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Introduction

The GAGA factor (GAF), produced by *Trithorax*-like gene, *Trl*, in *Drosophila* [1] operates by binding to its DNA recognition sequence, having a consensus sequence, GAGAG [2]. As a transcription factor, it has been found in the promoters and enhancers for the modulation of expression of various genes like the homeotic genes and developmental genes, like the *Ultrabithorax* (*Ubx*), *engrailed* (*en*), *fushi-tarazu* (*ftz*) *even-skipped* (*eve*), *hsp70*, *hsp 26*, *H3/H4*, *Adh*, *E74*, *actin-5C*, and *1-tubulin* [1,3-7]. Besides these roles, the factor is also involved in remodelling of the chromatin, in functions pertaining to the Polycomb responsive element (PRE), and insulator or boundary elements [5,9-14]. This factor shows a high proportion of pleiotropism owing to its localization on the promoter regions of a multitude of genes [8,9]. The gene, *Trl* is presumptively produced maternally [10] hence, a better understanding of its target genes is made by studying the phenotypes using combination of hypomorphic and hypomorphic or null *Trl* alleles. The expression of *Trl* is fundamental to all the stages and all tissues of the fly, even if the levels of mRNA change significantly in these stages [11]. Till date, the studies elucidating the roles of GAGA factor have been made in the embryonic stages. Studies on larval and imago stages have been very scantily made by knocking down or over-expressing different genes. Such experiments have clearly pointed that GAGA factor is an active player in the wing disc and salivary gland development.

Review Article

GAGA Factor Expedites Development in *Drosophila*

Summary

The development in *Drosophila* is a concerted mechanism, occurring via the interplay of a constellation of genes and factors, operating in intricate synchrony. These factors, produced at precise points in their developmental cycle, operate via the activation, through binding to the various transcription factors. The GAGA factor (GAF) is such a product of the *trithorax*-like gene, *Trl*, which binds to a consensus DNA sequence for the modulation of the homeotic gene functions. Besides this, the factor has a role in chromatin remodelling; through binding with the Polycomb responsive element (PRE). The protein has a unique structural conformation with a zinc-finger DNA-binding, a BTB/POZ and a polyglutamine-rich Q domain. It has a unique role of acting as an anti-repressor of the gene, *Kruppel*, releasing the repression on it by the other DNA binding proteins. This report accommodates the interplay in which the GAGA factor is involved in the *Drosophila* embryonic development.

Immuno-fluorescence studies of the salivary glands polytene chromosomes in *Drosophila* showed that this factor binds to a large number of euchromatic genes; hence it points out a role of GAGA factor in the maintenance of open, transcriptionally active chromatin regions.

The GAGA factor was for the first time identified [3], as an *in vitro* activator of the promoter of the gene, *Ultrabithorax* in *Drosophila*. Later on, it found to bind to GAGA elements (having stretches of GAGA or CTCT) over the *hsp70* heat shock promoter and H3/H4 histone gene promoter regions [3,12-14]. Still further reports showed it to have crucial roles in the activation of genes and in regulating the chromatin structure [3,10,14-16]. The GAGA factor also show an interaction with the promoter sequence upstream of genes, *E74* [17], *his3*, *hid*, *hsp26*, and *hsp70* [12] in *Drosophila*. However, the activation of transcription is found only for the genes, *Kr* and *Ubx*. Exceptionally, *Kr* gene is actively transcribed when the GAGA factor binds to the anchoring site located downstream to the target *Kr* gene.

