Loss of Cables, a Cyclin-Dependent Kinase Regulatory Protein, Is Associated with the Development of Endometrial Hyperplasia and Endometrial Cancer

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ABSTRACT

Endometrial cancer is the most common gynecological cancer in Western industrialized countries. Cables, a cyclin-dependent kinase binding protein, plays a role in proliferation and/or differentiation. Cables mutant mice are viable, but develop endometrial hyperplasia and carcinoma in situ at a young age. Exposure to chronic low levels of estrogen results in development of endometrial cancer, similar to that observed in the postmenopausal female. In vitro and in vivo studies demonstrate that levels of Cables mRNA in benign human endometrial epithelium are up-regulated by progesterone and down-regulated by estrogen. Furthermore, nuclear immunostaining for Cables is lost in a high percentage of cases of human endometrial hyperplasia and adenocarcinoma, which are likely the product of unopposed estrogen. The loss of Cables immunostaining in the human endometrial cancer samples correlates with a marked decrease in Cables mRNA. Ectopic expression of Cables in human endometrial cells dramatically slows cell proliferation. Collectively, these data provide evidence of abnormal growth and/or differentiation in rapidly growing and differentiating tissues (i.e., endometrium). A Cables mutant mouse was generated and found to have a unique phenotype with abnormal uterine/endometrial growth and proliferation. This phenotype was additionally explored and supported by in vivo and in vitro studies using benign and malignant human tissue and endometrial cell lines.

INTRODUCTION

Cables, located at 18q11–12 in humans, encodes a 568 amino acid protein with a predicted molecular weight of 63,000 (1) and is found predominantly in the nucleus of proliferating cells (e.g., epithelium) of embryonic and adult tissues (1, 2). In some fully differentiated cells, such as mature neurons, a significant portion of Cables is present outside the nuclear membrane. Cables interacts with cell cycle regulatory proteins (2) and appears to act as a linker protein or “cable.” Cables enhances cyclin-dependent kinase (CDK) tyrosine phosphorylation by nonreceptor tyrosine kinases (1, 2). In neurons, Cables links cdk5 and c-Abl. Cables enhances cdk5 tyrosine 15 phosphorylation and results in increased cdk5 activity, which is important in neurite outgrowth (1). In proliferating cells, Cables functionally links Cdk2 and Wee1, a dual specificity kinase. Cdk2 regulates the G1 to S phase transition of the cell cycle, and phosphorylation of cdk2 on tyrosine 15 by Wee-1 leads to decreased cdk2 activity and slows cell proliferation (3, 4). Cables enhances this Cdk2 inhibitory phosphorylation by Wee-1 (2). In addition to cdk5 and cdk2, Cables has been shown to interact with two regulators of apoptosis, p53 and p73 (5). Although the physiological relevance of this interaction is not fully understood, Cables augments p53-induced apoptosis in human osteosarcoma cells (U2OS; Ref. 5).

Given the functional interaction of Cables and cell cycle regulatory proteins, and an in vitro role in cell proliferation and/or differentiation, we hypothesized that a Cables mutant mouse might have evidence of abnormal growth and/or differentiation in rapidly growing and differentiating tissues (i.e., endometrium). A Cables mutant mouse was generated and found to have a unique phenotype with abnormal uterine/endometrial growth and proliferation. This phenotype was additionally explored and supported by in vivo and in vitro studies using benign and malignant human tissue and endometrial cell lines.

MATERIALS AND METHODS

Cloning and Characterization of the Mouse Cables. The Cables mouse cDNA (1) was digested with NotI to yield a 411 bp NH2-terminal fragment. This was used as a probe for screening a 129/Sv mouse bacterial artificial chromosome genomic library (RPCI-22 Research Genetics; Invitrogen, Carlsbad, CA) made from adult female mouse spleen. Three positive bacterial artificial chromosome clones were obtained. On the basis of sequencing data, we replaced 1.7 kb of the 5’ end of the Cables with the neo resistance cassette. The deleted region starts at a HindIII site, located 617 bp upstream of the ATG, and ends at a SpeI site located 1.1 kb downstream of the ATG. This removes all of exon 1, which contains the ATG codon, 617 bp of 5’ untranslated sequence, as well as the splice donor site and 371 bp from the 5’ end of intron 1. Two probes were developed for Southern blot analysis of ES cell clones.

