HOXA5-Twist Interaction Alters p53 Homeostasis in Breast Cancer Cells*

The homeotic gene HOXA5 has been shown to play an important role in breast tumorigenesis. We have shown that loss of p53 correlated with loss of a developmentally regulated transcription factor, HOXA5, in primary breast cancer. Searching for potential protein interacting partners we found that HOXA5 binds to an anti-apoptotic protein, Twist. Furthermore, Twist-overexpressing MCF-7 cells displayed a deregulated p53 response to γ-radiation and decreased regulation of downstream target genes. Using a p53-promoter-reporter system, we demonstrated that HOXA5 could partially restore the inhibitory effects of Twist on p53 target genes. These effects are likely mediated through both the transcriptional up-regulation of p53 and the protein-protein interaction between HOXA5 and Twist. Thus, the loss of HOXA5 expression could lead to the functional activation of Twist resulting in aberrant cell cycle regulation and promoting breast carcinogenesis.

The HOX family of homeobox-containing genes encodes transcription factors that are highly conserved from Drosophila to Homo sapiens (1, 2). Transcription factors encoded by the HOX genes are essential for maintaining the positional identity of cells along the major body axis. Activation of HOX genes establishes a developmental guide that remains conserved throughout development (1–3). Failure of the molecular systems that control development results in a prevention of normal embryo growth and disruptions in this control system have been shown to be involved in a wide variety of cancers (4–7).

Several studies have linked HOX function to neoplastic growth, where translocations involving HOX genes were shown to be the underlying cause of leukemias and lymphomas (8–10). Selected HOX genes have been shown to be differentially expressed in neoplasms of the colon, lung, kidney, and breast, but their functional relationship to the neoplastic phenotype remains to be elucidated (11).

We have shown that HOXA5 expression is higher in normal breast epithelium than in breast carcinomas (7). Seeking a functional role for HOXA5, we observed consensus HOX binding sites within the p53 promoter and showed that HOXA5 is a potent transactivator of the p53 promoter. In an effort to identify protein-protein interacting partners of HOXA5, we performed a yeast two-hybrid screen that identified Twist as an interacting partner.

Twist was initially discovered as a gene required for the formation of mesodermal patterns in early Drosophila zygotic development (12, 13). The Twist protein belongs to the family of basic helix-loop-helix transcription factors that exert their activity as transactivating factors through dimer formation (14). Mutations in the Twist gene can give rise to Saethre-Chotzen syndrome, an autosomal dominant disease, which results in craniosynostosis (15–17). In addition, mutations in the helix domain of the Twist gene can cause subcellular mislocalization and increased degradation of its protein product (18), which results in the repression of pro-inflammatory cytokine gene expression (19). Moreover, recent evidence indicates that Twist can be involved with several pathways that lead to the formation of cancer by: halting differentiation, controlling apoptosis, interfering with the p53 tumor suppressor pathway (20), and inducing an epithelial-mesenchymal-like transition (21). Twist can also bind to p300 and decrease its histone acetyltransferase activity (22). It is established that homeobox and basic helix-loop-helix containing proteins interact in different organisms (23, 24). Thus, the HOXA5-Twist interaction fits this class of interactions and taken together the above results indicate that it may play a role in carcinogenesis.

We have previously shown that HOXA5 protein binds to the p53 promoter and activates p53 expression (7). On the other hand, Twist has been shown to reduce the activity of the p53 promoter as well as the production of p19 ARF mRNA (20). In this paper, we demonstrate that the addition of HOXA5 to MCF-7 cells stably transfected with Twist largely reverses the Twist-mediated suppression on p53 target sequences. Furthermore, Twist overexpression in MCF-7 cells alters p53 phosphorylation and cell cycle progression in response to radiation an effect that can partially be reversed by a Twist-specific small interfering RNA.

