The Gene Encoding the Mitogen-responsive Phosphoprotein Dab2 Is Differentially Regulated by GATA-6 and GATA-4 in the Visceral Endoderm*

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Gene targeting studies have demonstrated that the zinc finger transcription factor GATA-6 lies upstream in a transcriptional cascade that controls differentiation of the visceral endoderm. To understand the function of GATA-6 in the visceral endoderm and to identify genes regulated by GATA-6 in this tissue, subtractive hybridization was performed using template cDNAs derived from differentiated wild-type embryonic stem (ES) cells and GATA-6−/− ES cells, respectively. These analyses revealed that the gene encoding Dab2, a mitogen-responsive phosphoprotein, is differentially expressed in wild-type and GATA-6-deficient ES cells. Consistent with these findings, Dab2 is expressed in the visceral endoderm of wild-type embryos but not in the visceral endoderm of GATA-6-deficient embryos. Cotransfection experiments demonstrate that the human Dab2 promoter can be transactivated by forced expression of GATA-6 in NIH-3T3 cells. In contrast, forced expression of GATA-4 does not transactivate the human Dab2 promoter and Dab2 is expressed in the visceral endoderm of GATA-4 null embryos. Surprisingly, the specificity of GATA-6-induced transactivation of the Dab2 promoter is not mediated through its zinc finger DNA-binding domain. Taken together, these data demonstrate that the mitogen-responsive phosphoprotein Dab2 is a downstream target of GATA-6 in the visceral endoderm. Moreover, these data demonstrate that molecular mechanisms have evolved that direct, and distinguish, the functional specificity of GATA family members when they are developmentally coexpressed.

Members of the GATA family of zinc finger transcription factors play key roles in transducing nuclear events that modulate cell lineage differentiation during vertebrate development (for review see Refs. 1–3). This ancient family of transcription factors has been conserved through evolution with family members identified in yeast, Caenorhabditis elegans, Drosophila (4–7). Six GATA factors have been identified in vertebrates, each of which is expressed in a unique developmentally regulated, lineage-restricted pattern (1, 8–10). Each vertebrate GATA factor contains two conserved (C-X2-C-X17-C-X2-C) zinc fingers that mediate DNA binding to the consensus nucleotide sequence (WGATAR) (11, 12). This domain also mediates homo- and heterodimerization with other transcriptional activators and repressors (13–19). Despite overlapping patterns of expression in the embryo, gene targeting studies revealed that mice harboring null mutations in each respective GATA factor exhibit distinct phenotypes (20–27). However, the molecular mechanisms governing the functional specificity of each GATA factor in the developing embryo are poorly understood.

Several lines of evidence suggest that a primordial function of GATA factors is to regulate specification and/or differentiation of endoderm and endodermally derived tissues. In C. elegans, end-1 encodes a single zinc finger GATA factor (6). In end-1 mutants, the E cell, which normally gives rise to endoderm, instead gives rise to mesoderm and ectoderm (6, 28). In Drosophila, mutation of the GATA factor serpent results in transformation of the endodermally derived midgut to ectoderm (5). The GATA-4/5/6 subfamily of vertebrate GATA factors is expressed in an overlapping pattern in the primitive endoderm and some endodermally derived tissues (8, 10). In addition, GATA-4/5/6 are expressed in the developing heart (8, 10). As early as the egg cylinder stage, GATA-4 and GATA-6 are coexpressed in the visceral and parietal endoderm (9, 10, 22). Subsequently, GATA-4, -5 and -6 are coexpressed in the primitive gut epithelium where the genes continue to be expressed throughout postnatal development (8–10). In addition, coincident with formation of the embryonic lung bud, GATA-6 is expressed in the endodermally derived bronchial epithelium (9).

