GATA transcription factors as tissue-specific master regulators for induced responses

Dena HS Block¹ and Michael Shapira¹,²,*

¹Department of Integrative Biology; University of California; Berkeley, CA USA; ²Graduate Group in Microbiology; University of California; Berkeley, CA USA

Keywords: ATF-7, ELT-2, ELT-3, GATA, infection, NHR-25, p38, SKN-1, STA-2, stress response

GATA transcription factors play important roles in directing developmental genetic programs and cell differentiation, and are conserved in animals, plants and fungi. C. elegans has 11 GATA-type transcription factors that orchestrate development of the gut, epidermis and vulva. However, the expression of certain GATA proteins persists into adulthood, where their function is less understood. Accumulating evidence demonstrates contributions of 2 terminal differentiation GATA transcription factors, ELT-2 and ELT-3, to epithelial immune responses in the adult intestine and epidermis (hypodermis), respectively. Involvement in other stress responses has also been documented. We recently showed that ELT-2 acted as a tissue-specific master regulator, cooperating with 2 transcription factors activated by the p38 pathway, ATF-7 and SKN-1, to control immune responses in the adult C. elegans intestine. Here, we discuss the broader implications of these findings for understanding the involvement of GATA transcription factors in adult stress responses, and draw parallels between ELT-2 and ELT-3 to speculate that the latter may fulfill similar tissue-specific functions in the epidermis.

Introduction

GATA transcription factors contain one or 2 zinc finger domains, which bind to DNA motifs with the WGATAR consensus sequence, and are conserved in animals, plants and fungi. GATA factors perform various roles, but in their best-characterized role, serve as regulatory switches contributing to long-term cell fate decisions. Examples include fungal GATA transcription factors, which are pivotal for morphological cell differentiation and activation of metabolic networks⁠; Drosophila’s Serpent and Pannier, which drive heart and haematopoietic differentiation⁠; the vertebrate GATA4, 5 and 6, which play pivotal roles in endoderm differentiation⁠; and the vertebrate GATA1, 2, and 3, which are important for haematopoietic differentiation, including lymphocyte terminal differentiation.⁶⁻⁸ In addition to their roles in differentiation, GATA transcription factors have been shown to take part in the regulation of induced stress responses. Examples include GATA3-dependent induction of Th2 cytokines by allergens,⁹ regulation of antimicrobial peptides during Drosophila innate immune responses by Serpent or dGATAe,¹⁰,¹¹ or GATA4-dependent responses to mechanical stress in the heart.¹² Induced responses to environmental conditions are rapid and transient, and thus different from developmental switches, or even from metabolic switches. This suggests different modes of action for GATA transcription factors in the different processes, following different rules, and dependent on interactions with different proteins.

C. elegans has 11 GATA-type transcription factors, and all but one (elt-1) are homologous to the vertebrate GATA4-6 subgroup.¹³ As in other animals, C. elegans GATA transcription factors are involved in cell differentiation and tissue specification. elt-1, elt-3, egl-18(elt-5) and elt-6 guide epidermal specification and differentiation¹⁴,¹⁵: elt-3 is expressed in all epidermal cells except for the seam cells, while egl-18 (elt-5) and elt-6 are expressed mostly in seam cells and are further required for vulval development.¹⁶,¹⁷ med-1, med-2, end-1, end-3, elt-2 and elt-7 orchestrate intestinal development and differentiation,¹⁸ but elt-4, which is also expressed in the intestine, encodes a truncated protein and is likely non-functional.¹⁹ elt-2 and elt-3 are regulators of terminal differentiation in their respective tissues, and were proposed to be autoregulated, consistent with their contributions to a stable developmental switch, and with their persistent expression into adulthood.¹⁹,²⁰,²¹ Adult expression of elt-2 was assumed to be responsible for maintaining tissue structure and function, but accumulating evidence points at additional roles of adult elt-2, as well as of elt-3, in regulating tissue-specific immune responses, and potentially other stress responses.²²⁻²⁸ Recent work in our lab, focusing on the roles of adult elt-2 in regulating immune responses, suggested that ELT-2 functioned as a master regulator for induced immune responses in the intestine, cooperating with signal-activated transcription factors.²⁹ This commentary will focus on these results and will take advantage of the insights gained to consider similar functions for elt-3 in epidermal induced responses.