**EXPERIMENTAL PROCEDURES**

*Plasmid Construction for Yeast Two-hybrid Assays—Full-length HOXA5 gene was released (EcoRI digest) from the parental plasmid (25) and ligated into pAS2-1 (Clontech) creating pAS2-1-HOXA5. Truncated HOXA5 vector, designated pAS2ΔHOX, devoid of homeodomain was generated by digesting the full-length HOXA5 with BspHI, end filling, EcoRI digestion, and ligating into pAS2-1. PCR was used to generate the N/C-terminal deletion construct (ΔNC, i.e. Δamino acids 81–187), which was ligated into the appropriate sites of pAS2-1 and used for the two-hybrid screen. For delineation of protein binding sites of HOXA5 and Twist, the appropriate coding sequences were inserted into pBD-GAL4 Cam and pAD-GAL4–2.1 (Stratagene), respectively. The use of these vectors enabled us to prepare C-terminal deletion constructs of pBD-ΔNC and pAD-Twist using the Erase-a-Base system.
as described by the manufacturer (Promega). All pBD-JNC and pAD-Twist plasmids were isolated and sequenced. pAD-Lamin C (Clontech) and pAD SV40T (Clontech) were co-transformed with pBD-p53 (Clontech) and served as negative and positive controls for the yeast two-hybrid assay, respectively.

**Yeast Two-hybrid System**—The Matchmaker yeast two-hybrid system (Clontech) was used for the interaction assays. To screen for proteins that interact with HOXA5, a human brain cDNA library and an E. coli 7.5 mouse embryonic library in Gal4-AD vector pACT2 were screened, according to the manufacturer's instructions (Clontech), using pBD-p53 (Clontech) as bait. Subsequently, individual plasmids were used to transform Y190 yeast cells to establish positive binding.

**Plasmid Construction for Glutathione S-Transferase (GST) Binding Assays**—The HOX5 insert was cloned into the pGEX-6P1 vector (Amersham Biosciences) to yield the plasmid pGEX-HOXA5. Plasmid pGEX-HOXA5ΔC was generated by digesting the parent plasmid pAS2ΔHOX (as described above) and the pGEX-6P1 vector with EcoRI and ligating the ΔHOX insert to the purified pGEX-6P1 vector. Plasmid pGEX-HOXA5ΔCP was generated by digesting pGEX-HOXA5 with BglII and Sall. The vector containing the HOXA5ΔCP fragment was blunt-ended and self-ligated.

Plasmid pCr3.1-HOXA5 was generated by inserting FLAG-HOXA5 into an E.coli-linearized pCR3.1 vector (Invitrogen). Twist gene, released from plasmid pCMV-Twist (Twist), was cloned into the BamHI- and Sall-digested pGEX-6P1 vector to generate pGEX-Twist.

**GST Binding Assays, Immunoblotting, and 35S-Protein Labeling**—GST protein affinity kits were used according to the manufacturer (Amersham Biosciences). Briefly, pGEX-HOXA5, pGEX-HOXA5ΔC, pGEX-HOXA5ΔCP, pGEX-Twist, and empty pGEX-6P1 vector were transformed into BL21(DE3) pLysS Escherichia coli, grown in 2YT medium (10 g of yeast extract, 16 g of tryptone, 5 g of NaCl) induced with 0.1 mM isopropyl-β-D-thiogalactopyranoside (Sigma) for 1 h at 25 °C, and pelleted. Pellets were lysed with B-PER reagent ( Pierce), mixed with 50% slurry of Sepharose-GST beads (Amersham Biosciences) and incubated at 30 min at room temperature. Subsequently, the pellets were washed three times with PBS and incubated overnight at 4 °C with 35S-labeled proteins, previously prepared using the T7 transcription and translation rabbit reticulocyte lysate (TNT RRL) kit, as described by the manufacturer (Promega). Immobilized protein-protein complexes were washed three times with PBS, and samples were resuspended in a reducing urea-containing buffer. Samples were then subjected to SDS-PAGE and immunoblotting with preimmune serum, anti-HOXA5, anti-Twist, and anti-p21.