Structure of the GAGA protein

GAF bears a very unique structure having a single zinc finger DNA-binding domain, a BTB/POZ domain, a known protein-protein interaction motif [18], and a polyglutamine-rich Q domain [16,19]. The gene encodes 2 alternatively spliced isoforms of the GAF-GAGA-519 and GAGA-581 of varying length and glutamine-rich C-terminal domain sequences. Each of the isoforms have 3 distinct structural domains: a zinc finger DNA-binding domain (DBD), a broad complex tramtrack

bric-a-brac/ poxvirus domain (BTB/POZ), that involves in protein-protein interaction, and the C-terminal Q domain of a glutamine-rich C-terminus area involved in transcription activation [20-22] (Figure 1). Contrary to initial notion, of the Q domain acting as a transcriptional activator [18,23,24], GAF, in fact operates as an anti-repressor. It is constituted of the following components:

The DNA-binding domain or the DBD: The C-terminus of the GAF possesses a single classical C2-H2 zinc finger DNA-binding domain of 82 amino acid residues from 310-391 after a basic helix flanked of 3 short tracts of basic amino acid residues: BR1, BR2, and BR3 [20,21]. The consensus binding sequence bears a minimal penta-nucleotide, GAGAG [21] of which the tri-nucleotide sequence GAG is essential for recognition and binding [25]. Once that a zinc finger binds the major groove, identifying the GAG sequence, it gets stabilized through interactions with an extension of basic amino acids, at the N-terminal [20,21]. The tract BR1 also wraps around the minor groove with Adenine in the fourth position of the sequence GAGAG [20].

BTB/POZ domain: The BTB/POZ domain of the GAF occurs in all groups of organisms has 122 amino acids located in the N-terminal region of the GAF. This domain provides an interface for the occurrence of protein-protein interactions during transcriptional activation and transcriptional factor repression [18,26-32]. The protein oligomers are actually the result of 3 specific residues- D35, G93, and L112 and there are 3 -helices adjacent to these residues that help in capping, stabilizing the dimerizing at interface [33]. The GAF BTB/POZ domain in GAF forms higher order functional multimeric complexes by virtue of self-association [22,33,34].

Q domain: The C-terminal bears a Q domain that have been involved in promoter distortion, single-strand binding and multi-merization [35]. Because of the single-stranded DNA binding affinity, GAF is able to interact with triple-stranded DNA [36]. In *Drosophila* S2 cells, the Q domain was found to play a role of trans-activation domain. Combinatorial studies

indicate that the Q domain is primarily involved in the larger GAF complex formation, but is not needed for heat shock response functions of the gene, hsp83 [19,35].

DNA-binding activity of the GAGA factor

When the GAGA factor binds to the major groove of DNA and the zinc finger of DBD, additionally interacting with the basic region BR1 at the minor groove [20], it results in a distorted DNA via the interactions of the Q domain at the promoter regions that melts the duplexes [35], especially when GAF binds to the single- and triple-stranded DNA over stretches of (GA)_n [35,36]. The DNA binding over multiple GA or CA stretches is due to the multimer formation caused by Q domain [35] and the BTB/POZ domain [34]. GAF binding sites are more frequent in the introns that suggest a possibility of regulatory role in transcriptional elongation [37]. The protein may to bind to long GA-rich repeats as evident in case of satellite DNA [38,39]. GAF can cause the maintenance of heterochromatic regions in the transcriptionally repressed state by recruiting arrays of GAF at the high density binding sites for GAF.

Interacting partners of GAGA factor

Being a multi-functional protein, GAF, can interact with a significant number of partners executing functions apart from binding single, double, and triple stranded DNA, such as providing multiple binding sites and support for the cofactors to form a feasible functional complex. GAF has depicted to possess the ability to show self-associate as well as associate with other BTB/POZ functional proteins like tramtrack (Ttk), Pipsqueak (Psq), and batman (ban) [6,40,41].

Tramtrack

Tramtrack or *ttk*, is a gene regulating development, that codes for a protein important in oocyte development [A factor that regulates the class II major histocompatibility complex gene DPA is a member of a subfamily of zinc finger proteins that includes a *Drosophila* developmental control protein [42]. The protein, Ttk may be expressed as two proteins-p69 and p88, that bind to the regulatory regions of several segmentation genes [42], like *ftz* to show novel expression pattern in embryos. During the transition from the mitotic to endocycle in the follicle cells, *ttk* promotes the activity of JNK pathway by passing the notch signalling pathway [43]. The *ttk* also codes for proteins that represses the expression of engrailed with the help of *runt* [44]. The *ttk*, thus represses several *Drosophila* genes, the activity of such genes are counteracted by GAF *in vivo*, which functions as anti-repressor [6].

