The Pipsqueak Protein of *Drosophila melanogaster* Binds to GAGA Sequences through a Novel DNA-binding Domain* (Received for publication, July 14, 1998)  

Michael Lehmann†, Thomas Siegmund, Karl-Georg Lintermann, and Günter Korge  

From the Institute of Genetics, Free University Berlin, Arnimallee 7, D-14195 Berlin, Germany

Pipsqueak (Psq) belongs to a family of proteins defined by a phylogenetically old protein-protein interaction motif. Like the GAGA factor and other members of this family, Psq is an important developmental regulator in *Drosophila*, having pleiotropic functions during oogenesis, embryonic pattern formation, and adult development. The GAGA factor controls the transcriptional activation of homeotic genes and other genes by binding to control elements containing the GAGAG consensus motif. Binding is associated with formation of an open chromatin structure that makes the control regions accessible to transcriptional activators. We show here that Psq contains a novel DNA-binding domain, which binds, like the GAGA factor zinc finger DNA-binding domain, to target sites containing the GAGAG consensus motif. Binding is suppressed, as in the GAGA domain, which we call the Psq domain, is identical with a previously identified region consisting of four tandem repeats of a conserved 50-amino acid sequence, the Psq motif. The Psq domain seems to be structurally related to known DNA-binding domains, both in its repetitive character and in the putative three-a-helix structure of the Psq motif, but it lacks the conserved sequence signatures of the classical eukaryotic DNA-binding motifs. Psq may thus represent the prototype of a new family of DNA-binding proteins.

Members of the BTB/POZ protein family play important roles in development and reproduction of *Drosophila melanogaster*. These proteins contain a protein-protein interaction motif that was first identified in zinc finger proteins encoded by the *Drosophila* Broad-Complex and tramtrack genes (1, 2), and later also in the bric à brac gene product (3). The domain, which was thereupon designated as BTB (Broad-Complex, Tramtrack, Bric à brac) domain (3), has since been found in proteins of a variety of species, as diverse as slime molds (4) and humans (for a review, see Ref. 5). Many of these proteins are DNA-binding C_{2}H_{2} zinc finger proteins, but the presence of the domain in a family of pox virus proteins (6) soon indicated that coupling to a DNA-binding domain is not mandatory. The domain is therefore also referred to as the POZ (pox virus, zinc finger) domain (7). In BTB/POZ proteins that contain a zinc finger DNA-binding motif, DNA binding is strongly inhibited by the BTB/POZ domain. This inhibitory effect on DNA binding is also observed in chimeric proteins in which the BTB/POZ domain is associated with a heterologous DNA-binding domain, for instance a POU domain (7). Inhibition of DNA binding appears to be the result of oligomerization through protein-protein interactions mediated by the BTB/POZ domain.

The tendency of BTB/POZ proteins to oligomerize in solution and their localization in distinct nuclear substructures (7–10) suggests that they might act by modifying chromatin structure (5). In fact, such a mode of action is supported by different lines of evidence for the E(var)3–93D product (11) and the GAGA factor of *D. melanogaster*. The two known isoforms of the GAGA factor, GAGA-519 and GAGA-581, which share the same BTB/POZ and zinc finger DNA-binding domains (12), bind to GAGAG consensus sites in the control regions of their target genes, which include homeotic genes (13) and heat shock genes (for a review, see Ref. 14). Binding leads to generation of an open chromatin conformation and thereby makes the control regions accessible to transcriptional activators (15–17). The role of the GAGA factor in establishing active chromatin structures is supported by the finding that a mutation of the GAGA factor-encoding *Trithorax*-like gene acts, like *E(var)3–93D*, as an enhancer of position effect variegation (18). Position effect variegation is observed as a mottled eye phenotype caused by the clonally inherited inactivation of a gene (e.g. white) that is juxtaposed to centromeric heterochromatin by a chromosomal rearrangement. Factors enhancing or suppressing position effect variegation are believed to be chromatin constituents or modulators of chromatin structure (reviewed in Ref. 19).