**Immunofluorescence**—MCF-7 cells transiently transfected (24 h) with FLAG-tagged HOXA5 and Myc-tagged Twist encoding plasmids were fixed and probed with anti-FLAG or anti-Myc antibodies. pp denotes pentapeptide, HD denotes homeodomain, and bHLH denotes basic helix-loop-helix.

**Co-immunoprecipitation Experiments**—Co-immunoprecipitation experiments were performed using MCF-7 extracts. Briefly, the cells were washed, resuspended in lysis buffer (50 mM of Tris-HCl, pH 7.4, 150 mM NaCl, 1 mM EDTA, 1% TritonX-100, and 0.1% SDS), and precleared using preimmune serum and recombinant protein A (Pierce). To the clear lysate, 5 μg of the respective antibody was added per 500 μg of protein and incubated overnight at 4 °C. Following incubation, recombinant protein A was added and incubated for an additional 2 h. Subsequently, the resin was washed 10 times in wash buffer (50 mM Tris-HCl, pH 7.4, 150 mM NaCl), resuspended in urea-containing SDS-PAGE buffer, subjected to SDS-PAGE, and analyzed by immunoblotting using anti-HOXA5 and Twist.

**Immunofluorescence**—MCF-7 cells (2 × 10⁴) were plated onto collo-
gen treated 4-well chamber glass slides (Lab-Tek) and transfected with FLAG-HOXA5 and Myc-Twist plasmids or with pCR3.1 vector alone. After 24 h, cells were washed twice in PBS, fixed with 4% paraformaldehyde, permeabilized with 0.1% Triton X-100, and blocked with 5% normal donkey serum. After incubating with primary antibodies for HOXA5 (mouse anti-FLAG at 1:1000, Stratagene) and Twist (rabbit anti-Myc 1:500, Panvera) the samples were incubated with donkey Cy3-conjugated anti-rabbit IgG (Molecular Probes) and examined using a Nikon TS-100 fluorescence microscope.

Cell Culture and Transfections—Plasmids were transfected at the concentrations indicated in the legend to Fig. 5. p53Luc plasmid was a gift of Dr. Maureen Murphy (26). MCF-7 cells were cultured in McCoy's 5A medium (Invitrogen) supplemented with 10% fetal bovine serum. For transfections, cells were grown to 70% confluence in 60-mm dishes, washed twice with cold PBS and resuspended in a solution containing 0.56% Nonidet P-40, 3.7% formaldehyde and 0.01 mg/ml Hoechst 33258 in PBS. Laser scanning cytometry was performed using a BD Biosciences LSR. MCF-7Myc-Twist-overexpressing cells were transfected with either control siRNA or siRNA for Twist, and the levels of Twist and p53 were analyzed by Western blotting at 24 and 48 h post-transfection.

RESULTS AND DISCUSSION

HOXA5 Interacts with Twist—In an effort to identify the mechanisms by which loss of HOXA5 may promote tumorigenesis in breast cancer, we performed yeast two-hybrid analysis to isolate HOXA5 interacting proteins. As bait we used a HOXA5 deletion construct (ΔNC, amino acids 81–187), which is devoid of any inherent transcriptional activity (Fig. 1A). From these experiments, we identified four potential HOXA5 binding partners, including the anti-apoptotic protein referred to as Twist. The interaction of HOXA5 with Twist was confirmed using individual clones in a yeast two-hybrid genetic analysis (data not shown). To verify the interaction in the yeast environment, ΔNC and full-length Twist were cloned in the similar yeast-two hybrid vectors pBD-GAL4 Cam and pAD-GAL4–2.1 (Stratagene). Yeast-two hybrid analysis using these constructs also verified the interaction between ΔNC and Twist (Fig. 1B).

