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Review

Evolution goes GAGA: GAGA binding proteins across kingdoms

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ABSTRACT

Chromatin-associated proteins (CAP) play a crucial role in the regulation of gene expression and development in higher organisms. They are involved in the control of chromatin structure and dynamics. CAP have been extensively studied over the past years and are classified into two major groups: enzymes that modify histone stability and organization by post-translational modification of histone N-Terminal tails; and proteins that use ATP hydrolysis to modify chromatin structure. All of these proteins show a relatively high degree of sequence conservation across the animal and plant kingdoms. The essential *Drosophila melanogaster* GAGA factor (dGAF) interacts with these two types of CAP to regulate homeobox genes and thus contributes to a wide range of developmental events. Surprisingly, however, it is not conserved in plants. In this review, following an overview of fly GAF functions, we discuss the role of plant BBR/BPC proteins. These appear to functionally converge with dGAF despite a completely divergent amino acid sequence. Some suggestions are given for further investigation into the function of BPC proteins in plants.

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1. Introduction

Chromatin is a complex molecular ensemble of genomic DNA, RNA and – directly or indirectly – associated proteins. This dynamic structure is necessary for the correct recruitment of transcription factors and coordinated gene transcription. Chromatin-associated proteins (CAP) contribute to DNA replication, mitosis, recombination and gene transcription through their role in chromatin remodeling. CAP are classified into two major groups: enzymes modifying histone stability and organization by post-translational modification; and proteins using ATP hydrolysis to modify chromatin structure. When focusing on DNA compaction, nucleosomes are the basic unit of chromatin DNA packaging and consist of approximately 147 bp of DNA wrapped around a protein histone core. Specific CAP carry out a wide range of histone N-terminal modifications that determine the transcriptional state of the locus considered. Acetylation and methylation in particular, have been implicated in the regulation of gene expression and chromatin structure [1]. These modifications lead to the recruitment of specific factors, which confer a transcriptional repressive or permissive status to chromatin. Histone acetylation is usually associated with an active chromatin state and HDACs (Histone deacetylases) are consequently considered as repressors. In comparison, histone tail methylation appears to be a far more complex process. Mono, di or tri-methylation of the lysine 4 or 36 of histone H3 (H3K4me1/me2/me3; H3K36me1/me2/me3) is globally considered as an active mark of gene expression. On the other hand, mono, di or tri-methylation of the lysine 9 or 27 of histone H3 (H3K9me1/me2/me3; H3K27me1/me2/me3) is associated with repression of gene expression [2].

The second strategy used to alter chromatin structure and mobilize nucleosomes is dependent on ATP hydrolysis. To date, four classes of ATP-dependent chromatin remodeling complexes are known (each containing one of the following ATPases belonging to the SNF2 ATPase family: SWI2/SNF2, ISWI, CHD/Mi-2, or INO80) (Table 2) [3–6] and were found favorable to a transcriptionally active and nucleosome free chromatin region [7,8].

In *Drosophila*, one of the most studied models, many CAP were found to act in complexes with the GAGA factor (dGAF) in a wide range of cellular contexts. Furthermore, in keeping with their fundamental role in gene expression, most CAP are conserved across the animal and plant kingdoms [9,10]. Surprisingly, however, dGAF orthologs have only been found in animals. In this review we will first give an overview of the multiple functions played by GAF proteins in animals. We will then discuss the functional similarities between dGAF and the plant protein family named BBR/BPC, despite the fact that their amino-acid sequences are fully divergent.

2. The *Drosophila* GAGA factor

dGAF or *Trl* was first identified in *Drosophila* as a positive regulator of homeotic genes, a position-effect variegation modifier [11] and a nucleosome disrupter at the *hsp70* locus [12]. Later, it was found to act in boundary activity [13], chromosome segregation and nuclear division [14]. Genome-wide analysis showed that dGAF targets

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Table 1
GAGA functions across kingdoms.

	Organisms	
	Animals	Plants
Insulator function	+[14,26,27,28]	−
Insulator function	+[15]	?
Insulator function	+[15]	?
Nucleosome sliding	+[13]	?
Histone modification	+[43,58,59,67]	?
PIC stabilization	+[47]	?
Gene transcription activation	+[12,45]	+[71,82]
Gene transcription repression	+[54,58,67]	+[83]
Chromatin remodeling	+[13,14,41,43]	+[83]
Homeobox genes regulation	+[12]	+[83]
Hormone response	+[87]	+[80]

include up to 250 members involved in at least 28 cellular pathways [15].

dGAF exists in two isoforms (GAGA519 and GAGA581) produced from alternative splicing [16], which share a BTB/POZ protein–protein interaction domain and DNA binding region (C_2H_2 zinc finger domain). They diverge in their C-terminal region, which contains a glutamine rich domain (Q domain) essential for transcriptional activation [17–19] (Fig. 1). As the BTB/POZ domain is crucial for homo and hetero-dimer formation [16], this certainly implies that dGAF acts by recruiting different interactors. Interestingly, several of the identified partners, such as Pipsqueak, Batman or Lolalike, which associate with dGAF to regulate homeobox genes expression, also contain a BTB/POZ domain [20,21]. Interaction of dGAF with other BTB/POZ domain proteins can also counteract the Tramtrack repressor activity at the *eve* locus [22]. In addition, oligomerization of BTB/POZ proteins was shown to form higher order complexes that contribute to open chromatin and increase the DNA binding specificity at promoters with multiple GAF binding sites [23].