Pipsqueak (Psq) is a BTB/POZ protein with pleiotropic functions during development of *D. melanogaster*. Maternal psq function is required early in oogenesis (10, 20), and psq is one of the posterior group genes that are responsible for pole cell formation and proper abdominal segmentation of the embryo (20). Moreover, psq directs correct localization of the *gurken* product, which is involved in establishment of the dorsoventral axis of the embryo (10). During metamorphosis, *psq* is required for formation of photoreceptors R3/4 in the eye and for proper differentiation of other adult structures, such as wings and legs (21). The nuclear localization of Psq suggests that it acts, like many other BTB/POZ proteins, through binding to DNA (10).
However, none of the Psq isoforms that appear to be expressed by psq contains a homology to a known DNA-binding motif (10, 21). Instead, a tandem repeat of four copies of a 50-amino acid sequence, called the Psq motif (10), is found at the C terminus. A sequence with homology to the Psq motif is present in another Drosophila protein, encoded by the Drosophila tyrosine kinase-related gene, Thr (22), but the function of the motif remained unknown (10, 21). Interestingly, cDNA structures suggest that, other than isoforms containing both the BTB/POZ domain and the Psq repeat region, there is at least one Psq isoform that contains the Psq repeats but lacks the BTB/POZ domain.

Here we show that the C-terminal region of Psq containing the four Psq repeats functions as a DNA-binding domain, which we call the Psq domain. The Psq domain binds to DNA consisting of direct repeats of the GAGAG consensus motif, which is otherwise recognized by the GAGA factor. Psq is thus the second GAGA-binding protein identified in D. melanogaster. Binding to DNA is sequence-specific and is inhibited by the BTB/POZ domain. The Psq domain appears to be structurally related to the DNA-binding domain of prokaryotic recombinases as well as to the eukaryotic homeodomain and Myb-like DNA-binding domains. However, it cannot be classified into any of these classes and may thus define a new class of eukaryotic DNA-binding domains.

**EXPERIMENTAL PROCEDURES**

**Expression Library Screening**—A cDNA library in λ-ZAPII (Stratagene) from brains of adult honeybees (a gift of D. Eisenhardt, Freie Universität Berlin) was screened essentially as described by Vinson et al. (23), except that the denaturation/renaturation steps were omitted. The sequence of oligonucleotide hspGAGA1, which was used for preparation of the concatenated probe, is given in Fig. 2E. A plasmid containing cDNA AmPSQ (pBlueAmPSQ) was recovered by in vitro excision using helper phage R408 (Stratagene). AmPSQ was confirmed to originate from the honeybee by Southern hybridization and sequenced by automated cycle sequencing (MWG-BIOTECH).

**Plasmids**—Constructs for expression of truncated Psq derivatives were generated from pBlueAmPSQ by digestion with the following restriction enzymes: SalI/Eco471 (Psq Δ240), SalI/BccI (Psq Δ333), SalI/XhoI (Psq Δ384), SalI/HaelI (Psq Δ474), XhoI/HaelI (Psq Δ229), BclI (ΔΔΔΔ insertion), and restriction fragment length polymorphism analysis revealed that the appropriate sequencing of the four Psq fragments containing the Psq repeats were recovered after agarose gel electrophoresis. Single-stranded overhangs were blunt-ended using Klenow fragment, except for the SalI/XhoI fragment, and the plasmids were then circularized by ligation. In Psq Δ232 and Psq Δ228, ligation results in a frameshift, which adds 21 and 6 amino acid residues, respectively, to the C terminus of the Psq derivatives. A plasmid containing cDNA Dm1.67, isolated from a Drosophila third larval instar cDNA library in Agt11,2 was used for in vitro transcription of full-length GAGA-519.

**Protein Synthesis and Mobility Shift DNA Binding Assay**—Proteins were synthesized from the plasmid constructs in two parallel sets of reactions by cell-free in vitro transcription/translation (TNT T7/T3 Coupled Reticulocyte lysate system; Promega) using radiolabeled or non-radiolabeled or non-

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2 K.-G. Lintermann, unpublished results.