Pipsqueak (Psq)

Psq, essentially regulates development via recognition of the GAGA sequences. However, it needs the GA stretch to be longer than the GAF [2]. Psq has been found to co-localize with GAF for numerous loci in the polytene chromosomes [40], where it and GAF, being members of the polycomb group of complexes, bind to the polycomb response element of the *bxd* gene [45,46]. The interaction between them occurs through their BTB/POZ domains [40].

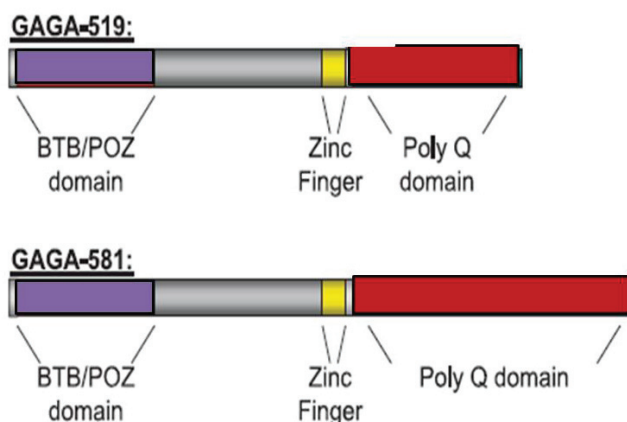


Figure 1: GAGA factor domains: The GAF or GAGA Factor is encoded by the gene which undergoes alternate splicing to form two isoforms- GAGA-519 and GAGA-581 having a zinc finger DNA-binding domain (DBD), a broad complex tramtrack bric-a-brac/ poxvirus domain (BTB/POZ), and the C-terminal Q domain of a glutamine-rich C-terminus.

Batman or ban

The batman or ban co-localizes with GAF and causes the activation and repression of homeotic genes [41]. Besides ban, the proteins, Corto and the sin3-associated polypeptide SAP18, form complexes with GAF's BTB/POZ domain [47,48] and causes histone deacetylation. GAF interacts with the large subunit, NURF 301 of the NURF [49,50], dSSRP1 subunit of FACT [51,52].

GAGA arrests the spreading of heterochromatin

Developmental activities of an organism are under the stringent epigenetic maintenance of the genomic expression. The complex called "facilitates chromatin transcription" or FACT in *Drosophila*, interact with GAGA factor to modulate the structure of the chromatin expression. The gene expression is epigenetically maintained through post-translational modifications of the four core histones on the nucleosome [53]. The expression of two such epigenetic genes- the *Hox* gene, whose expression is governed by Polycomb and Trithorax group genes [54,55] and the position effect variegation (PEV) [56,57], has been extensively studied. Both these phenomena involve silencing and counteracting the maintenance of the active state. The methylation of histone H3 at K27 and/or K9 cause silencing, which then leads to the binding of the Polycomb group or heterochromatin proteins that recognize these silent marks [55,57-60].

The GAF and FACT replace histone H3 into H3.3, by associating HIRA with d1, resulting in the maintenance of expression of the *white* gene in the heterochromatic environment. The active state is sustained through the replacement of Histone H3.3 by the removal of a nucleosome, replacing with H3.3 containing nucleosome with stepwise assembling and disassembling of a nucleosome at the DNase-hypersensitive site of d1. Heterochromatin formation is marked by K9-methylated histone H3 and its binding protein HP1, and has a tendency to spread into neighbouring regions [57,58]. The process of reassembling of the nucleosome, following the replacement of histone, keep on removing K9-methylated histone H3 at d1 and prevent the spreading of the heterochromatin (Figure 2).