Despite their overlapping patterns of expression in the visceral endoderm and heart, gene targeting studies demonstrated that GATA-4 and GATA-6 regulate distinct functions in the mouse embryo. GATA-4-deficient embryos die between embryonic days (E)1 8.5 and 10.5 and exhibit a gross defect in ventral morphogenesis, including failure to form a linear heart tube (20, 21). GATA-4/5/6 embryos contain intact yolk sacs and express high levels of early and late endodermal markers (20, 21). However, lacZ-tagged GATA-4−/− embryonic stem (ES) cells contribute to the primitive heart tube of GATA-4−/−/C57BL/6 chimeric embryos, and wild-type extra-embry-
oncic endoderm partially rescues the morphogenetic defects observed in GATA-6-deficient embryos, suggesting that endoderm-mediated signaling may be responsible for the defect(s) observed in GATA-4-deficient embryos (20, 29). In contrast, GATA-6-deficient embryos do not survive past the primitive streak stage (E7.5) (22, 27). The extra-embryonic visceral endoderm is specified in GATA-6-deficient embryos, but a specific block is observed in differentiation of the visceral endoderm, including absence and/or down-regulation of both early and late endoderm markers, which include HNF-4, GATA-4, and HNF-3β (22). In GATA-6-deficient embryos, apoptosis is observed throughout the epiblast, which underlies the visceral endoderm, suggesting that GATA-6 regulates an endoderm-ectoderm signaling pathway required for survival of the embryo (22).

To examine the molecular basis of the defect observed in GATA-6-deficient embryos, subtractive hybridization was performed. A cDNA clone encoding the mitogen-responsive 96-kDa phosphoprotein Dab2 was identified and shown to be differentially expressed in the visceral endoderm of wild-type and GATA-6-deficient embryos. In the studies described in this report, we demonstrate that the genes encoding Dab2 and GATA-6 are coexpressed in the visceral endoderm of the mouse embryo. In addition, we observe that the human Dab2 promoter is activated directly by forced expression of GATA-6, but not GATA-4, and the specificity of GATA-6-mediated transcription of the Dab2 promoter is regulated by domains other than its zinc finger DNA-binding domain. Finally, we show that Dab2 is expressed in GATA-4-deficient embryos, indicating that GATA-4 does not regulate Dab2 in vivo. Taken together, these studies demonstrate that Dab2 is a bona fide downstream target of GATA-6 in the visceral endoderm and is differentially regulated by GATA-6 and GATA-4 in the mouse embryo.

**EXPERIMENTAL PROCEDURES**

**Subtractive Hybridization and Cloning of the Mouse Dab2 cDNA**—The generation of GATA-6−/− RW ES cells has been described previously (9). Wild-type and GATA-6−/− ES cells were differentiated in suspension into embryoid bodies as described (20, 22). After 10 days of differentiation in vitro, poly(A)+ RNA was prepared from GATA-6−/− and GATA-6+/− embryoid bodies using the FastTrack mRNA isolation kit (Invitrogen). Subtractive hybridization was performed utilizing 2 μg of poly(A)+ RNA and the PCR-Select™ subtractive hybridization kit (CLONTECH) according to the manufacturer’s instructions. To identify novel differentially expressed cDNA clones, >10 6 cDNA clones from an E7.0 mouse embryo cDNA library (CLONTECH) were screened with the radiolabeled subtracted cDNA pool (cDNAs that are expressed in embryoid bodies derived from wild-type ES cells, which are not expressed in embryoid bodies derived from GATA-6−/− ES cells) as described previously (10). In addition, an aliquot of the subtracted cDNA pool was digested with EcoRI and subcloned into pBluescript II (Stratagene) for direct automated DNA sequence analyses. Homology searches for each cDNA sequence were performed using the BLAST software program and the GenBank™ database. Finally, to confirm differential patterns of expression, isolated cDNAs were radiolabeled and hybridized to Northern blots containing RNA prepared from wild-type and GATA-6−/− ES cell after 10 days of in vitro differentiation.