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**RESULTS AND DISCUSSION**

Isolation of a cDNA Encoding the Psq Homologue of A. mellifera—To investigate the evolutionary conservation of proteins related to the GAGA factor of Drosophila melanogaster, we screened a cDNA expression library from honeybees (A. mellifera) using a radiolabeled probe containing GAGA factor binding sites. The probe was obtained by concatemerization of an oligonucleotide, hspGAGA1 (Fig. 2E), that had previously been used successfully to isolate GAGA factor cDNAs by expression screening (29). From 4.3 × 10⁶ cDNA clones screened, three clones reproducibly showed strong binding of the GAGA probe. Southern hybridization and sequencing revealed that only one of these clones represented a cDNA from A. mellifera. The cDNA, hereafter referred to as AmPSQ, contains an open reading frame encoding a 652-amino acid protein that shows high similarity to the Psq protein of D. melanogaster (Fig. 1). Although overall sequence conservation is only 53%, two domains show strikingly high conservation. First, the BTB/POZ domain is 73% identical with the BTB/POZ domain of D. melanogaster Psq. This means that despite the large evolutionary distance between D. melanogaster and A. mellifera, the degree of similarity between these domains is higher than the standard identity of 53% between the BTB/POZ domains of different Drosophila proteins (30). Second, the region containing the four Psq repeats shows 80% identity with the Psq domain of the Drosophila protein. At the same time, not only the amino acid sequence of the single repeat units, but also the sequence of the repeats themselves is conserved (Figs. 1C and 5). We therefore conclude that AmPSQ encodes the Psq homologue of A. mellifera. The sequence between the BTB/POZ and Psq domains of D. melanogaster Psq contains several regions that are particularly rich in certain amino acid residues, including two glutamine-rich regions and a region of 17 histidine residues alternating with other residues (Fig. 1A). Regions of this kind are believed to serve as interfaces for protein-protein interactions (31, 32) and are frequently found in transcription factors (33, 34). Poly-
FIG. 1. Comparison of Psq proteins of *D. melanogaster* and *A. mellifera*. A, domain structures of the Psq protein encoded by the longest open reading frame detected in *Drosophila psq* cDNAs (10, 21) and of *A. mellifera* Psq encoded by cDNA AmPSQ. Open boxes within the region located between the BTB/POZ and Psq domain (Psq repeats) mark regions particularly rich in the indicated amino acid residues. The (HX)17-box denotes a region of 17 histidine residues alternating with residues of other amino acids. B, comparison of the predicted N-terminal amino acid sequences of the fly and honeybee Psq proteins. The arrows mark the boundaries of the BTB/POZ domain. Sequences with identical residues between the *D. melanogaster* and *A. mellifera* proteins are boxed. C, alignment of the amino acid sequences of the *D. melanogaster* and *A. mellifera* Psq domains. Starts of the single Psq repeats are indicated by arrows, and identical amino acid sequences are boxed.

FIG. 2. The Psq domain is responsible for binding of *A. mellifera* Psq to DNA. A, structures of the full-length and truncated Psq proteins used for binding experiments. Designations of the truncated derivatives indicate the number of amino acid residues eliminated by the deletion. Amino acid sequences C-terminal to the deletions in PsqΔ232 and PsqΔ282 (black boxes) result from a frameshift. The arrows within the Psq domain mark positions of the Psq repeats. B, Psq proteins synthesized by cell-free translation in a reticulocyte lysate system. Proteins were labeled by incorporation of [35S]methionine, separated in a 12.6% SDS-polyacrylamide gel, and visualized by fluorography. The molecular masses in kilodaltons of marker proteins run in parallel are indicated on the right. Note that in all of the translation reactions truncated proteins are produced in addition to the full-length products. The sizes of the truncated products correspond with the predicted sizes of products that would result from the use of internal AUG triplets as start codons. These products thus represent N-terminal rather than C-terminal truncation derivatives that would result from precocious termination of translation or proteolytic cleavage. C, binding of full-length Psq and truncated Psq derivatives to DNA. Unlabeled translation products, produced by reactions run in parallel to the reactions analyzed in B, were incubated with radiolabeled hspGAGA2. The formation of protein-DNA complexes was then analyzed by a mobility shift assay. Complexes formed by full-length translation products are marked by arrows. Minor complexes marked by asterisks are probably formed by products derived from internal translation start sites (see above). The slowly migrating complex obtained with PsqΔ384 may indicate an unusual conformation adopted by some PsqΔ384-DNA complexes that is caused by the absence of 15 amino acid residues at the N terminus of the Psq domain. D, binding of full-length Psq and truncated Psq derivatives in the presence of magnesium. Binding of PsqΔ240 and PsqΔ333 is strongly stimulated by the addition of magnesium, compared with the binding of PsqΔ240, which is not or is only marginally stimulated. Binding of full-length Psq is not observed under these conditions, but binding of the putative N-terminal truncation products (see above) is enhanced. Amounts of protein loaded per lane and exposure time are reduced about 2-fold compared with the assay shown in C. The arrows and asterisks mark the same complexes as in C. E, structure of the oligonucleotides used for library screening (hspGAGA1) and as probes in mobility shift assays (hspGAGA2).
The Psq domains of both *A. mellifera* and *D. melanogaster* Psq specifically recognize a DNA sequence containing the GAGAG-consensus motif. A, binding of *A. mellifera* Psq Δ240 to radiolabeled hspGAGA2 was analyzed in the presence of increasing amounts of unlabeled competitor oligonucleotides. Oligonucleotides O3 (42 base pairs) and O30 (50 base pairs) uncover nonoverlapping sequences in the upstream region of the *Drosophila Sgs-4* gene (see “Experimental Procedures”). Each of the indicated competitor DNAs was added in a 10-, 30-, and 100-fold molar excess over the probe. The faster migrating complex is formed by a truncated by-product of the translation reaction (see Fig. 2). B, binding of the *D. melanogaster* Psq domain to hspGAGA2, O3, and O30 was tested as in A.