GAGA in primordial germ cell migration and gonad development

The development of gonad is possible through the migration of primordial germ cells (PGCs). The germ cell progenitors are formed at the posterior pole of the embryo in the region where the maternal germplasm reside. Once specified, after several mitotic divisions, these cells separate from the embryonic syncytium and move inside the embryo [61,62]. The migration of PGC has two stages- passive and active. While passive migration occurs during morphogenetic events of gastrulation, leading to the shifting of germ cells to the midgut pocket by cellular invagination of the prospective endoderm, active migration takes place within the embryo via the autonomous movement of the PGCs. PGCs cross the primary gut wall forming pseudopodia like structures and then

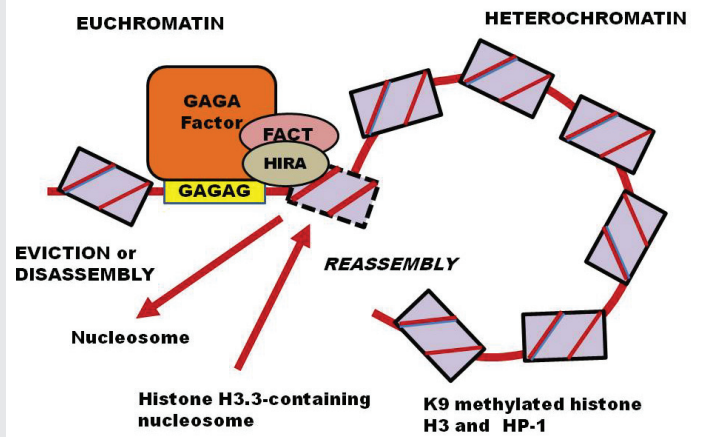


Figure 2: Silencing and counteracting of silencing sites: The replacement of the histone H3.3 by Histone H3 by the GAGA factor (GAF) binding to its consensus binding site, in association with HIRA, leads to the maintenance of silent state of the gene, white. For the active state, the H3.3 nucleosome is replaced by the H3 to cause the eviction of that very nucleosome.

join the mesodermal cells to form the somatic progenitor cells of the gonads, localized to either sides of the ventral groove in the fifth abdominal embryonic segment [61-63].

The GAGA factor encoding gene, *Trl* is expressed in various stages of *Drosophila* are found to regulate several developmental processes like embryogenesis, oogenesis, eye and wing development, and formation of dorsal processes [2,10,64-67]. In developing male germ cells in *Drosophila*, a loss-of-function in *Trl* has been found to lead to partial germ cell loss [68]. A recent study pointed that a mutant for *Trl* shows an early activation of migration and movement to the inward of the embryo. Such a premature drift lead to loss of orientation and an absence of a normal gonad formation. The migrations of the cells are under the JAK-STAT signalling pathway factors that activate the GPCR coded by gene *tre1* or *trapped in endoderm 1* [69-71], whose product is normally limited to the germ cells. In some cases, the somatic environment can modulate spatiotemporal regulation of germ cell migration as in mutants of the *hopscotch* gene, encoding a Janus kinase, causing a premature migration of primordial cells [72]. This suggests that the GAGA factor does influence the migration of primordial cells via their contact with the somatic cells.

GAGA in wing development

The over-expression of GAF has been found to alter the gene expression of many genes in the wing disc. Depletion in GAGA, caused by the deletion at 69B was found to consistently reduce the size of the wing by about 10%. Using *NubbGAL4* with *Dicer2* reduction was by 55% and in case of *ptcGAL4* by 35%. Presumptively the wing size diminished was due to the defect in the proliferation of the cell. The abdominal segment A6 showed a transformation to A5, in males having a depleted GAGA factor. It is well known fact that a defective *Abd-B* is responsible for homeotic transformation of the abdominal segments. The above findings thus correlate that GAGA factor was capable of initiating a defective transformation of segmentation of the embryo. A heterozygous null *Trl* male was

found to have a similar transformation owing to the deficiency (Trl67/Df(3R)Sbd26) [4,8]. A phenotype of loss-of-function due to usage of *pannier GAL4* (*pnrGAL4*) showed a cleft with loss of bristle at the dorsal of the notum while over-expression was found to completely affect the dorsal closure with embryonic death before the first instar stage is reached.