Targeted Deletion of Cables in Embryonic Stem (ES) Cells and Generation of Mice with Germ-Line Mutation of Cables. Low-passage ES cells (W9.5; The Jackson Laboratory, Bar Harbor, ME) derived from white-bellied agouti strain 129 S1/Sv blastocysts were maintained on irradiated feeder layers of embryonic fibroblasts. The linearized Cables targeting vector was transfected into actively growing (105) ES cells by electroporation. Positive ES clones were injected into the inner cell mass of blastocysts from inbred C57BL/6J (The Jackson Laboratory). Injected blastocysts were then transferred to the uterus of pseudopregnant females, which were F1 hybrid of B6 × CBA. The offspring were genotyped by analyzing tail DNA by Southern blots. The chimeras were also rechecked to confirm that they contained the targeted band. Wild-type (WT) and Cables-deficient female mice were generated by mating heterozygous male and female mice. Female mice were genotyped by PCR analysis of tail-snip genomic DNA using specific primers.

Determining the Mendelian Ratio, Cyclicity, and Fertility Rates of Cables Mutant Female Mice. Cables mutants, heterozygotes, and WT mice were bred to evaluate offspring viability and Mendelian ratios. Vaginal swabs were taken daily from mature females (>6 weeks of age) for 15 consecutive days (~3 continuous estrous cycles) to evaluate the overall length of the estrous cycle of the homozygous nulls, heterozygous, and WT females. The number of offspring from individual matings of the various genotypes was evaluated to determine whether there was an effect on fecundity as a result of gene mutation. In addition, 11 mice (6 mutant and 5 WT females) were evaluated at 1 year of age for any gross effects.

Estrous Synchronization. For comparative analysis between genotypes it was necessary to verify that tissues were from the same physiological state (i.e., proliferating endometrium observed immediately before ovulation). To accomplish this 10 IU of equine chorionic gonadotropin (Professional Compounding Centers of America, Houston, TX) was injected into the i.p. cavity of 3-month-old female mice (6). The female mice were euthanized 46 h later, immediately before ovulation; a point that represents an estrogen-dominant uterine environment (7).
Chronic Estrogen Exposure. To subject animals to chronic low levels of estrogen, silastic capsules (1.54-mm inner diameter × 3.18-mm outer diameter, 11-mm total length; 5-mm contain active ingredient; Fisher Scientific, Springfield, NJ) filled with crystalline E2 (16 μg of 17β estradiol; Sigma, St. Louis, MO) and 1.6 mg of cholesterol (Sigma) were implanted dorsally s.c. in female mice at 6 weeks of age. Control animals (WT and Cables mutant mice) received capsules containing cholesterol alone.

Animal Protocols. All of the animal protocols were reviewed and approved by the Massachusetts General Hospital Institutional Animal Care and Use Committee, and were performed in strict accordance with the NIH Guide for the Care and Use of Laboratory Animals.

Human Endometrial Tissue. Discarded benign and malignant human endometrial tissue was collected in accordance with Massachusetts General Hospital Institutional Review Board Committee guidelines. No patient identifiers were linked to this tissue during or after its collection. An institutional pathologist evaluated a subsection of each tissue sample to determine the phase of the menstrual cycle, grade, and/or type of tumor from which the sample represents. The tissue was then prepared for immunohistochemical analysis as described previously (1, 2).

Northern Analysis of Cables mRNA Expression in Benign and Malignant Human Endometrial Samples. Total RNA was isolated from benign and malignant endometrial samples using TriReagent (Sigma) as per the manufacturer’s instructions. The level of Cables mRNA was analyzed by Northern blotting as described previously (8). Briefly, samples of RNA (15 μg/lane) were separated through a 1.5% agarose denaturing gel, transferred to nylon membranes (Fisher Scientific, Springfield, NJ), and hybridized to a radiolabeled cDNA (human Cables). To control for equal loading the blots were reprobed with an 18S cDNA. The bands were measured by densitometry, and the ratio of Cables to 18S was compared among the benign secretory and malignant samples.