From Embryonic to Adult Functions

ELT-2 is the dominant factor required for terminal differentiation in the intestine, and its ectopic expression was shown to be sufficient to drive expression of intestinal markers (i.e. the
carboxylesterase gene ger-1 and the intestinal intermediate filament gene ifb-2) outside of the intestine. Moreover, elt-2 expression is maintained into adulthood, through autoregulation. This suggested that elt-2 was required for maintenance of intestinal function and structure in the adult. However, a study following the expression of intestinal markers showed that elt-2 was not the sole intestinal regulator. For most tested intestinal genes, including ifb-2 and ges-1, expression was co-dependent on a second intestinal GATA transcription factor, elt-7, which functions redundantly with elt-2. Redundancy is a common theme in the contribution of GATA transcription factors. Furthermore, knock-down of elt-2 in adults was found to be insufficient to affect ifb-2 expression, or the expression of other genes encoding intestinal structural proteins, including the intestine-specific actin isoform act-5, and the adherens junction protein let-413. Nevertheless, elt-2's contribution remains dominant in adults for the expression of a more specific subset of intestinal genes enriched for genes encoding hydrolytic enzymes, such as lysozymes, peptidases and lipases. Such genes were previously shown to make up a significant part of those expressed in the adult C. elegans intestine, and may contribute both to digestive functions and to protection from bacterial pathogens.

Similar to the developmental contributions of elt-2 in the intestine, activation of elt-3 expression (by ELT-1) immediately following the terminal division of cell lineages that give rise to most epidermal cells, is thought to signify a shift from epidermal cell fate specification to epidermal differentiation. Supporting its importance for epidermal cell identity, ectopic expression of elt-3 activated the expression of epidermal markers in non-epidermal tissues. However, worms lacking elt-3 are viable, and maintain epidermal cell differentiation, attesting to redundancy in elt-3's contribution to epidermal development. ELT-1 was suggested to be the transcription factor complementing the function of ELT-3 in elt-3 mutants. Alternatively, an ELT-1-induced second transcription factor, NHR-25, was shown to share 50% of its targets (identified by chromatin immunoprecipitation, or ChIP) with ELT-3, suggesting that it might be the one functioning redundantly with ELT-3 instead of ELT-1. ELT-3 expression peaks at embryonic stages, but persists at low levels (putatively through autoregulation) into late larval stages and adulthood. Supporting autoregulation, ChIP-identified ELT-3 targets included the elt-3 promoter.

Contributions to Induced Stress Responses

ELT-2

Accumulating evidence indicates that in adults ELT-2 contributes to immune protection. Disruption of elt-2 results in decreased resistance to various bacterial pathogens, including Pseudomonas aeruginosa, Salmonella typhimurium and Enterococcus faecalis, as well as to ingested fungi like Cryptococcus neoformans. Contribution to immune protection is not a by-product of general malaise, as worms in which elt-2 was knocked down only during adulthood still have a normal lifespan. ELT-2 is also required for protection from osmotic stress. This may represent involvement in adaptation to environmental conditions, but was alternatively suggested to represent toxin-induced damage caused by certain pathogens, as osmotic stress responses showed a significant overlap with those caused by Cry5B, a pore-forming toxin from Bacillus thuringiensis. Support for the emerging theme of ELT-2 as a regulator of pathogen resistance was further provided by a study of Burkholderia pseudomallei infection in C. elegans, which highlighted ELT-2 as a target in the evolutionary arms race, targeted for proteosomal degradation, which depended on the pathogen's type III secretion system. Studies of elt-2-dependent immune responses focused on those induced in response to the Gram negative pathogen P. aeruginosa, identifying 100-200 elt-2-regulated induced genes, with known or putative anti-bacterial functions. Since ELT-2 was reported to be constitutively localized to the nucleus, it was not clear how it responded to a signal originating extracellulary. In lymphocytes, GATA3 was shown to move into the nucleus following phosphorylation by the stress-activated p38 MAPK; the endodermal GATA4 is instead modified by the GSK3b kinase. In Drosophila, on the other hand, Serpent, a GATA protein mostly restricted to the immunogenic fat body, was shown to contribute to circadian gene expression by interacting with 2 broadly expressed oscillating regulators. The first clue of how the C. elegans ELT-2 may mediate induced responses was provided by a comparison between identified elt-2-dependent genes and genes previously shown to be regulated by the p38 pathway, which demonstrated a significant overlap, suggesting that ELT-2 may function downstream of the p38 pathway.