To identify the regions of the proteins responsible for this interaction, deletion mutagenesis was performed on pBD-ΔNC and pAD-Twist. The deletion mutants generated were assayed for binding using a yeast two-hybrid approach, and results are summarized in Fig. 1B. These results indicated that the amino acids 81–105 of HOXA5 and amino acids 1–50 of Twist are necessary and sufficient for interaction between HOXA5 and Twist.

To confirm the interaction between HOXA5 and Twist, in vitro GST pull-down assays were performed. HOXA5, as well as C-terminal deletion constructs of HOXA5 (amino acids 1–187 and amino acids 1–176), were expressed as GST fusion proteins using standard GST expression and purification procedures in...
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E. coli BL21(DE3)/pLysS cells (Fig. 1C). Proteins expressed from GST-HOXA5 (full-length) and C-terminal deletion constructs were bound to in vitro transcribed and translated 35S-labeled Twist protein (Fig. 1C). Also, the pentapeptide motif (amino acids 177–181) of HOXA5, which has been shown to be an important site for protein-protein interactions (28), was not critical for direct binding to the Twist protein (Figs. 1, B and C).

In the converse experiment, GST-Twist fusion protein also interacted with the in vitro translated 35S-labeled HOXA5 (Fig. 1D). To verify this interaction in the breast cancer cellular environment, immunoprecipitation reactions were carried out in epithelial MCF-7 cells. As shown in Fig. 1E, Twist and HOXA5 were pulled down using anti-HOXA5 and anti-Twist antibodies in MCF-7 cellular lysate. In addition, a control Co-IP with preimmune serum and anti-p21 antibody did not show any binding (Fig. 1E). From the results obtained, we have demonstrated that the pro-apoptotic protein HOXA5 interacts with Twist, a protein shown to down-regulate p53 functions.

Furthermore, immunolocalization studies demonstrated that transiently transfected Myc-tagged Twist was predominantly localized in the nucleus of MCF-7 cells and less in the cytoplasm, while FLAG-HOXA5 was exclusively localized in the nucleus of MCF-7 cells (Fig. 1F). These results show that HOXA5 and Twist may form protein-protein complexes in the nucleus of MCF-7 cells.

Twist Compromises the p53 Response to γ-Radiation—The p53 response to exogenous stimuli, such as γ-radiation, leads to arrest at the G1 to S transition of the cell cycle (29). A key effector of this response is a cdk inhibitor known as p21Waf/1Cip1, which also inhibits the Cyclin E-cdk2 complex from phosphorylating the retinoblastoma protein (30, 31). MCF-7, MCF-7Myc-epitope (vector control), and MCF-7Myc-Twist-overexpressing cells were subjected to γ-radiation (10 Gy) and analyzed for activation of the key p53 targets, MDM-2 and p21Waf/1Cip1 at 1, 2, and 4 h after irradiation (Fig. 2A). p53 levels were induced 1 h after irradiation, but maximum induction was observed 2 h after irradiation in non-transfected MCF-7 and MCF-7Myc-epitope expressing cells. p21Waf/1Cip1 and MDM-2 proteins were also markedly induced in both cell types 4 h following irradiation and 2 h after the highest p53 levels were observed. However, Twist-overexpressing cells showed a constant level of p53, no induction of p21Waf/1Cip1, and a reduced induction of MDM-2. It is interesting to note that Twist-overexpressing cells have a high level of endogenous p53 (prior to irradiation). However, this p53 protein is probably repressed, as it did not activate p21Waf/1Cip1 or MDM-2 prior to radiation. The p53 function is likely to be repressed because the levels of p21Waf/1Cip1 and MDM-2 were comparable with those of control cells before radiation. We propose that the accumulated level of p53 is a result of a deregulated p53 response, which includes a reduced p53 turnover over prior to radiation. Moreover, the expression of Twist did not interfere with the down-regulation of p14ARF (data not shown) or the nuclear import of p53 (Fig. 2B) or the ability of p53 to be ubiquitinated in response to treatment with the proteasome inhibitor MG-132 (data not shown).