Loss of Heterozygosity. Archival DNA was extracted from formalin-fixed endometrial samples as described previously (2). Briefly, non-neoplastic tissue was removed from 4-μm thick sections mounted on glass slides. The tissue was removed with a clean blade by superimposing the unstained section with the corresponding stained section. The tissue was deparaffinized, rehydrated through xylene and alcohol, scraped into a microcentrifuge tube, and the DNA was extracted with phenol chloroform. As a control the DNA was also isolated from normal tissue in a paired sample in all of the cases assessed. Loss of heterozygosity in the region of the Cables on chromosome 18 was examined by using the highly polymorphic markers D18S44 and D18S1107, which map to 18q11. Loss was scored as described previously (9).

Progesterone and Estrogen Effects on Cables mRNA Expression in Human Endometrial Cell Lines. To examine the effects of hormone treatment a human endometrial cell line derived from benign proliferative endometrium (HES; provided by Dr. Douglas Kniss, Ohio State College of Medicine, Columbus, OH) was treated with progesterone or estrogen. Cells were seeded at 100,000 cells/100-mm dish in DMEM containing 1,000 IU penicillin, 1,000 IU streptomycin, 2 mM l-glutamine, and 10% FBS, and allowed to reach 50% confluency. The wells were then treated with or without progesterone (10–1,000 ng/ml), estrogen (1,000 pg/ml), or vehicle (ethanol) for 24 h. Total RNA was isolated, and Cables expression analyzed by Northern blotting and autoradiography as described (8). To control for equal loading of RNA the gels were reprobed with a cDNA probe complimentary to 18S rRNA. Autoradiograms were quantified by densitometry.

Overexpression of Cables in Endometrial Cells. Four stable HES cell lines overexpressing Cables (HES_cables) were generated by techniques described previously (2). Briefly, HES cells propagated in DMEM with 4.5 g/liter glucose, 10% FCS 1000 IU penicillin, 1000 IU streptomycin, and 2 mM l-glutamine. A plasmid containing full-length Cables in a pCIN vector described previously by Wu et al. (2) was transfected into HES cell using Lipofectamine (Invitrogen). Stably transfected cells were selected by growth in 1200 μg/ml G418. Controls transfected with vector alone (no insert; HES_control). The proliferation rate of the cell lines (HES cables and HES control) were determined by seeding 1 × 10^5 cells/well and counting the cells in triplicate for up to 12 days.

Colony Formation Efficiency. Colony-formation efficiency was determined by plating single cells at 1 × 10^5/100-mm dish and incubating plates undisturbed for 10 days at 37°C to allow for colony formation. At the end of the incubation period the cells were fixed and Geimsa stained. Colonies of 25 or more cells were considered positive. Seeding efficiency was determined by seeding 1 × 10^7 cells per/60-mm dish and counting the number of adherent cells after 6 h.

RESULTS

Generation of Cables Mutant Mice. A Cables mutant mouse was generated by replacing 1.7 kb of the 5′-end of the Cables with a neo resistance (neo+) cassette (Fig. 1A). The deleted region starts at a HindIII site, located 617 bp upstream of the ATG, and ends at a SpeI site located 1.1 kb downstream of the ATG. This removed all of exon 1, which contains the ATG start codon, 617 bp of 5′ untranslated sequence as well as the splice donor site, and 371 bp from the 5′ end of intron 1. The loss of Cables mRNA and protein in homozygous-null offspring provided verification that Cables was lost (Fig. 1B).

Medelian Ratio, Cyclicity, Fertility, and Fecondity. Cables knockout mice (−/−) were viable, and heterozygous crosses gave expected Mendelian ratios. Cables−/+ females mated with Cables−/− males had reduced fertility and fecundity compared with their WT female littersmates; whereas 14 matings between WT females mated with WT males resulted in 100 pups, nearly twice the number (n = 26) of matings between Cables−/+ females and Cables−/− males resulted in only 71 pups. From a fecundity end point, the Cables−/− mutant females averaged significantly smaller litter sizes (2.73 ± 2.71 pups per litter) than their WT female counterparts (7.21 ± 3.24 pups per litter). The overall length of the estrous cycle was assessed by vaginal cytology in 5 WT and 5 Cables mutant females, and determined not to be different (P > 0.05).