The C. elegans p38 pathway plays pivotal roles in C. elegans stress responses, in particular in responses to oxidative stress and infection. Two transcription factors have been shown to mediate its contributions – ATF-7 for infection responses, and SKN-1 for both oxidative stress and infection responses. Genetic analyses performed could not weigh-in on whether the p38 pathway interacted directly with ELT-2; however, they showed that elt-2 functioned downstream of the p38 pathway, and cooperated with both atf-7 and skn-1 in inducing different subsets of the infection response (Fig. 1). While induction of genes of one subset was fully dependent on elt-2 and atf-7, induction of genes of the other subset required, in addition, skn-1. ATF-7 is a repressor of infection-response genes, which becomes an enhancer upon phosphorylation by the p38 kinase PMK-1. Accordingly, RNAi-mediated knock-down of atf-7 dramatically increased target gene expression in the absence of infection. However, a simultaneous disruption of elt-2 abolished this increase, demonstrating a dominant role for ELT-2 in gating ATF-7 and in regulating its targets. With regards to SKN-1, it is yet unknown whether its contribution to immune responses was due to direct activation by the p38 MAPK pathway, or secondary to production of reactive oxygen species as part of the immune response; previous studies have demonstrated both modes of activation. These results support a model in which ELT-2 functions as a master regulator of intestinal immune gene expression, cooperating with transcription factors that are directly activated by the p38 pathway. This is reminiscent of the model proposed for the contribution of Drosophila’s Serpent to
worms, contributing to lifespan extension in an insulin receptor mutant. A second study attributed DAF-16-dependent gene down-regulation to the transcription factor PQM-1, which localized to the nucleus when DAF-16 was cytoplasmic, but was displaced when DAF-16 entered, and was suggested to operate through the DAE. Based on all of the above, it seems likely that PQM-1 interacts with ELT-2 in this regulation.

Altogether, the results from our lab and from others support the notion that in the adult worm elt-2 holds the role of a tissue-specific master regulator, enabling stress responses by cooperating with signal-activated transcription factors downstream to condition-specific signaling pathways.

**ELT-3**

ELT-3 is not as well-characterized as ELT-2, but similar to ELT-2, it is localized to the nucleus, and has been shown to take part in tissue-specific induced responses, regulating late larval, or adult, responses to the cuticle-adhering fungal pathogen *Drechmeria coniospora*. |

**Figure 1.** GATA transcription factors in intestinal and epidermal stress responses. A schematic depicting the regulation of epithelial immune responses, focusing on downstream mechanisms associated with ELT-dependent gene expression. Summary of current knowledge (solid lines), as well as inferred or putative modes of activation (dotted lines). Induced responses are exemplified in the context of the *Pseudomonas aeruginosa* model of intestinal infection, and *Drechmeria coniospora* model of epidermal infection. Highlighted are different gene subsets represented by specific genes or gene families, showing their respective regulatory programs. Question marks highlight general effects for which mediators are yet unknown.

As mentioned above, elt-2 is also required for non-infection stress responses. This was shown for osmotic stress, as well as for TOR-dependent hypoxia responses, and responses to high levels of dietary zinc. In addition, elt-2 was recently reported to contribute to recovery from *Salmonella* infection: beyond its previously-described role in protecting worms during the course of infection, this study focused on gene expression following treatment of infection with antibiotics, identifying a significant contribution of elt-2 to post-infection induction of detoxification genes, which seem to represent a general stress response. It is important to note that in the above-mentioned stress responses the p38 pathway is not always the upstream activator; osmotic stress responses and induction of detoxification genes require elt-2, but not the p38 pathway.