glutamine tracts, in particular, have the potential to interact with components of the basal transcription machinery and can thus act as transcription activation domains (for a review, see Ref. 35). The interdomain sequence of the *A. mellifera* protein, which is only half as long as the interdomain sequence of *Drosophila* Psq, lacks these regions of special amino acid composition and contains a single asparagine-rich region instead. Since such asparagine-rich regions are also present in many transcription factors, particularly homeodomain proteins (34), we speculate that, despite their low sequence identity of only 13%, the interdomain regions of *A. mellifera* and *D. melanogaster* Psq have similar functions in both proteins.

**The Psq Domain Is a Novel DNA-binding Domain**—Since AmPSQ was isolated by an expression screen using a DNA-binding site probe, we reasoned that the conserved Psq domain might represent a novel DNA-binding domain. To test this hypothesis, we constructed plasmids encoding truncated Psq proteins (Fig. 2A) and expressed these proteins, as well as full-length Psq, using a reticulocyte *in vitro* translation system. Fig. 2B shows that the Psq proteins were correctly expressed in the *in vitro* system. However, using a mobility shift DNA binding assay, we detected binding of neither full-length Psq nor of the truncated derivatives to the hspGAGA1 oligonucleotide (data not shown). Considering the repetitive structure of the Psq domain and the fact that a concatenated probe had been used for library screening, we suspected that a more extended binding sequence might be required for Psq binding. We therefore tested binding of the Psq proteins to oligonucleotide hspGAGA2, which is equivalent to the ligation product of two hspGAGA1 oligonucleotides (Fig. 2F). While binding of full-length Psq could not be detected also with this probe (Fig. 2C, lane 1), a truncated form of Psq that lacks an essential part of the BTB/POZ domain showed strong binding (Psq Δ240, Fig. 2C, lane 2). This result is consistent with the finding of Bardwell and Treisman (7) that BTB/POZ domains generally inhibit the interaction of their associated DNA-binding domains with DNA. If the N-terminal truncation of Psq is further extended to essentially remove the N-terminal half of the protein, the DNA binding ability is retained (Psq Δ333; Fig. 2C, lane 3). Even if the truncation advances into the first amino acid residues of the Psq domain (removing the first 15 amino acids of Psq repeat 1), the resulting 268 amino acid protein is still able to recognize the DNA target sequence (Psq Δ384; Fig. 2C, lane 4). However, if the truncation removes the first two Psq repeats, DNA binding ability is lost (Psq Δ474; Fig. 2C, lane 5). Truncations removing the Psq domain but leaving the BTB/POZ domain intact result in proteins that exert no specific DNA binding (Psq Δ232 and Psq Δ282; Fig. 2C, lanes 6 and 7). Since also full-length Psq does not appear to bind to DNA unless the BTB/POZ domain is removed, this result is not surprising. However, it is interesting to note that complexes formed by proteins that are probably translated from internal AUG start sites are absent in lanes loaded with the Psq Δ232 and Psq Δ282 translation products. Such complexes are observed in all lanes loaded with translation products of constructs encoding a Psq domain, whether they encode a BTB/POZ domain or not (Fig. 2C, lanes 1–4). This suggests that also products lacking both the Psq and BTB/POZ domain are unable to bind DNA. Taken together, these data indicate that the Psq domain is responsible for DNA binding of the Psq protein. Since Psq repeats 3 and 4 together are not sufficient for DNA binding (Psq Δ474; Fig. 2C, lane 5), it seems likely that at least three complete repeat units are required for DNA binding. This is consistent with the requirement for a comparatively long DNA target sequence to detect binding. Interestingly, Horowitz and Berg (10) isolated a cDNA encoding a putative Psq isoform that resembles the Psq Δ384 derivative in that it also lacks the first