**Plasmids and Subcloning**—The pBS/Dab2 plasmid encodes the mouse Dab2 cDNA (base pairs (bp) 1–3245) subcloned into EcoRI/XhoI-digested pBluescript SK. The pDab2Pr.luc luciferase reporter plasmid was used for the transcriptional control of the 766-bp human Dab2 promoter (30) was generating by subcloning the NheI/XhoI-linked human Dab2 promoter into pGL3basic (Promega). The following oligonucleotide primers were utilized to amplify the promoter from human genomic DNA: sense, 5′-CCGCTAGCTTGGTTACATGAAGTGTCG-3′; antisense, 5′-CCCTCGAGGGCGGACATTCCAGGAGTCCTC3′.

The pVP16/GATA-4 and pVP16/GATA-6 plasmids were generated by ligating in-frame cDNA encoding the DNA-binding domains of GATA-4 (aa 209–328) and GATA-6 (aa 231–351), respectively, to the 139-aa transcriptional activation domain of the herpes simplex virus VP16 gene (31) and subcloning the fused cDNAs into KpnI/XhoI-digested pcDNA3. The following oligonucleotides were used to amplify the different cDNA fragments: GATA-4 sense, 5′-CACTTCTTGGACCTCAGAAGAGGACAGAGAG-3′; GATA-4 antisense, 5′-CCTCCGAGCTTGGTTACATGAAGTGTCG-3′; GATA-6 antisense, 5′-CCTCCGAGCTTGGTTACATGAAGTGTCG-3′; GATA-4 sense, 5′-CACTTCTTGGACCTCAGAAGAGGACAGAGAG-3′; GATA-4 antisense, 5′-CCTCCGAGCTTGGTTACATGAAGTGTCG-3′.

**RESULTS**

**Isolation and Characterization of Differentially Expressed cDNA Clones**—GATA-6-deficient embryos fail to survive past the early primitive streak stage and exhibit a specific block in differentiation of the visceral endoderm, including absence of both early and late markers of endodermal differentiation (22, 27). To identify genes that are regulated by GATA-6 in the visceral endoderm, subtractive hybridization was performed utilizing mRNAs harvested from in vitro differentiated embryoid bodies derived from wild-type (GATA-6+/−) and GATA-6-deficient (GATA-6−/−) ES cells. Of note, Southern blot analyses confirmed that mRNA levels of GATA-4 and a-fetoprotein, which we have previously reported to be down-regulated in the visceral endoderm of embryoid bodies derived from GATA-6−/− ES cells (22), were each enriched 50- to 100-fold in the subtracted cDNA pool (data not shown). Consistent with this finding, DNA sequence analysis of 72 random differentially expressed cDNA clones identified several genes that were reported previously to be down-regulated in differentiated GATA-6−/− ES cells, including a-fetoprotein and HNF-4 (Table I) (22). In ad-
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To characterize and identify potentially novel cDNA clones that are regulated by GATA-6 in the primitive streak embryo, the differentially expressed cDNA pool was radiolabeled and hybridized to an E7.0 mouse embryonic library. 4 of 22 cDNA clones isolated from the E7.0 library encoded a protein variably designated as Dab2, p96, or DOC-2 (34, 35). This protein will heretofore be designated Dab2. Dab2 was also identified in the random screen of 72 subcloned cDNAs that were differentially expressed (i.e. down-regulated) in the GATA-6+/- -differentiated ES cells (Table I). Consistent with previous reports, the mouse Dab2 cDNA encodes a 767-amino acid polypeptide with homology to the Drosophila disabled protein contains a putative actin-binding motif (aa 25–29), SH3-binding domains physically associate with the scaffold protein Grb2 (36).