DAF-16 is arguably the best-characterized stress-activated transcription factor, known for its pivotal role in lifespan extension following disruption of insulin signaling. DAF-16 is translocated into the nucleus following heat shock, oxidative stress or UV radiation (as well as other conditions), where it activates stress protective responses. A GATA-like DNA motif was long-recognized in promoters of DAF-16-regulated genes, where it was dubbed the DAF-16-associated element (DAE). A recent study showed that ELT-2 in fact bound this element, and was essential for intestinal DAF-16-dependent expression in adult worms, contributing to lifespan extension in an insulin receptor mutant. A second study attributed DAF-16-dependent gene down-regulation to the transcription factor PQM-1, which localized to the nucleus when DAF-16 was cytoplasmic, but was displaced when DAF-16 entered, and was suggested to operate through the DAE. Based on all of the above, it seems likely that PQM-1 interacts with ELT-2 in this regulation.

Altogether, the results from our lab and from others support the notion that in the adult worm elt-2 holds the role of a tissue-specific master regulator, enabling stress responses by cooperating with signal-activated transcription factors downstream to condition-specific signaling pathways. ELT-3

ELT-3 is not as well-characterized as ELT-2, but similar to ELT-2, it is localized to the nucleus, and has been shown to take part in tissue-specific induced responses, regulating late larval, or adult, responses to the cuticle-adhering fungal pathogen *Drechmeria coniospora*. While ChIP analyses were carried out in L1 larvae, the results of Pujol et al. support the persistence of elt-3-dependent antimicrobial gene regulation into adulthood. Comparisons of ChIP-identified target lists further shows that a third of ELT-3’s targets are also bound (in L4 larvae) by the stress regulator SKN-1, much more than would be expected by chance, suggesting a greater involvement of ELT-3 in stress gene regulation than currently appreciated. Lastly, while ELT-2 was shown to be essential for DAF-16-dependent expression of many intestinal targets, ELT-3 seems to have a similar role in epidermal DAF-16-dependent gene expression, although it does not demonstrate a significant contribution to lifespan. **Figure 1.** GATA transcription factors in intestinal and epidermal stress responses. A schematic depicting the regulation of epithelial immune responses, focusing on downstream mechanisms associated with ELT-dependent gene expression. Summary of current knowledge (solid lines), as well as inferred or putative modes of activation (dotted lines). Induced responses are exemplified in the context of the *Pseudomonas aeruginosa* model of intestinal infection, and *Drechmeria coniospora* model of epidermal infection. Highlighted are different gene subsets represented by specific genes or gene families, showing their respective regulatory programs. Question marks highlight general effects for which mediators are yet unknown.

As mentioned above, elt-2 is also required for non-infection stress responses. This was shown for osmotic stress, as well as for TOR-dependent hypoxia responses, and responses to high levels of dietary zinc. In addition, elt-2 was recently reported to contribute to recovery from *Salmonella* infection: beyond its previously-described role in protecting worms during the course of infection, this study focused on gene expression following treatment of infection with antibiotics, identifying a significant contribution of elt-2 to post-infection induction of detoxification genes, which seem to represent a general stress response. It is important to note that in the above-mentioned stress responses the p38 pathway is not always the upstream activator; osmotic stress responses and induction of detoxification genes require elt-2, but not the p38 pathway.

DAF-16 is arguably the best-characterized stress-activated transcription factor, known for its pivotal role in lifespan extension following disruption of insulin signaling. DAF-16 is translocated into the nucleus following heat shock, oxidative stress or UV radiation (as well as other conditions), where it activates stress protective responses. A GATA-like DNA motif was long-recognized in promoters of DAF-16-regulated genes, where it was dubbed the DAF-16-associated element (DAE). A recent study showed that ELT-2 in fact bound this element, and was essential for intestinal DAF-16-dependent expression in adult worms, contributing to lifespan extension in an insulin receptor mutant. A second study attributed DAF-16-dependent gene down-regulation to the transcription factor PQM-1, which localized to the nucleus when DAF-16 was cytoplasmic, but was displaced when DAF-16 entered, and was suggested to operate through the DAE. Based on all of the above, it seems likely that PQM-1 interacts with ELT-2 in this regulation.