Comparative Histological Analysis of Uterine Tracts from WT and Cables Mutant Mice. Macroscopic analysis of the female mice provided no obvious evidence of abnormalities in any tissue with the exception of the uterus. The uterine tracts of Cables mutant mice were abnormally large and distended. Microscopic examination of 20 mutant females (3–6 months) of age showed the luminal endometrium to be disorganized and hyperplastic with tortuous glands, glandular

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complexity, and prominent overgrowth of the luminal epithelium forming epithelial knots protruding into the lumen (Fig. 2, top panel, ko). The surface and glandular epithelium showed severe cytologic atypia characterized by large cells with rounded hypochromatic nuclei containing coarse chromatin and numerous mitoses. The atypia ranged from atypical hyperplasia to carcinoma in situ.

It remained possible that the abnormal endometrium could be a reflection of different phase of the estrous cycle between the mutant and the WT mice. However, after evaluation of uteri collected from mice euthanized just before ovulation, a point that represents an estrogen-dominant uterine environment (middle: WT, left, and KO, right). Lastly, chronic estrogen exposure for 12 weeks increases the severity of the epithelial atypia and induced multifocal adenocarcinoma in the Cables mutant females (bottom: WT, left, and KO, right).

No invasive carcinoma was identified in untreated WT or knockout mice (n = 11) followed for >1 year. However, the Cables mutant mice still had evidence of atypical and cystic hyperplasia, although the proliferative component was not as great as that observed in the females at 3–6 months of age, and more cystic changes were noted. The endometrium of the WT females appeared atrophic.

**Effects of Chronic Estrogen Exposure.** Cables mutant mice exposed to chronic estrogen (n = 3) had evidence of endometrial adenocarcinoma, which was not observed in the WT females similarly treated (n = 3; Fig. 2, bottom panels). The endometrial glands showed crowding and complexity with cribiform changes forming epithelial nodules that pushed aside normal intervening endometrial stroma. The cells were large and hypochromatic with frequent mitoses. The architectural and cytological changes were those of well-differentiated endometrial adenocarcinoma.

**Immunohistochemical Analysis of Cables Protein Expression in Benign and Malignant Human Endometrium.** There were menstrual cycle stage-specific differences in the level of Cables expression in the endometrial epithelium. Essentially all of the lu-
minal and glandular cells of the secretory (nonproliferating) endometrium have pronounced nuclear Cables expression. However, in the growth or proliferative phase of the menstrual cycle, nuclear Cables was present in all of the cases, but its expression was patchy, even within the same gland (Fig. 3). Moreover, Cables nuclear staining was lost in 50% of cases of atypical endometrial hyperplasia (12 of 20 cases) and 90% of endometrial cancers (19 of 20 cases; Fig. 3). Thus, Cables protein expression is greater \( (P < 0.05) \) during the secretory phase of the menstrual cycle when compared with the proliferative phase.

**Northern Analysis of Cables mRNA Expression in Benign and Malignant Endometrial Samples.** Immunohistochemical evidence for a decrease in Cables expression was supported by Northern blotting. The level of Cables mRNA expressed in endometrial tumors was dramatically reduced \( (P < 0.05) \) in endometrial tumor samples \( (n = 4) \) when compared with that expressed in endometrium collected from the secretory phase \( (n = 3; \text{Fig. 4}) \).

**Loss of Heterozygosity.** No evidence of Cables deletion or loss of heterozygosity of the chromosome 18q 11.2–12.1 was detected in 10 endometrial cancer samples studied (data not shown).

**Progesterone and Estrogen Effects on Cables mRNA Expression in HES Cells.** Progesterone up-regulated Cables expression in HES cells in a dose-dependent manner, whereas estrogen down-regulated Cables expression (Fig. 5).