To confirm that Dab2 is differentially expressed in wild-type and GATA-6+/- ES cells during in vitro differentiation, Northern blot analyses were performed. As shown in Fig. 1B, Dab2 mRNA was expressed in embryoid bodies derived from wild-type ES cells, but Dab2 gene expression was severely down-regulated in RNA prepared from embryoid bodies derived from GATA-6-/- ES cells (compare WT and /- lanes). To determine whether Dab2 is regulated by GATA-6 in the mouse embryo, in situ hybridization analyses were performed on staged wild-type and GATA-6-deficient mouse embryos using a radiolabeled Dab2 antisense cRNA probe. As reported previously, E6.5 GATA-6-deficient embryos are smaller in appearance but contain morphologically identifiable visceral and parietal endoderm (22). Fig. 2A shows that, in E6.5 wild-type mouse embryos, GATA-6 is expressed in the visceral endoderm. Similarly, Dab2 mRNA is expressed abundantly in the extra-embryonic visceral endoderm (Fig. 2B). In contrast, Dab2 mRNA was not detectable in E6.5 GATA-6-/- mutant embryos (Fig. 2C). This observation was confirmed in multiple GATA-6-/- embryos. No hybridization of the control Dab2 sense cRNA probe to wild-type or mutant embryos was observed (data not shown). These data demonstrate that, in the late egg cylinder stage embryo (E6.5), GATA-6 and Dab2 are coexpressed in the visceral endoderm (compare Fig. 2A with 2B). In addition, these data confirm that Dab2 is regulated by GATA-6 in the visceral endoderm of the embryonic mouse (compare Fig. 2B with 2C).

Dab2 Is Expressed in the Visceral Endoderm of the Developing Mouse—Relatively little is understood about the function of Dab2 in developing vertebrates. To characterize the temporal and spatial pattern of Dab2 gene expression in the embryonic mouse and to define the cell specificity of Dab2 gene expression, in situ hybridization analyses were performed. In the primitive streak mouse embryo (E7.5), the gene encoding Dab2 is expressed exclusively within the visceral endoderm at the extra-embryonic pole of the embryo (Fig. 3A, arrowhead). This pattern of expression overlaps with GATA-6, which is expressed throughout the visceral endoderm and within the primitive streak mesoderm (9). At E9.5, expression of Dab2 mRNA was observed throughout the yolk sac endoderm (Fig. 3B, white arrowhead). Expression was also observed in the branchial arch mesenchyme (Fig. 3B, black arrowhead) and the septum transversum (Fig. 3B, arrow). To determine which cells within the developing yolk sac expressed Dab2, in situ hybridization analyses were performed on serial sections through E9.5 embryos using a digoxigenin-labeled Dab2 riboprobe. As shown in Fig. 3C, Dab2 mRNA was restricted to the visceral endoderm. The Dab2 gene was not expressed in other cells within the yolk sac, including the blood islands. This pattern of expression in the visceral endoderm is similar to that of GATA-6 (20). Taken together, these data demonstrate that, in the embryonic mouse, Dab2 is expressed in the visceral endoderm of the yolk sac in a pattern that overlaps with GATA-6.

The Human Dab2 Promoter Is Differentially Activated by GATA-6 and GATA-4—The finding that Dab2 was not expressed in the visceral endoderm of GATA-6-deficient embryos suggested that the gene encoding Dab2 was regulated either
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FIG. 3. Embryonic expression pattern of the mouse Dab2 gene. In situ hybridization analysis was performed on staged mouse embryos with a Dab2 cRNA probe. A, specific hybridization (white signal) was observed in the extra-embryonic visceral endoderm (white arrowhead) at E7.5. B, Dab2 mRNA is observed in the yolk sac (white arrowhead), and the branchial arch mesenchyme (black arrowhead) at E9.5. C, nonradioactive in situ hybridization shows that expression of Dab2 (blue signal) is confined to the visceral endoderm of the yolk sac (black arrow) and is not apparent in blood islands (black arrowhead). Magnification, ×400 (A and C) and × 100 (B).

Directly or indirectly by GATA-6. To determine whether forced expression of GATA-6 directly activates the human Dab2 promoter in nonendodermally derived cells, NIH-3T3 cells were cotransfected with a luciferase reporter plasmid under the transcriptional control of the 766-bp human Dab2 promoter and an expression plasmid encoding GATA-6. Of note, DNA sequence analysis of the human Dab2 promoter revealed seven consensus GATA binding sites (Fig. 4A) (30). As shown in Fig. 4B, a 7-fold increase in luciferase activity was observed when NIH-3T3 cells were cotransfected with the pcDNA6 expression plasmid and the pDab2Pr.luc reporter plasmid above levels observed following cotransfection of pDab2Pr.luc and pcDNA3 control expression plasmid.