GAGA factor as anti-repressor of Kruppel

Kruppel is the *Drosophila* gap gene that plays a crucial role in the early embryonic development by forming the antero-posterior boundaries. The syncytial blastoderm stage shows the expression of the *Kr* in the form of a circular band girdling around 45 to 55% of the egg [73]. The *Kruppel* transcripts are formed at around 2 to 5 hr later from hatching [74] and protein coded thereafter bears zinc fingers [75-77] that in turn regulate the expression of the other genes, both spatially and temporally.

The analysis of the proximal promoter of the *Drosophila Kruppel* (*Kr*) gene shows a 44-base pair length fragment bearing the RNA start sites having prominent promoter activity. This promoter has both upstream and downstream flanked by sites binding with the GAGA factor. The GAF interacts with the *Kr* promoter region downstream in a sequence-specific fashion, and the purified protein is found to activate the *in vitro* transcription of *Kr* and *Ubx*. The GAF is acting as an anti-repressor acting in the presence of the binding site to repress the inactivation of the *Kr* by undoing the repression by the DNA binding factor. The transcriptional anti-repression model of the gene describes that DNA binding factors may bind with the gene's promoter and enhancer sequence repressing the gene function. GAGA factor is able to nullify the repressive effect of such factors resulting in allowing transcription of *Kr*.

GAGA factor relieves the repression of tailless

The development of both the anterior and posterior poles, which are the terminal domains of *Drosophila* embryos, is specified by the maternal terminal system [78]. One of such gene is *tailless*, which is crucial for the development of terminal structure like telson and the posterior gut as well as head portions as head structures and the brain development [79-82]. The syncytial blastoderm stage of the embryo expression this transcript at the poles occur after the indirect activation by the maternally produced Torso receptor tyrosine kinase pathway at the embryonic termini. It partly relieves the repression caused by the HMG transcription repressor, *Capicua* and the co-repressor, *Groucho* [83,84]. The other repressor that it negates is the BTB domain zinc finger protein, *Tramtrack69* [85]. A successful functional *tailless* ensures the normal expression of other gap genes such as *Kruppel* and *Knirps*, and later on genes like *hunchback*, *brachyenteron*, and *forkhead* [79-82]. The reduction of concentration of the repressor causes a loss in a well-defined edge of expression domains [86,87]. It is seen that if the binding affinity of GAGA factor to the tor-RE is low, and multiple tor-REs are present in the *tll* cis-regulatory region [85,88] the boundary of *tll* expression gets poorly defined.

Zelda as a candidate for GAGA

The DNA-binding protein Zelda or Vielfaltig in *Drosophila* is an active transcriptional activator of the zygotic genome and produces an open chromatin state. Once that, the chromatin open, it facilitates the recruitment of the transcriptional factor. This leads to the remodelling of the genome, causing the target gene to express. But sometimes absence of the Zelda can also lead to transcriptional activation in case of factors like the GAGA factor binding motif and the GAGA factor in embryo. The 14th nuclear cycle is the testimony to the initiation of zygotic transcription, where Zelda is key activator of the zygotic genome in the maternal to zygotic transition [89,90]. Zelda binding sites have been found to be critical for regulation of DNA binding by transcriptional factors Dorsal (Dl), Twist (Twi), and Bicoid (Bcd) [91-93]. The Zelda also potentiates transcription factor binding sites by determining sites of open chromatin [94,95]. The density of histone H3 increases when the Zelda decreases in wild-type embryos [96], the Zelda thus, dictate the expression of the initial set of zygotic genes, transcribed post fertilization and also binds to the locus for genes that need to be activated later such that a precise sequence of gene activation ensues during gastrulation.

