study reports an increase in ZIP-10 expression with age in wild-type animals, but *daf-2* mutants, which are long-lived due to reduced insulin signaling, have subdued expression of ZIP-10. This reduction in the ZIP-10 level in *daf-2* confers pathogen resistance in older *daf-2* mutants. ZIP-10 does it by regulating the expression of an insulin-like peptide, INS-7. As worms age, high levels of ZIP-10 lead to higher levels of *ins-7*, which promotes immunosenescence. On the contrary, upon inhibition of ZIP-10 in *daf-2* mutants, INS-7 is downregulated, which contributes to delayed immunosenescence [34].

Interestingly, a recent study has shown the role of GPCR/FSHR-1 in stress response, where FSHR-1 orchestrates a signaling cascade in response to freeze/thaw stress (FTS), causing organismal death (phenoptosis). The FSHR pathway has been characterized by the G-protein-coupled receptor FSHR-1, which mediates immune responses against both Gram-negative and Gram-positive bacterial pathogens [21]. Subsequent studies have revealed its significant role in managing oxidative stress [35]. The study identifies ZIP-10 as a downstream effector of the FSHR-1/ GPCR pathway in *C. elegans,* which connects severe stress to programmed organismal death. Triggered by severe stress, ZIP-10

activates genes associated with lipid metabolism and proteostasis. Altogether, this suggests that the ZIP-10's role in stress responses, including immune and metabolic regulation, is context-dependent, because it may not be activated under less severe or different types of stress [36]. The interaction between FSHR and ZIP-10 underscores the broader role of ZIP-10 in coordinating immune and stress responses.

These observations suggest that ZIP-10 is embedded within a complex regulatory framework that balances growth, development, and immune function in the worm.

## Mir-60/ZIP-10 Axis in Immune-Stress Response

It has been documented that ZIP-10 plays a critical role in the adaptive response against long-term and mild oxidative stress in C. elegans, particularly in the context of an intestinally expressed micro-RNA gene, mir-60. MicroRNAs can fine-tune gene expression and function as key players in adaptive responses against stress. ZIP-10 has been predicted to be a direct target of mir-60. In mir-60 mutants, ZIP-10 expression has been found to be upregulated, suggesting negative regulation of ZIP-10 under mir-60, possibly through directly binding to complementary sequences in ZIP-10 untranslated regions (UTR) and exon regions [37]. This study aimed to understand the role of mir-60 in lifespan and stress resistance, particularly oxidative stress in C. elegans. It revealed that the knockdown of ZIP-10 in mir-60 mutants significantly reduces mir-60 loss-induced lifespan extension. Interestingly, the study highlights the mir-60/zip-10 axis role in linking the contribution of the innate immune system to the adaptive response against oxidative stress in mir-60 mutants, independent of daf-16 and skn-1. The study shows that loss of mir-60 extends lifespan and enhances an adaptive response to long-term mild oxidative stress.

The stress response was non-canonical and possibly linked to innate immunity and detoxification pathways, which were modulated by downstream target genes of mir-60, including GSTs, UGTs, and cyt CYP450s. ZIP-10 was found to be significantly contributing to this process and was shown to regulate genes linked to pathogen defense, such as P-glycoproteins (Pgps). Pgps take part in the removal of toxins generated by pathogens from the cell, which ensures maintenance of cellular homeostasis [38,39]. Thus, ZIP-10 mediates oxidative stress resistance, detoxification, and immune responses, expediting an adaptive mechanism that promotes survival under long-term mild oxidative stress conditions.

Furthermore, research suggests evidence of negative regulation of ZIP-10 by ISY-1 in the context of stress-induced phenoptosis, also known as programmed organismic death. The mechanism involves suppression of ZIP-10 by *mir-60* and reveals a pro-death role of ZIP-10 in response to prolonged cold-warm stress [40].

There has been growing interest in recent years to develop an understanding of how positive and negative regulators of innate immunity coordinate to maintain immune homeostasis. Particularly negative regulators of innate immunity remain poorly understood despite their fundamental role in maintaining immune homeostasis. A recent study has reported ZIP-10 as a negative regulator of innate immunity in *C. elegans* [41]. This study reveals that during pathogen infection of *Pseudomonas aeruginosa* PA14, *mir-60* is downregulated, which in turn allows higher ZIP-10 expression levels. Consequently, the upregulated ZIP-10 attenuates PMK-1/p-38 signaling that drives lower expression levels of immune genes via an unknown mechanism. Thus, the animals lacking *zip-10* exhibited enhanced resistance against PA14 infection.

The p38 mitogen-activated protein kinase (MAPK) pathway is an evolutionarily conserved innate immunity pathway to fight off pathogens [5,42]. The canonical NSY-I/SEKI/PMK-I signaling cascade regulates activation and nuclear localization of SKN-1 to induce the expression of the phase-2 detoxification gene in response to oxidative stress [43,44].