**FIG. 3.** The Psq domains of both *A. mellifera* and *D. melanogaster* Psq specifically recognize a DNA sequence containing the GAGAG-consensus motif. A, binding of *A. mellifera* Psq Δ240 to radiolabeled hspGAGA2 was analyzed in the presence of increasing amounts of unlabeled competitor oligonucleotides. Oligonucleotides O3 (42 base pairs) and O30 (50 base pairs) uncover nonoverlapping sequences in the upstream region of the *Drosophila Sgs-4* gene (see “Experimental Procedures”). Each of the indicated competitor DNAs was added in a 10-, 30-, and 100-fold molar excess over the probe. The faster migrating complex is formed by a truncated by-product of the translation reaction (see Fig. 2). B, binding of the *D. melanogaster* Psq domain to hspGAGA2, O3, and O30 was tested as in A.

**FIG. 4.** Psq and GAGA proteins bind independently to GAGA sequences in *vitro*. *In vitro* translated full-length Psq and GAGA-519 proteins as well as the N-terminal truncation derivative Psq Δ240 were incubated with radiolabeled hspGAGA2 either alone or in the indicated combinations. Protein-DNA complexes were then separated in a mobility shift gel. The products of each of the translation reactions form several complexes. Complexes marked by asterisks are likely to be formed by truncated products derived by the use of internal translation start sites (see Fig. 2). The arrow indicates the complex formed by the main Psq Δ240 translation product. *In vitro* translated GAGA-519 forms a strong complex marked by an arrowhead. It is unknown if this complex is formed by full-length GAGA-519 or a derivative lacking the BTB/POZ domain. The GAGA-519 translation products also form a slowly migrating complex, marked by an open triangle, indicating the simultaneous binding of two or more protein molecules. Such oligomeric complexes are not observed with Psq Δ240, suggesting that the length of hspGAGA2 is not sufficient for interaction with more than one Psq molecule. This is consistent with the putative structure and size of the Psq domain (see “Results and Discussion”).
Fig. 5. Comparison of amino acid sequences of Psq motifs with the DNA-binding domains of prokaryotic recombinases. The Psq motifs of D. melanogaster Psq (A. mellifera Psq (Amp Psq), TKR, and the polypeptide predicted by C. elegans codon T01C1 (T01C1.3) are aligned with selected recombinase domains of the recombinase block identified by searching the Blocks Data base (see “Experimental Procedures”). The recombinases are known or suspected to catalyze various kinds of site-specific recombination reactions. Positions that are identical in at least 40% of the aligned sequences are indicated by black boxes. The positions of the three α-helices of the Hin recombinase DNA-binding domain, as determined by x-ray crystallography (37), are marked under the sequence alignment. Helix 3 is the recognition helix and forms a helix-turn-helix-like motif together with helix 2. The open circles and the triangle mark positions occupied by nonpolar amino acid residues in all of the aligned sequences. Residues marked by open circles form part of the hydrophobic core of the α-helices of yb-resolvase and are conserved in the DNA resolvase and invertase family (38). Vertical arrows mark positions occupied by polar amino acid residues in all of the aligned sequences. Note that highest similarity is observed between A. mellifera and D. melanogaster Psq repeats, which take the same position within the Psq domain, indicating that not only are the repeats themselves conserved, but also the sequence of the repeats in the fly and honeybee Psq protein.