Altogether, the results from our lab and from others support the notion that in the adult worm elt-2 holds the role of a tissue-specific master regulator, enabling stress responses by cooperating with signal-activated transcription factors downstream to condition-specific signaling pathways.

ELT-3

ELT-3 is not as well-characterized as ELT-2, but similar to ELT-2, it is localized to the nucleus, and has been shown to take part in tissue-specific induced responses, regulating late larval, or adult, responses to the cuticle-adhering fungal pathogen *Drechmeria coniospora*. While ChIP analyses were carried out in L1 larvae, the results of Pujol et al. support the persistence of elt-3-dependent antimicrobial gene regulation into adulthood. Comparisons of ChIP-identified target lists further shows that a third of ELT-3’s targets are also bound (in L4 larvae) by the stress regulator SKN-1, much more than would be expected by chance, suggesting a greater involvement of ELT-3 in stress gene regulation than currently appreciated. Lastly, while ELT-2 was shown to be essential for DAF-16-dependent expression of many intestinal targets, ELT-3 seems to have a similar role in epidermal DAF-16-dependent gene expression, although it does not demonstrate a significant contribution to lifespan.
Interestingly, knock-down of NHR-25, the same transcription factor mentioned above as a potential redundant partner for ELT-3 during epidermal differentiation, was found to result in induction of epidermal infection genes, including the ELT-3-regulated nlp genes. Unlike ELT-3, NHR-25 can be found both in the cytoplasm and in the nucleus. Thus, while nhr-25 knock-down may affect immune gene expression indirectly through impairment to epidermal cell structures, it is tempting to speculate that there are conditions in which NHR-25 cooperates with ELT-3 in regulating induced immune responses. The observation that knock-down of nhr-25 leads to nlp gene induction, indicating involvement in gene repression under normal conditions, further suggests that a cooperation between ELT-3 and NHR-25 may be similar to that observed between ELT-2 and ATF-7.

Two additional response activators are intriguing as potential partners of ELT-3 in regulating epidermal immune and stress responses. First, STA-2, a STAT transcription factor-like protein, was proposed to be phosphorylated by the p38 pathway following either fungal infection or wounding, and was shown to regulate epidermal immune gene expression. Activation of the p38 pathway (which was shown by others to occur either downstream of the GPA-12 G-protein α subunit, or of the Tribbles-like kinase NPI1) was suggested to shift STA-2 into the nucleus to induce immune gene expression (Fig. 1); translocation of STA-2 from the apical membrane to the nucleus was reported by another study following severe structural damage to the epidermis, although under these conditions the p38 pathway was not required. Second, SMA-3, a downstream mediator of TGFβ signaling, was found to be necessary for gene induction during Drosophila infection. SMA-3 was necessary specifically for the induction of caenacin genes, which, as mentioned above, are also binding-targets of ELT-3. Thus, the involvement of ELT-3 in regulating immune responses may represent a more general theme in the function of GATA transcription factors.

Conclusions

Accumulating evidence supports the notion that in the adult intestine ELT-2 functions as a master regulator for induced responses, in particular during infection, but potentially also under other types of stress. In this capacity ELT-2 appears to differ from vertebrate GATA transcription factors, which were described to be directly activated by signal transduction pathways. Instead, it resembles Drosophila’s Serpent, which was reported to mediate gene regulation by other transcription factors. Certain functional characteristics of ELT-2 are shared with the epidermal GATA transcription factor ELT-3. Such parallels suggest a similar mode of function, and further suggest that ELT-2’s contribution to immune responses may represent a more general theme in the function of GATA transcription factors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We wish to thank Dr. Nathalie Pujol and Maureen Berg for useful comments.

Funding

Research leading to this commentary was supported by the Ellison Medical Foundation.