The Vertebrate homologue of GAGA factor

Although the essential and conserved role of PcG/trxG homolog was clearly proven in the *Drosophila melanogaster*, the vertebrate homologue for the *Drosophila* GAGA factor was unknown until the recent studies [55]. The recognition sites for the GAGA factor called the GAGA boxes were found in many genes in the vertebrates including the *hox* complexes but a putative GAGA factor was yet to be discovered [16,97-101]. Very recently, the vertebrate GAG factor homologue having properties similar to the *Drosophila* in terms of domain structure and capacity for DNA recognition and binding. Various analysis including the structural modelling, phylogenetic analysis and cross-reactivity studies have exposed that GAGA factor can bind to DNA sequences rich in GAGA in the *hox* complex. In mouse and human, cKrox (Kruppel-related zinc finger protein cKrox) or Th-POK (T-helper inducing POZ/Kruppel-like factor) was deemed as the homolog of the *Drosophila* GAGA factor. It is found to be encoded by the *zbtb7b* or *Zfp67* gene. Th-POK mainly regulates the commitment towards the lineages CD4 and CD8. It is found that the mice having a mutated Arginine Glycine in the X position of the second zinc finger are of Th-POK show immune-compromisation. This means that the Arginine is responsible for the recognition of the invariant G of the target and any mutation in the third position of the consensus sequence, GAGAG alters the target binding specificity [20]. This highlights the role of G in binding and arginine in specific DNA binding, both in fly as well as in mammals. The binding sites of c-Krox/Th-POK are found to be rich in purine with the pentamer sequence GAGA in the target. Some studies have also shown that Th-POK/c-Krox binds to the collagen promoter region to cause transcriptional activation [102-104] and the deletion of the C-terminal region, the transcriptional activity is reduced in mice [105].

The *Evx2* and *Hoxd13* genes have tracts rich in GA in mouse, human, and zebrafish and functions in blocking the enhancer in both transgenic flies and cultured human cells [106]. Mutating the GAGA binding sequence prevents it from functioning as an insulator [106]. The murine *Hox* clusters with Histone free regions associate with the GAF recognition sites and regulate the binding of *Th-POK*. Thus, the mammalian GAGA factor acts in nucleosome reorganization at the *Hox* clusters providing a platform for binding regulatory proteins, organizing chromatin regulatory activities of the chromatin, including the formation of boundaries.

Conclusion

The evidence cited in this report, clearly indicates that the GAGA factor is involved at several levels in gene expression regulation. Hence, it would be improper to consider it as a simple transcription factor or anti-repressor. Its role as a structural protein on the chromatin conformation, from its primary to its tertiary structure, depicts a potential role as a transcriptional activator and repressor. The actual role of GAF in maintaining the secondary and tertiary structure still remains more speculative than quantitative; even the functional significance of GAF multimers still remains cryptic. The multimers may affect the topology of the regulatory region where they bind, changing the rotational phase of the nucleosomes to enable the proteins to co-interact. The purification of GAF and the fully characterized chromatin system may reveal the full structural analysis data. The chromatin folding and cis-trans interaction of the regulatory sequences may also give additionally unique information about the effect of the GAGA factor in the folding of the chromatin.

The diversified role of the GAGA factor in binding sequence-specifically to chromatin, DNA, transcriptional factors, metal ions and leading to protein homo-dimerization as well as hetero-dimerization has very critical roles in the normal execution of biological processes like the cell division, chromatin assembly, chromatin modification, chromatin organization, dosage compensation, imaginal disc-derived wing morphogenesis, mitotic nuclear division, negative regulation of transcription, nuclear division, oogenesis, positive regulation of chromatin silencing, positive regulation of transcription, positive regulation of transcription from RNA polymerase II promoter, protein oligomerization, sensory perception of pain, spermatogenesis and syncytial blastoderm mitotic cell cycle. Such a multi-faceted protein does require further detailed analysis for still some functions not yet discerned completely. The numerous avenues that this factor enlightens its role in, clearly pinpoint the possibility of exploiting this factor in abating some diseases that are caused by an aberrant cell cycle progression, like the various cancers, cell proliferation, tumor development and pattern formation, during embryogenesis. Thus, it still requires focussed and multi-disciplinary efforts to dissect the yet unknown transcriptional regulatory mechanisms that regulate *Drosophila* development.

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Authors' contributions

The initial write-up was done by PD. Figures were drawn by PD. Final write-up and the concept was contributed by UB and MPB.

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