Despite the fact that GATA-6 and GATA-4 are coexpressed in the visceral endoderm, GATA-6 and GATA-4 null embryos exhibit distinct phenotypes (9, 20). Therefore, it was of interest to determine whether GATA-4 also activated the human Dab2 promoter. To test this possibility, NIH-3T3 cells were cotransfected with an expression plasmid encoding GATA-4 and the pDab2Pr.luc reporter plasmid. Surprisingly, forced expression of GATA-4 failed to activate the human Dab2 promoter (Fig. 4B). This result was confirmed in multiple independent transfections. These data strongly suggested that the Dab2 promoter was differentially activated by GATA-4 and GATA-6 in the developing embryo. To confirm that Dab2 is in fact differentially regulated by GATA-6 and GATA-4 in vivo, the pattern of Dab2 gene expression in wild-type and GATA-4-deficient embryos was determined. In contrast to GATA-6-deficient embryos, which do not express Dab2 mRNA (see Fig. 2C), abundant Dab2 mRNA was observed in the visceral endoderm of E9.5 GATA-4-deficient embryos (Fig. 5B). These data confirm that, in vivo, Dab2 is differentially regulated by GATA-6 and GATA-4 in the visceral endoderm of the embryonic mouse. It is noteworthy that we reported previously that GATA-6 is up-regulated in GATA-4−/− embryos (20).

Specificity of GATA-6-induced Transactivation of the Dab2 Promoter—Previous studies have revealed that the specificity of GATA factors may be mediated in whole or part, by the two zinc fingers that mediate DNA-binding activity and heterodimerization with other transcriptional regulators (13, 14, 17–19, 37). In fact the phenotype of GATA-1 null ES cells can be partially rescued by forced expression of the zinc finger DNA-binding domain of GATA-1 (38). To examine whether the functional specificity of GATA-6 is mediated solely through its zinc finger DNA-binding domain, expression plasmids encoding the DNA-binding domains of GATA-6 and GATA-4, respectively, fused to the VP16 transcriptional activation domain were cotransfected with the pDab2Pr.luc promoter-driven reporter plasmid in NIH-3T3 cells. As shown in Fig. 6, both the pVP16/GATA-4 and pVP16/GATA-6 constructs transactivated the human Dab2 promoter. These data demonstrate that the
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Fig. 6. The Dab2 promoter is transactivated by GATA-4/VP16 and GATA-6/VP16 fusion proteins. NIH-3T3 cells were cotransfected with either the pcDNA3 control vector (pcDNA3), the expression vector pVP16/GATA-6 encoding the mouse GATA-6 DNA-binding domain fused to the VP16 activation domain, or the expression vector pVP16/GATA-4 encoding the mouse GATA-4 DNA-binding domain fused to the VP16 activation domain, along with the pDab2Pr.luc reporter plasmid and the pMSVβ-gal reference plasmid. 48 h after transfection, cells were harvested and relative luciferase activity was measured and normalized to the activity obtained following transfection with the pcDNA3 and pDab2Pr.luc plasmids. Differences in transfection efficiencies were corrected using a β-galactosidase assay. The data are presented as relative luciferase activity ± S.E.

specificity of GATA-6-induced transactivation of the Dab2 promoter is not mediated solely through its zinc finger DNA-binding domain and may involve either N- or C-terminal regions of the protein.

DISCUSSION

GATA-6 lies upstream in a transcriptional cascade that regulates differentiation of the visceral endoderm (22, 27). However, the molecular mechanisms by which GATA-6 regulates differentiation of the visceral endoderm remain to be elucidated. In the studies described in this report, we demonstrate that the 96-kDa phosphoprotein, Dab2, is a direct and specific downstream target of GATA-6 in the visceral endoderm. Dab2 is expressed in the visceral endoderm of wild-type mouse embryos, but not in GATA-6-deficient embryos. In the primitive streak embryo, Dab2 and GATA-6 are coexpressed in the visceral endoderm. Finally, we demonstrate that forced expression of GATA-6, but not GATA-4, transactivates the human Dab2 promoter. Consistent with this finding, the gene encoding Dab2 is differentially expressed in the visceral endoderm of GATA-6- and GATA-4-deficient embryos.