ISY-1 regulates *zip-10* expression levels via *mir-60*, likely through the processing of microRNAs. Under typical conditions, the knockdown of *isy-1* relieves the negative regulation of *zip-10* [37]. Collectively, if the p38/PMK-1 pathway operates to mitigate pathogen burden, one might anticipate the induction of p38/PMK-1 during pathogen infection. Contrary to this, researchers have shown that ZIP-10 suppresses innate immunity by attenuating the p38/PMK-1 pathway during PA14 infection. However, the underlying mechanism was not investigated [41]. This finding highlights the need to

explore under what conditions ZIP-10 could attenuate the p38/PMK-1 pathway. Because an activated p38/PMK-1 pathway is necessary to stabilize *skn-1* nuclear localization under oxidative stress conditions to confer immunity.

Does this intriguing dynamic between pathogen and host defenses suggest a deliberate mechanism employed by the pathogen that could enhance its survival? By targeting the downregulation of ZIP-10, the pathogen weakens host defenses that would otherwise direct the clearance of pathogens. Addressing such hypothetical possibilities intended to fill this research gap awaits further investigation.

Overall, ZIP-10 inhibition via *isy-1/mir-60* axis has the potential to influence several physiological processes, including innate immune response, stress adaptation, and lipid metabolism. Plausible hypotheses can be tested to study this balancing effect that could be important to evade excessive immune activation triggered by environmental stressors, as well as pathogens. The ultimate goal of a host is to maintain immune homeostasis by fine-tuning positive and negative regulators of innate immunity.

Moreover, a previous study has validated NHR-42 as the first transcription factor that negatively regulates innate immunity in *C. elegans* [45]. This study shows that NHR-42 acts downstream of HLH-30/TFEB to repress host defense genes. Particularly, NHR-42 represses infection resistance and drives lipid catabolism during infection. RNAi and mutant analysis confirmed that the animals lacking *nhr-42* exhibited higher expression levels of host defense genes during infection.

Future investigation into the negative regulation of innate immunity can be tested in mutant worms of *zip-10* and *nhr-42*. Negative regulation of innate immunity has been poorly understood, so it will be interesting to uncover how ZIP-10 prevents hyperactivation of immune systems by functioning as a negative regulator of immunity.

## Translation to Mammalian Immunity

The ZIP-10 ortholog, Basic Leucine Zipper ATF-like Transcription Factor 3 (BATF3), is a key transcription factor in mammalian immunity. In mammals, it is essential to differentiate the subsets of dendritic cells (DCs) classified as CD8 alpha+ and CD103+, which are vital in antigen cross-presentation [46].

In line with this area of research, another study established that BATF3 is essential for developing conventional Dendritic Cells (cDCs), and CD8 alpha+, also known as Cytotoxic T lymphocytes (CTLs) or Killer T cells. The CD8 alpha+ from Batf3-/-- mice were defective in cross-presentation of exogenous antigens to CD8+ T cells. This process of antigen cross-presentation is critical for initiating cytotoxic response specifically against viral and tumor loads. These mice failed to mount an effective CD8+ T cell response against West Nile Virus (WNV). Also, this study confirmed that Batf3-/-- mice failed to reject highly immunogenic syngeneic tumors, correlating with tumor-specific CTL responses and CD8+ T cell infiltration into tumors. Taken together, Batf3-/-- mice had impaired antiviral immunity and reduced tumor surveillance in them [47].

BATF-3 is remarkably important in cancer immunotherapy. A distinct DCs subset known as conventional type-1 Dendritic Cells (cDC-1) is of vital importance because they activate cytotoxic T-lymphocytes and provide anticancer immunity. It was found that cDC1-deficient Batf3 -/- mice were unable to recruit CD8+ effector T cells to the tumor site and thus failed to provide cDC-1-mediated anti-tumor immunity within the system [48,49]. Moreover, it has been documented that the BATF3-dependent DCs assist in the prevention of autoimmunity to maintain immune homeostasis [50].

Investigations of comparative immunological studies across species have provided new perspectives on BATF3-related conserved mechanisms in complex organisms. As already discussed in this review, the role of ZIP-10 in *C. elegans* is a negative regulator of innate immunity. The same study translated this finding with ZIP-10 ortholog BATF3 in mammalian cell lines [41].

Altogether, these findings briefly illustrate that mechanisms established in simpler organisms have the potential to provide foundational insights into more complex immune responses in vertebrates.

## Conclusion and Perspectives

Remarkably, ZIP-10 has emerged as a key regulator of immune and stress response in *C elegans*, playing a vital role in managing stress response, metabolism, and activation of IPR mechanisms essential in upholding host defenses.

Further investigation is needed to delineate the upstream signaling that regulates ZIP-10 and its downstream effectors, pathogen-derived signals, as well as the coordination between different tissues and organs during pathogenic infection. It will be interesting to delineate other signaling pathways that crosstalk with ZIP-10 and explore its role in non-bacterial infections such as microsporidia. ZIP-10 contributes to the management of a diverse array of pathogens, which facilitates the study of different types of infections.

How ZIP-10 regulates the intricacy of immune modulation will undoubtedly enhance our understanding of innate immunity, with broader prospects for biological and medical implications. The relevance and amenability of *C. elegans* in high-throughput screens serve in identifying new therapeutic strategies, especially considering challenges like antibiotic resistance.

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