dGAF was named for its capacity to bind GAGAG stretches, which are fine-tuned by post-translational modification at the DNA binding site. For instance, acetylation of two lysines, or phosphorylation of two serines, decreases the affinity of the factor for DNA without abolishing binding [24]. In *Drosophila*, genome-wide studies revealed that GAGAG motifs are dispersed evenly throughout the genome in active or inactive chromatin regions, introns and exons. Genome-wide analysis of GAF binding sites in vivo with the Dam method [15] revealed binding to both transcriptionally active and inactive regions, confirming its dual role in activation and repression. In active regions, only closely spaced GAGAG elements were bound [15], consistent with the hypothesis that dGAF oligomerization plays a role in DNA binding specificity [23]. In addition, a lack of binding in exons was also observed by van Steensel and collaborators [15], which can be explained by the low representation of closely located GAGAG repeats. This robust consensus led to research into the functions of GAF through the presence and prevalence of its DNA recognition sites.

Table 2
Glossary.

ACP	associated chromatin protein
ATP	Adenosine-5′-triphosphate
BBR	barley B recombinant
BTB/POZ	broad complex tramtrack bric a brac/poxvirus zinc finger
BPC	basic pentacystein protein
CHD	chromodomain Helicase/ATPase DNA binding protein
Dam	DNA adenine methyl transferase
eve	even skipped
FACT	facilitates chromatin transcription
GBP	GAGA Binding Protein
HDAC	histone deacetylase
hsp70	heat shock protein 70
ISWI	imitation of switch
NELF	negative elongation factor
NURF	nucleosomal remodeling factor
PcG	Polycomb group
PIC	preinitiation complex
PRE	polycomb repressive element
psq	pipsqueak
RNA polII	RNA polymerase II
SNF	sucrose non-fermenting
SWI	homothalic switching deficient
TAF3	TBP-associated factor 3
TBP	TATA binding protein
Trl	trithorax like
TrxG	trithorax group

3. dGAF in transcriptional activation processes

Mutations in dGAF recognition sites have provided important insights into dGAF functions. When GAGAG sequences located in the *Fab7* and *Evx2-Hoxd13* loci are mutated, they lose their insulator activity [13,25–27]. Insulator, or boundary, activity is specific to animal genomes and depends on the clustered organization of genes which require enhancers, sometimes located far away from the coding region, at a specific developmental stage. Insulators were first identified in the flanking regions of the *Drosophila hsp70* gene [28–31] and allow chromatin loops to isolate *cis*-regulatory elements from each other. Thus, dGAF can activate transcription by modifying chromatin structure to tether distant DNA sequences. dGAF binding sequences were found to co-localize with DNase I hypersensitive sites [12,32–36]. dGAF was also implicated in local modifications to chromatin structure, creating nucleosome free regions, consistent with its interaction with NURF301 [37] and FACT [38–40] which act in nucleosome sliding.

FACT is involved in transcriptional elongation, modifying nucleosome structure, [38,39] and its cooperation with dGAF is fully consistent with the co-localization of dGAF with RNA polII. An interaction between FACT and dGAF supports the hypothesis that dGAF can bind to its high affinity binding site and then moves alongside the gene to be induced, opening up the chromatin structure to the RNA polymerase II complex [41]. Indeed, ChIP experiments showed that dGAF binds to 3′-end gene regions [15]. In addition, the GAF/FACT association was shown to participate in the replacement of K9 methylated histone H3 by H3.3, which is not a repressive mark, preventing heterochromatin spreading [42]. Another partner, NURF301, is an ISWI family CAP that enhances nucleosome sliding, and was shown to interact in vitro and in co-IP experiments with GAF [37]. Furthermore, ISWI and GAF binding sites were found to partially overlap (about 30% of overlap) in double label immuno-fluorescence microscopy and ChIP-chip experiments [43].

In addition to its activity in nucleosome sliding, dGAF also plays a more direct role in the activation of target gene expression by interacting with the basal transcriptional machinery (Fig. 2). Indeed, dGAF was identified as a positive regulator of the Ultrabithorax gene of the bithorax complex in *Drosophila*, which itself interacts with dmTAF3, a component of the TFIID complex [44]. dGAF is also required to enhance TFIID binding [45] and stabilize PIC formation through its Q-domain [46]. dGAF can also play a repressive role in transcriptional elongation, acting with NELF for promoter proximal RNApolII pausing [47,48]. This is not the only example of GAF activating/repressing duality: in *Drosophila melanogaster* TrxG and PcG, that are responsible for the active H3K4me3 and the repressive H3K27me3 mark deposition respectively [49], can interact with dGAF and GAGAG sequences are essential for the recruitment of both (Fig. 2) [50].

4. Repressive activity of GAF

GAF recognition sites are often found in PREs, which are necessary for the recruitment of PcG complexes [51,52]. In PREs, GAGAG stretches are predominantly associated with PHO and Zeste recognition sites [53,54] and all three are essential for many PcG-mediated repression

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