GATA-6-deficient embryos do not survive past the primitive streak stage (E7.5) and exhibit increased cell death within the embryonic ectoderm (despite the fact that GATA-6 is not expressed in these cells) (22). The phenotype of GATA-6-deficient embryos led us to hypothesize that GATA-6-mediated signaling between the visceral endoderm and the embryonic ectoderm is required for survival of the primitive streak embryo. Thus it is noteworthy that Dab2 is growth factor responsive and has been implicated in inter- and intracellular signaling (34–36). Specific serine residues in Dab2 are phosphorylated in response to growth factors, including colony stimulating factor 1 (35). Moreover, Dab2 interacts with the scaffold protein Grb2, suggesting a role in the ras-Sos G protein signal transduction pathway (36). Thus, it will be interesting to examine the role that Dab2 plays in regulating signaling within the visceral endoderm in the primitive streak embryo.

It remains unclear what directs the functional specificity of GATA factors when two or more factors are developmentally coexpressed in a given tissue. We reported previously that GATA-4 and GATA-6 are developmentally coexpressed within the visceral endoderm (9, 10). However, GATA-4- and GATA-6-deficient embryos display distinct phenotypes. In GATA-6-deficient embryos, the primitive endoderm is specified, but these embryos do not express early or late markers of endoderm differentiation, including HNF-4 (22, 27). In contrast, GATA-4-deficient embryos express both early and late markers of endoderm differentiation but exhibit gross defects in ventral morphogenesis resulting from defective endoderm-mesoderm signaling in the embryo (20, 21). In vitro structure-function analyses revealed that, in addition to a conserved DNA-binding domain, GATA-4, -5, and -6 possess N-terminal activation domains that are not conserved in other GATA family members (32). Moreover, forced expression of either GATA-4, -5, or -6 transactivates the cardiac-specific troponin C promoter in noncardiac muscle cells (9, 10, 39). These data suggested that the functional specificity of GATA-4 and -6 in the visceral endoderm was mediated by subtle differences in their patterns of expression.

Therefore, it is surprising that the human Dab2 promoter, which contains multiple consensus GATA binding sites, is differentially activated by GATA-6 and -4 and that the gene encoding Dab2 is differentially expressed in GATA-6- and GATA-4-deficient embryos. Orkin and coworkers (38) reported previously that forced expression of the zinc finger DNA-binding (and heterodimerization) domain of GATA-1 alone is sufficient to partially rescue the phenotype observed in embryonic stem (ES) cells. Moreover, they observed that a “knock-in” of the GATA-3 cDNA into the GATA-1 locus partially rescues the block in erythroid differentiation observed in GATA-1-defective mice (40). These data suggested that the function of GATA factors in vivo may be mediated via their conserved DNA-binding domain. However, the finding that either the GATA-6 or GATA-4 zinc finger DNA-binding domain fused to the VP16 transcriptional activation domain transactivated the human Dab2 promoter suggests strongly that the divergent N- or C-terminal regions of GATA-4 and -6 play critical roles in regulating the function of these closely related transcription factors. Moreover, the finding that Dab2 is not expressed in GATA-6-deficient embryos, but is expressed in GATA-4 null embryos, demonstrates genetic consequences of this target gene specificity within the visceral endoderm in vivo. As such, these data begin to explain the differences in the phenotypes observed between GATA-6 and GATA-4-deficient embryos. Future experiments are necessary to determine whether post-translational modifications of each respective factor and/or the capacity to differentially associate with transcriptional activators and/or repressors underlies the functional specificity of GATA-6 and GATA-4 in the visceral endoderm.

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