References

1. Rohde JR, Cardenas ME. Nutrient signaling through TOR kinases controls gene expression and cellular differentiation in fungi. Curr Top Microbiol Immunol 2004; 279:53-72; PMID:14565991
2. Tudzynski B. Nitrogen regulation of fungal secondary metabolism in fungi. Front Microbiol 2014; 5:656; http://dx.doi.org/10.3389/fmicb.2014.00656
3. Sorrentino RP, Gajewski KM, Schaal RA. GATA factors in Drosophila heart and blood cell development. Semin Cell Dev Biol 2005; 16:167-16; PMID:15659345; http://dx.doi.org/10.1016/j.semcdb.2004.10.005
4. Bossard P, Zaret KS. GATA transcription factors as potentiation of gut endoderm differentiation. Development 1998; 125:4909-17; PMID:9811575
5. Lowry JA, Archley WR. Molecular evolution of the GATA family of transcription factors: conservation within the DNA-binding domain. J Mol Evol 2000; 50:103-12; PMID:10688444
6. Crispino JD. GATA1 in normal and malignant hematopoiesis. Semin Cell Dev Biol 2005; 16:137-47; PMID:15459348; http://dx.doi.org/10.1016/j.semcdb.2004.11.002
7. Breitling EH, Lee HY, Fujiwara T, Johnson KD, Keles S. GATA switches as developmental drivers. J Biol Chem 2010; 285:31087-93; PMID:20670937; http://dx.doi.org/10.1074/jbc.R110.159079
8. Wan Y. GATA3: a master of many trades in immune regulation. Trends Immunol 2014; 35:233-42; PMID:24780613; http://dx.doi.org/10.1016/j.it.2014.04.002
9. Manezocheswishu K, Xin Y, Ito K, Jazrawi E, Lee KY, Usmani OS, Barnes PJ, Adcock IM. Regulation of Th2 cytokine genes by p38 MAPK-mediated phosphorylation of GATA-3. J Immunol 2007; 178:2491-8; PMID:17277157; http://dx.doi.org/10.4049/jimmunol.178.4.2491
10. Petersen UM, Kadalayil L, Rehorn KP, Hoshizaki DK, Reuter R, Engstrom Y. Serpent regulates Drosophila immunity genes in the larval fat body through an essential GATA motif. Embo J 1999; 18:4013-22; PMID:10480606; http://dx.doi.org/10.1093/emboj/18.14.4013
11. Senger K, Harris K, Levine M. GATA factors participate in tissue-specific immune responses in Drosophila larvae. Proc Natl Acad Sci USA 2006; 103:15997-60; PMID:17032752; http://dx.doi.org/10.1073/pnas.0607601103
12. Teshunen O, Sarman B, Kerkela R, Szokodi I, Papp L, Toth M, Ruskoaho H. Mitogen-activated protein kinases p38 and ERK 1/2 mediate the wall stress-induced activation of GATA-4 binding in adult heart. J Biol Cell 2001; 21:2533-44; PMID:11259601; http://dx.doi.org/10.1128/MCB.21.7.2533-2544.2001
13. Koh K, Rothman JH. ELT-5 and ELT-6 are required continuously to regulate epidermal seam cell differentiation and cell fusion in C. elegans. Development 2001; 128:2867-80; PMID:11532991
14. Chisholm AD, Hisao TI. The Caenorhabditis elegans epidermis as a model skin. I: development, patterning, and growth. Wiley Interdiscip Rev Dev Bio 2012; 1:861-78; PMID:23539299; http://dx.doi.org/10.1002/wdev.79
15. Koh K, Perrot SM, Wood CG, Wagnmaister JA, Maduro MF, Eisenmann DM, Rothman JH. Cell fates and fusion in the C. elegans vulva primordium are regulated by the EGL-18 and ELT-6 GATA factors – apparent direct targets of the LIN-39 Hox protein. Development 2002; 129:5171-80; PMID:12399309
16. Maduro MF, Britman-Maduro G, Choi H, Carranza F, Wu AC, Rifkin SA. MED GATA factors promote robust development of the C. elegans endoderm. Dev Biol 2015; 404:64-79; PMID:25959238; http://dx.doi.org/10.1016/j.ydbio.2015.04.025
Fukushima T, Goczynsky B, Tian H, McGehee JD. The evolutionary duplication and probable demise of an endodermal GATA factor in Caenorhabditis elegans. Genetics 2003; 165:575-88; PMID:14537471