**Overexpression of Cables in HES Cells.** To further study the role of Cables in endometrial cell proliferation, we examined the Cables-dependent suppression of cell growth using a human endometrial cell line (HES). The growth rate of the HES cell lines stably expressing ectopic Cables was found to be different from HES cells which expressed the vector alone (HES; no insert). Four HES\textsubscript{vector} cell lines were generated and evaluated. All demonstrated only a minimal increase (≤2-fold) in the amount of Cables protein by Western blot when compared with the control cell line HES\textsubscript{control} (data not shown). No stable cell line could be generated that overexpressed more than two times the endogenous level of Cables in HES cells. Immunohistochemical analysis verified the nuclear localization of Cables similar to that observed in the parent cell line (no vector; data not shown). The proliferation rate of the HES\textsubscript{Cables} cell lines (doubling time 62–84 h) was significantly decreased compared with the control HES\textsubscript{control} cells (doubling time 28–30 h; Fig. 6), which showed the same growth rate
of untransfected HES cells. The seeding efficiency (attachment) of all of the cell lines was similar.

**Colony Formation Efficiency.** There was a significant reduction ($P < 0.001$) in colony-formation efficiency in all of the HES cell lines over expressing Cables protein when compared with the no insert vector controls (Fig. 7).

**DISCUSSION**

Cables appears to be involved in multiple cellular processes including neurite outgrowth in cultured cortical neurons, inhibition of proliferation in HeLa cells, and augmentation of p53-induced apoptosis in osteosarcoma U2OS cells (1, 2, 5). To better examine the *in vivo* function of Cables, a Cables mutant mouse was generated by replacing 1.7 kb of the 5'-end of the Cables with a neo resistance (neo') cassette. The Cables mutant mice were viable, and the heterozygous crosses gave expected Mendelian ratios, indicating that there was not an embryonic lethal phenotype. However, Cables−/− females mated with Cables−/− males had reduced fertility and fecundity compared with their WT female littermates. At this time the cause of the reduced fertility and fecundity is not clear. There was, however, evidence of fetal resorption in the mutant mice, which was not readily evident in the WT female mice.

The most readily recognizable phenotype found in the Cables mutants was observed in the uteri. Histological examination of the uteri provided evidence that the luminal endometrium was disorganized and hyperplastic with tortuous glands, increased glandular complexity, and considerable overgrowth of the luminal epithelium. The surface and glandular epithelium showed severe cytologic atypia.

The atypia ranged from atypical hyperplasia to carcinoma *in situ*. The irregular growth patterns were evident as early as 3 months of age. Arguably, some of the differences in the endometrial development observed could have been attributed to tissue collected during different physiological states or irregular ovarian function (i.e., irregular estrous cycle). Consequently, the overall length of the estrous cycle was assessed by vaginal cytology and found that the length of the estrous cycle was similar in the mutant mice and their WT counterparts. However, when the uteri of the WT and mutant mice were compared in an estrogen-dominant phase induced by exogenous gonadotropins, the mutant mice showed prominent endometrial epithelial proliferation with epithelial overgrowth forming protrusions into the glandular lumens, whereas the WT mice showed normal proliferative endometrium. A small group of untreated mutant and WT mice were sacrificed at 1 year of age, and no invasive carcinoma was identified. These data suggest that the phenotype did not progress with age alone. However, Cables mutant mice exposed to chronic estrogen had evidence of early endometrial adenocarcinoma, which was not observed in the WT females similarly treated.

On the basis of the knockout mouse phenotype, additional studies were conducted to survey the level of expression of Cables in the human endometrium. The level of Cables expression in the endometrial epithelium differed in accordance to the stage of the menstrual cycle. The majority of luminal and glandular cells of the secretory (nonproliferating) endometrium have prominent nuclear Cables expression. In contrast, the level of nuclear Cables was markedly less...
Evident in the growth or proliferative phase of the menstrual cycle. The expression of Cables was patchy at best with fewer cells within the same gland staining positive. This decrease in Cables is likely related to the increase rate of cell growth and lack of cellular differentiation during the growth (proliferative) phase of the menstrual cycle.

Similar to that observed in the proliferative phase, Cables nuclear staining was dramatically decreased or absent in >50% of cases of atypical endometrial hyperplasia and 90% of endometrial cancers. Immunohistochemical evidence for a decrease in Cables expression in the malignant tissue was associated with a decline in the mRNA encoding Cables. The level of Cables mRNA was dramatically reduced in endometrial tumor samples when compared with the endometrium collected from the progesterone dominant (secretory) phase of the menstrual cycle. Unlike what was observed in colon cancer (2), no evidence of Cables deletion or loss of heterozygosity of the chromosome 18q 11.2–12.1 was detected in the endometrial cancer samples studied. These data suggest transcriptional regulation. However, in the absence of any detailed sequence analysis there is always the possibility that a mutation could lead to unstable mRNA or inactivation of the protein. Alternatively, Cables may also be regulated post-transcriptionally. Although the phenotype in the mutant mice would argue otherwise, there remains the possibility that in the human the observed changes in Cables may be secondary to a more primary event not evident at this time.