To understand the implications of Twist overexpression on the cell cycle, MCF-7, MCF-7Myc-epitope, and MCF-7Myc-Twist cells were irradiated with 10 Gy and assayed for DNA content at 0, 12, and 24 h post-irradiation using laser scanning cytometry (Fig. 2C). MCF-7 and MCF-7Myc-epitope control cells were arrested 12 and 24 h after treatment predominantly at the G1/S cell cycle checkpoint. However, Twist-overexpressing cells displayed an increased synthetic phase at 12 h after irradiation, while after 24 h they had reverted to the preirradiation cell cycle profile. Finally, knockdown of Twist expression by siRNA in MCF-7Myc-Twist cells resulted in a decreased amount of p53 protein (Fig. 2D). These data demonstrate that Twist overexpression provides a potent inhibition signal on p53 mediated gene expression. Twist overexpression also overrides cell cycle checkpoint arrest in response to ionizing radiation thereby demonstrating the potential oncogenic effects of Twist overexpression on cell cycle.

Twist Alters p53 Serine 20 Phosphorylation in Response to γ-Radiation—The p53 response to stimuli involves the stabilization of the p53 protein through post-translational modifications (32). To understand the mechanism by which Twist compromises the p53 response, we examined the phosphorylation of p53 serines 15 and 20 in Twist-overexpressing cells in response to γ-radiation. Phosphorylation of these residues has been previously shown to be important for p53-mediated apoptosis (33, 34). In MCF-7 and MCF-7Myc-epitope cells, p53 Ser15 was phosphorylated 120 min following 10 Gy of γ-radiation, while in MCF-7Myc-Twist cells p53 Ser15 was phosphorylated as early as 30 min following 10 Gy of γ-radiation (Fig. 3A). In contrast, p53 Ser20 was only phosphorylated in MCF-7 and MCF-7Myc-epitope control cells but not in MCF-7Myc-Twist cells (Fig. 3A). This altered p53 Ser20 phosphorylation in MCF-7Myc-Twist cells could be partially rescued by down-regulating Twist protein levels using Twist-specific siRNA (Fig. 3B). Prevention of phosphorylation of p53 Ser20 has been described previously with desferoxamine (35). Intriguingly, in that study, desferoxamine inhibited the accumulation of p21Waf/1Cip1 and MDM-2, which, taken together with our results, may indicate an important role for the phosphorylation of Ser20 as a signal involved in regulating the p53 response.

HOXA5 Reverses the p53-suppressive Effects of Twist—Because HOXA5 was previously shown to have a potential tumor suppressor role, we investigated whether it could reverse the oncogenic effects of Twist. A canonical p53 binding site linked to a luciferase reporter gene (Fig. 4A) was co-transfected with either pCR3.1 empty vector, a full-length HOXA5 expressing vector, or ΔNC expression vector. In each case Renilla lucifer-
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HOXA5 might have the ability to augment p53 target gene p53 reporter construct. These results demonstrated that Twist (data not shown) were able to bind to or up-regulate the constitutively active p53 gene, neither HOXA5 (Fig. 4B) nor Twist (data not shown) were able to bind to or regulate the p53 reporter construct. These results demonstrated that HOXA5 might have the ability to augment p53 target gene expression because of its ability to bind to the Twist protein. Taken together these data indicate that HOXA5 may safeguard the p53 response by virtue of its direct interaction with Twist.

Additionally, Twist may inhibit p33-mediated gene transcription through its demonstrated ability to inhibit p300-mediated acetylation (22). Currently it is hypothesized that a ternary complex containing p53, MDM2, and p300 controls p53 protein stability (36). Overexpression of Twist and its increased binding to p300-p53 complexes may deregulate the finely balanced physiological p53 turnover and function.

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