Fukushima T, Hawkins MG, McGehee JD. The GATA-factor elt-2 is essential for formation of the Caenorhabditis elegans intestine. Dev Biol 1998; 198:286-302; PMID:9059934

Fukushima T, Hendzel MJ, Baer-Jones DP, McGehee JD. Direct visualization of the elt-2 gut-specific GATA factor binding to a target promoter inside the living Caenorhabditis elegans embryo. Proc Natl Acad Sci U S A 1999; 96:11883-8; PMID:10518545; http://dx.doi.org/10.1073/pnas.99.19.11883

Shapira M, Hanlin BJ, Rong J, Chen K, Ronen S, Tan MW. A conserved role for a GATA transcription factor in regulating epithelial innate immune responses. Proc Natl Acad Sci U S A 2010; 107:14086-91; PMID:16968778; http://dx.doi.org/10.1073/pnas.1009943

Kerry S, TeKippe M, Gaddis NC, Aballay A. Recovery from an acute infection in C. elegans requires the GATA transcription factor ELT-2. PLoS Genet 2014; 10:e1004609; PMID:25340560

Celniker SE, Dillon LA, Gerstein MB, Gunsalus KC, Henikoff S, Karpen GH, Kells M, Lai EC, Lieb JD, MacAlpine DM, et al. Unlocking the secrets of the genome. Nature 2004; 428:37-42; PMID:15396255; http://dx.doi.org/10.1038/459927a

Lee SH, Wong RR, Chin CY, Lim TY, Eng SA, Kong C, Iap NA, Lau MS, Lim MP, Gan YH, et al. Bur- holderia pseudomalvae suppresses Caenorhabditis elegans immunity by specific degradation of a GATA transcription factor. Proc Natl Acad Sci U S A 2013; 110:15067-72; PMID:23938018; http://dx.doi.org/10.1073/pnas.1311725110

Morisco C, Seta K, Harde S, Lee Y, Varner SF, Sadoshima J. Glycogen synthase kinase 3beta regulates GATA4 cardiac in myocytes. J Biol Chem 2001; 276:28586-97; PMID:11382772; http://dx.doi.org/10.1074/jbc.M101366200

Meindres-Filho AC, Bardek AF, Yanes-Cuna JO, Stampati AL, da Paz C, de Moraes MC. Developmental programs of a GATA transcription factor. BMCdev Biol 2010; 10:16; PMID:20495789; http://dx.doi.org/10.1186/1471-2121-10-16

Shao J, He K, Wang H, Hu W, Ren X, An X, Wong MK, Yai E, Xie D, Sui-qinganopostoj J. Collaborative regulation of development but independent control of metabolism by two epidermis-specific transcription factors in Caenorhabditis elegans. J Biol Chem 2013; 288:33411-26; PMID:24097998; http://dx.doi.org/10.1074/jbc.M113.487757

Rothman JH. Endoderm development in Caenorhabditis elegans intestine. Dev Biol 1998; 198:286-302; PMID:9659934

Goncharov A, Jin Y, Chisholm AD, Ewbank JJ. Dissection of nematode-microbe interactions. Cell Microbiol 2010; 12:1609-19; PMID:20372131; http://dx.doi.org/10.1111/j.1751-1080.2010.00629.x

Lin K, Dorman JB, Rodan A, Kenyon C.daf-16: An HNF-3/forhead family member that can function to double the life-span of Caenorhabditis elegans. Science 1997; 278:1519-22; PMID:9360933; http://dx.doi.org/10.1126/science.278.5341.1519

Henderson ST, Johnson TE. daf-16 integrates developmental and environmental inputs to mediate aging in the nematode Caenorhabditis elegans.Curr Biol 2001; 11:1975-80; PMID:11747825; http://dx.doi.org/10.1016/j.cub.2001.11.031