From a physiological standpoint, progesterone is a negative regulator of endometrial proliferation and mediates many of the regulatory components of the cell cycle (e.g., cyclins and CDKs). Recent studies have indicated that regulators of the cell cycle play a significant role in the incidence of tumors in reproductive tissues, including the endometrium (10). On the basis of the fact that Cables is elevated in the progesterone-dominant secretory phase it is also possible that progesterone directly regulates Cables expression. To examine hormonal regulation of Cables expression, cells were treated with progesterone or estrogen and Cables expression analyzed by Northern blotting techniques. Progesterone up-regulated Cables expression in a dose-dependent manner, whereas estrogen down-regulated Cables expression in HES cells. These data suggest that progesterone and estrogen may regulate transcription of Cables. Consequently, it is plausible that chronic elevated estrogen levels may be one mechanism for Cables loss in endometrial hyperplasia and cancer.

Cables regulates Cdk2. Cdk2 controls the G1 to S transition and is important in the initiation of DNA replication (11). Previous studies have shown that dysregulation of cdk2 by overexpression of cyclin E or A moderately accelerates entry into S phase (12, 13) and is involved in anchorage-independent growth (14). Ectopic Cables expression slows cell proliferation rate in benign endometrial cells (HES). HES cells appear to be exquisitely sensitive to overexpression of Cables, and no stable cell line with more than mild (2 times endogenous) expression could be established. The sensitivity of the endometrial cells to the overexpression of Cables was additionally demonstrated by the reduced number of colonies formed in cell-overexpressing Cables. These data are again consistent with the patchy expression of Cables in growing (proliferative) endometrium compared with uniform Cables expression in differentiating (secretory) endometrium. Collectively, these data provide additional support for Cables as regulator of the cell cycle and cell proliferation rate.

Endometrial cancer is the most common gynecologic malignancy. Endometrioid adenocarcinoma, the most common subtype, is generally related to overexpression to unopposed estrogens. This subtype is often termed type I, which includes tumors that are categorized as grade 1 (well-differentiated) or grade 2 (moderately differentiated), retain progesterone and estrogen responsiveness, a significant percentage evolve from atypical endometrial hyperplasia, and finally are usually associated with loss of pTEN, ras, and/or microsatellite instability (15–17). In contrast, type II endometrial tumors are poorly differentiated (grade 3) or nonendometrioid subtypes (serous, clear cell; Ref. 15). These tumors are more aggressive clinically and are not believed to result from unopposed estrogen. Coincidentally, there is also a high incidence of mutated p53 (18–20). Similar to pTEN, loss of Cables expression occurs in a high percentage of endometrial hyperplasias, and atypical endometrial hyperplasia is the precursor lesion of endometrial cancer. Therefore, loss of Cables function could be directly involved in the pathogenesis of abnormal endometrial epithelial cell proliferation leading to endometrial cancer.

To date there are no accepted alternative treatment modalities for endometrial cancer other than surgical removal of tumor manifestations. To this end more experimental models are needed to explore alternative treatment modalities. The importance of Cables loss in the pathogenesis of endometrial cancer is supported by the Cables-deficient mouse, which shows atypical endometrial hyperplasia and endometrial cancer at an early age. Older Cables mutant mice (>1 year) show decreasing endometrial abnormalities suggesting that estrogen levels are important in maintaining the hyperplastic/cancerous phenotype. In contrast the severity of the atypical hyperplasia and/or cancer is increased in Cables mutant mice when exposed to chronic estrogen. This suggests that loss of Cables may be linked more closely to type I endometrial cancers (15) typically attributed to exposure of unopposed estrogen. Thus, the Cables-deficient mouse will serve as an important new model for type 1 human endometrial cancer, because few experimental models that “mimic” human endometrial hyperplasia/cancer currently exist (21).

REFERENCES


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