DNA Binding Specificity of the Psq Domain—We next asked whether binding of the Psq domain to DNA depends on the nucleotide sequence of the DNA or if it recognizes DNA in a rather nonspecific manner. Fig. 3 shows that binding of Psq Δ240 to the radiolabeled hspGAGA2 oligonucleotide is specifically inhibited already at a 10-fold molar excess of the nonlabeled oligonucleotide (Fig. 3A, lanes 2–4). Two different oligonucleotides, similar in length and G/C content to hspGAGA2, formed (Fig. 3, lane 1). As observed before, full-length Psq showed no binding and Psq Δ240 showed strong binding to this oligonucleotide (Fig. 4, lanes 1 and 4). Whether either of these two proteins is mixed with the in vitro translated GAGA-519 isoform, the resulting pattern of DNA-protein complexes is the sum of the complex patterns observed in the presence of only the single proteins (Fig. 4, lanes 3 and 5). Thus, the GAGA-519 isoform does not seem to be able to promote DNA-binding of full-length Psq in vitro. It remains to be shown whether Psq isoforms containing both the BTB/POZ and Psq domains in fact bind to GAGA sites or other DNA-binding sites in vivo or if they exert their functions independent of DNA binding. Since also isoforms lacking the BTB/POZ domain seem to be expressed in vivo (10), binding to GAGA sites or related target sites may be reserved to these isoforms.

The Psq Domain Is Similar to the DNA-binding Domain of Prokaryotic Recombinases—Psq cannot be easily assigned to any of the known families of eukaryotic DNA-binding proteins. Repetitive homology to the Psq motif is present in at least one additional Drosophila protein, the TKR protein (22), suggesting that also this protein is able to bind to DNA. Interestingly, Zollman et al. (30) identified a Drosophila BTB/POZ domain-encoding gene (BTB-III) that has an embryonic RNA distribution pattern very similar to that of Tkr and that maps to the same chromosomal position. It is thus interesting to speculate that the Tkr locus is more complex than previously supposed, encoding several protein isoforms, one of which con-
tains a BTB/POZ domain in addition to the Psq domain. Beyond Drosophila, a homology to the Psq motif is found in a polypeptide predicted by an open reading frame of Caenorhabditis elegans cosmid T01C1 (Ref. 10; Fig. 5). The Psq domain may thus define a new class of DNA-binding domains. At present, an extensive search of the protein sequence data bases reveals no other eukaryotic proteins with clear cut homology to the Psq motif. However, searching the Blocks Data base (25, 26) with a multiple alignment of the eight Psq repeats reveals significant sequence similarities to the DNA-binding domain of prokaryotic recombinases (Fig. 5) and thereby provides a link between the Psq domain and the homeodomain, for which such similarities have been described as well (36). Co-crystal structures with DNA of two recombinases, Hin recombinase (37) and yα-resolvase (38), show that their DNA-binding domains consist of three α-helices flanked by extended arms, which make contacts to the minor groove. The highest similarity between the Psq motif and the recombinase DNA-binding domain is observed within the C-terminal recognition helix, which forms a helix-turn-helix motif with helix 2 (Fig. 5) and inserts into the major groove. Remarkably, the recognition helix of members of the Hin recombinase family makes specific major groove contacts to a sequence that is closely related to the GAGA motif (37). The Psq motif has the same size of about 50 amino acid residues as the recombinase DNA-binding domains, and secondary structure predictions for the Psq motif are compatible with the triple-helix structure of these domains. A similar triple-helix structure is formed by the homeodomain (39) and Myb DNA-binding domain (40). It is interesting to note that, like the Psq domain, also the Myb DNA-binding domain consists of imperfect tandem repeats of a conserved sequence motif (40). The Psq domain thus seems to be structurally related, both in its conformation and in its repetitive structure, to known DNA-binding motifs, but it eludes the classification into one of the prevalent categories of eukaryotic DNA-binding domains. Identification of additional members of the Psq family and determination of the structure of the Psq domain complexed with DNA will help to better define this new class of DNA-binding domains.

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