Murphy CT, McCarthy CA, Bergmann CI, Fraser A, Kamath RS, Ahnger JI, Ts Li, Kenyon C. Genes that act downstream of DAF-16 to influence the lifespan of Caenorhabditis elegans. Nat Re\2003; 242:277-83; PMID:12032658; http://dx.doi.org/10.1073/pnas.1101471100

Zhang P, Judy M, Lee SJ, Kenyon C. Direct and indirect gene regulation by a life-extending FOXO protein in C. elegans: roles for GATA factors and lipid gene regulators. Cell Metab 2013; 17:85-100; PMID:23312285; http://dx.doi.org/10.1016/j.cmet.2012.10.013

Tepper RG, Ashard J, Kaledys KL, Kleemann G, Murphy CT, Bussemaker HJ. POU-1 complements DAF-16 as a key transcriptional regulator of DAF-2-mediated development and longevity. Cell 2013; 154:676-90; PMID:23911329; http://dx.doi.org/10.1016/j.cell.2013.07.006

Gilleard JS, Shaw Y, Barry JD, McGehee JD. ELT-3: A Caenorhabditis elegans GATA factor expressed in the embryonic epidermis during morphogenesis. Dev Biol 1995; 190:265-80; PMID:10191040; http://dx.doi.org/10.1006/dbio.1999.9202

Pujol N, Zugasti O, Wong D, Couillault C, Kurz C, Schulenburg H, Ewbank JJ. Anti-fungal innate immunity in Caenorhabditis elegans is enhanced by evolutionary diversification of antimicrobial peptides. PLoS Pathog 2008; 4: e1000105; PMID:18636113; http://dx.doi.org/10.1371/journal.ppat.1000105

Ward JD, Muilleyen B, Schiller BJ, He le D, Penic SE, Costello DC, Pujol N. Unusual regulation of immune gene action in Arabidopsis. Plant Physiol 2008; 147:707-18; PMID:18417639; http://dx.doi.org/10.1104/pp.108.120137

Bose N, Zugasti O, Squiban B, Belougne J, Kurz CL, Wright JK, Matsumoto K. The C. elegans p38 MAPK regulates expression of immune response genes and contributes to longevity in C. elegans. PLoS Genet 2006; 2:e183; PMID:17096597

Ward JD, Muilleyen B, Schiller BJ, He le D, Penic SE, Costello DC, Pujol N. Unusual regulation of immune gene action in Arabidopsis. Plant Physiol 2008; 147:707-18; PMID:18417639; http://dx.doi.org/10.1104/pp.108.120137

Xiong H, Mohler WA, Soto MC. The branched actin nucleator Arp2/3 promotes nuclear migrations and cell polarity in the C. elegans zygote. Dev Biol 2011; 357:356-69; PMID:21729925; http://dx.doi.org/10.1016/j.ydbio.2011.07.008

Dierking K, Polonowska J, Omi S, Engelska G, Gut M, Lembo F, Ewbank JJ, Pujol N. Unusual regulation of a STAT protein by an SLC6 family transporter in C. elegans epidermal immune cell. Cell Host Microbe 2011; 9:425-52; PMID:24651852; http://dx.doi.org/10.1016/j.chom.2011.07.004

Zagata O, Bose N, Squiban B, Belougne J, Kurz CL, Schneider FC, Pujol N, Ewbank JJ. Activation of a G protein-coupled receptor by its endogenous ligand trig- gers the innate immune response of Caenorhabditis elegans. Nat Immunol 2014; 15:833-8; PMID:25086774; http://dx.doi.org/10.1038/ni.2957

Zhang Y, Li W, Li L, Li Y, Fu R, Zhu Y, Li J, Zhou Y, Xiong S, Zhang H. Structural damage in the C. elegans epidermis causes release of STA-2 and induction of an innate immune response. Immunity 2015; 42:309-20; PMID:25296204; http://dx.doi.org/10.1016/j.immuni.2015.01.014

Zagata O, Ewbank JJ. Neuroimmune regulation of antimicrobial peptide expression by a noncanonical TGF-beta signaling pathway in Caenorhabditis elegans. Nat Immunol 2005; 16:255-65; PMID:15918952; http://dx.doi.org/10.1038/ni.1700

http://www.tandfonline.com