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

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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[1,2]; *Drosophila*'s Serpent and Pannier, which drive heart and haematopoietic differentiation[3]; the vertebrate GATA4, 5 and 6, which play pivotal roles in endoderm differentiation[4,5]; 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 differentiation[14,15]: *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.[14,20,21] 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

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carboxylesterase gene *ges-1* and the intestinal intermediate filament gene *ifb-2*) outside of the intestine.[20,30,31] Moreover, *elt-2* expression is maintained into adulthood, through autoregulation.[21] 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*.[31] Redundancy is a common theme in the contribution of GATA transcription factors.[32-35] 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*.[22,29] 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.[29] Such genes were previously shown to make up a significant part of those expressed in the adult *C. elegans* intestine,[30] and may contribute both to digestive functions and to protection from bacterial pathogens.[29]

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.[14] However, worms lacking *elt-3* are viable, and maintain epidermal cell differentiation, attesting to redundancy in *elt-3*'s contribution to epidermal development.[14] 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[36]. ELT-3 expression peaks at embryonic stages, but persists at low levels (putatively through autoregulation) into late larval stages and adulthood.[14] Supporting autoregulation, ChIP-identified ELT-3 targets (http://data.modencode.org)[37] 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*.[22,23] 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.[22] 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*.[25] 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.[38]

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.[22,29] Since ELT-2 was reported to be constitutively localized to the nucleus,[21] it was not clear how it responded to a signal originating extracellularly. In lymphocytes, GATA3 was shown to move into the nucleus following phosphorylation by the stress-activated p38 MAPK[9]; the endodermal GATA4 is instead modified by the GSK3β kinase.[39] 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.[40] 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 to the p38 pathway.[29,41]

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.[42-45] 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**).[29,46] 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*[29]. ATF-7 is a repressor of infection-response genes, which becomes an enhancer upon phosphorylation by the p38 kinase PMK-1[45]. 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.[29] 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.[42,43] 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

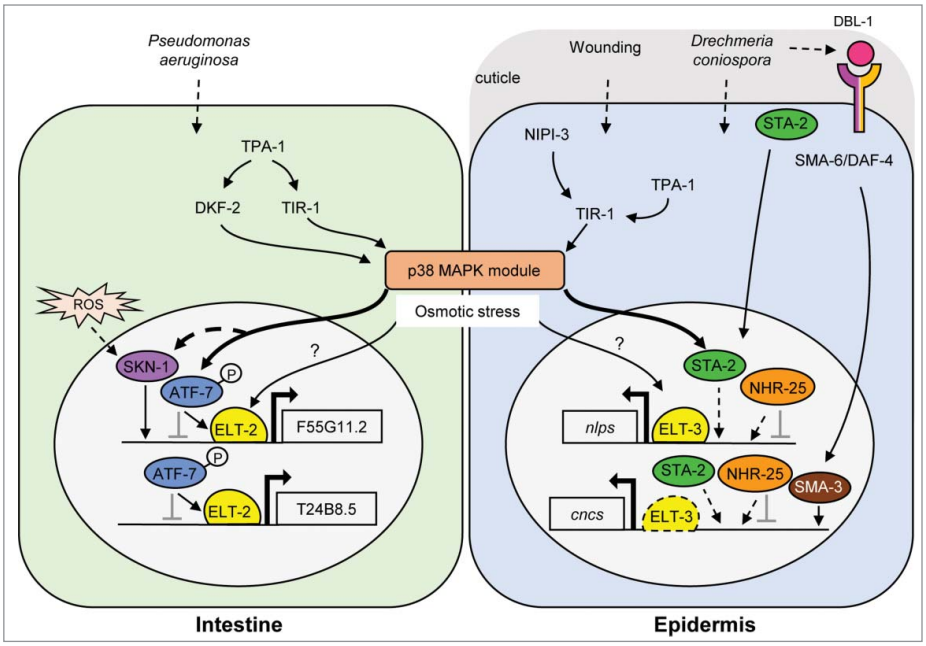

Figure 1. GATA transcription factors in intestinal and epidermal stress responses. A schematic depicting the regulation of epithelial immune responses, focusing on downstream mechanisms associated with ELT-dependent gene expression. Summary of current knowledge (solid lines), as well as inferred or putative 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.

circadian gene expression in which a combination of a tissue-specific stable regulator with inputs from broadly-expressed, signal-activated transcription factors provides tissue-specific induction.

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.[26,27] 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.[28] 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.[25,28]

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.[47,48] 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).[49] 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.[50] 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.[51] 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,[52] 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*, to wounding, and to osmotic stress.[25,53] In regulating responses to infection or to wounding, ELT-3 shares targets with the p38 pathway[24]; however, this is not true for osmotic stress responses, where *elt-3* contributes to a p38-independent response (**Fig. 1**).[25]

Genome-scale characterization of *elt-3*-dependent responses has not yet been carried out, but *elt-3* was shown to contribute to the expression of neuropeptide-like proteins (NLPs), which are a hallmark of both epidermal immune responses and wounding in young adults.[24] Indeed, results from ChIP analysis demonstrate ELT-3 binding to the promoters of many antimicrobial peptide genes, including *nlp* as well as caenacin (*cnc*) genes (http://data.modencode.org).[37] 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.[50] Taken together, different lines of evidence support the possibility that much like ELT-2 in the intestine, ELT-3 may serve as an epidermal master regulator enabling local stress responses.

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.[54] Unlike ELT-3, NHR-25 can be found both in the cytoplasm and in the nucleus.[55] Thus, while *nhr-25* knock-down may affect immune gene expression indirectly through impairment to epidermal cell structures, it is tempting to speculate an alternative possibility 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.[29]

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.[56] 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 NIPI-3[24,57]) was suggested to shift STA-2 into the nucleus to induce immune gene expression (**Fig. 1**)[56]; 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.[58] Second, SMA-3, a downstream mediator of TGFβ signaling, was found to be necessary for gene induction during *Drechmeria* infection. SMA-3 was necessary specifically for the induction of caenacin genes, which, as mentioned above, are also binding-targets of ELT-3[59]. Thus, the involvement of ELT-3 in either STA-2-, or SMA-dependent gene expression would be of interest.

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.

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