Hormonal Regulation of the Human Pepsinogen C Gene in Breast Cancer Cells

IDENTIFICATION OF A CIS-ACTING ELEMENT MEDIATING ITS INDUCTION BY ANDROGENS, GLUCOCORTICOIDS, AND PROGESTERONE*

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Pepsinogen C is an aspartic proteinase mainly involved in the digestion of proteins in the stomach, which is also synthesized by certain human breast tumors. To examine the possibility that extragastric production of this proteolytic enzyme could be mediated by hormonal factors, we have analyzed pepsinogen C gene expression in human breast cancer cells subjected to different hormonal treatments. Northern blots analyses revealed the expression of pepsinogen C gene by T-47D breast cancer cells after induction with dexamethasone, dexamethasone, and progestin but not with estradiol, retinoic acid, or ethanol. Reverse transcription-polymerase chain reaction analysis in a series of breast cancer cell lines confirmed the amplification of pepsinogen C mRNA after induction with dexamethasone, in those cells expressing the androgen receptor mRNA. The promoter region of the pepsinogen C gene was functionally characterized by transient expression of a vector containing the promoter region cloned in front of the chloramphenicol acetyltransferase (CAT) reporter gene. CAT activity in T-47D cells was stimulated in the presence of dexamethasone, dexamethasone, and progesterone but not by estradiol. By further deletion mapping of the pepsinogen C promoter, a minimal region (AGAATattTGTTCC) was identified as being responsible for glucocorticoid-, androgen-, and progestosterone-regulated gene expression.

Pepsinogen C, also known as progastricin, is the inactive precursor of pepsin C (gastriccin), a member of the aspartic proteinase family of proteolytic enzymes, which is mainly synthesized in gastric mucosa and secreted into the gastric lumen where it is converted to the corresponding active enzyme under acidic conditions (Foltmann, 1981; Tang and Wong, 1987; Moore et al., 1995). Pepsinogen C is more widely distributed in the gastrointestinal tract than pepsinogen A and in some species, such as rodents, constitutes the major proteinase found in the gastric juice (Furuki et al., 1980; Samloff, 1989). Structural characterization of genomic and cDNA clones for human pepsinogen C has revealed that this protein is composed of a polypeptide chain of 488 residues, including a 16-residue leader sequence that targets this proteinase for secretion, a 43-residue activation peptide, and the 329 amino acids corresponding to the mature protein (Hayano et al., 1988; Taggart et al., 1989; Pals et al., 1989). The overall organization and nucleotide sequence of the human pepsinogen C gene are similar to those of the genes encoding other human aspartic proteinases including pepsinogen A (Sogawa et al., 1983), prorenin (Hobart et al., 1984; Miyazaki et al., 1984), procathepsin D (Redecker et al., 1991), and procathepsin E (Azuma et al., 1992), supporting the proposal that these functionally related proteins have diverged from a common ancestor that has been subsequently adapted to digest a wide variety of proteins or peptides in different locations (Foltmann, 1981; Tang and Wong, 1987).

The unexpected relationship of pepsinogen C to human breast diseases has arisen after our finding that pepsinogen C accumulates in cyst fluid from women with gross cystic disease of the breast (Sánchez et al., 1992a). In addition, we have recently provided evidence that a significant percentage of breast carcinomas have the ability to synthesize and secrete this aspartic proteinase (Díez-Itza et al., 1993). These findings, together with the absence of pepsinogen C in normal resting mammary gland, have raised the possibility that this proteinase might play a role in the lytic processes associated with invasive breast cancer lesions, as already found for other proteinases including matrix metalloproteinases (Monteagudo et al., 1990; Basset et al., 1990), plasminogen activators (Fedekens et al., 1992; Grondahl-Hansen et al., 1993; Jänicke et al., 1993), or secreted lysosomal enzymes (Sloane et al., 1981; Rochefort et al., 1987; Chauhan et al., 1991). However, very recent analysis of the relationship between pepsinogen C levels in breast tumors and the clinical outcome of the corresponding patients has revealed that, in contrast to most studies on the prognostic significance of proteolytic enzymes in cancer, pepsinogen C production by breast cancer cells is associated with lesions of favorable evolution (Vizoso et al., 1995). A possible explanation to the fact that pepsinogen C expression by breast cancer cells confers a prognostic advantage to breast cancer patients is that its presence may reflect the existence of a complete hormone receptor pathway. According to this hypothesis, extragastric expression of pepsinogen C may be a consequence of the hormonal alterations presumably involved in the development of breast carcinomas, without causing any direct effect on the spread of cancer.

From these considerations, we were prompted to examine the possibility that production of pepsinogen C by human breast cancer cells could be mediated by hormonal factors. In this report, we show that androgens, glucocorticoids, and progestins up-regulate pepsinogen C expression in human breast cancer cells. In addition, we have performed a functional characterization of the promoter region of the human pepsinogen C...
gene and identified a 15-bp cis-acting sequence with the ability to mediate the hormonal induction of this gene in breast cancer cells.

EXPERIMENTAL PROCEDURES

Materials—For cell culture were obtained from Life Technologies, Inc. Fetal calf serum, trypsin, and restriction endonucleases were from Boehringer Mannheim. Other supplements for cell culture, acetyl coenzyme A, steroid hormones, and dexamethasone were from Sigma. [3H]-Chlorambucil was from Du Pont-New England Nuclear (37 Ci/mmol). Oligonucleotides were synthesized in an Applied Biosystems DNA synthesizer, model 392 A. Plasmid pSV50R (Brinkmann et al., 1989) containing an SV40 promoter that directs the transcription of the full-length human androgen receptor cDNA was kindly provided by Dr. A. O. Brinkmann (Erasmus University, Rotterdam, The Netherlands).

Construction of Chimerical Acetyltransferase Fusion Plasmids—All plasmid constructs were prepared using standard methods (Sambrook et al., 1989). The promoterless basic plasmid pCAT-Basic (Promega Corp., Madison, WI) was used as cloning vector. Cloning of the human pepsinogen C gene (Hayano et al., 1988) upstream of the bacterial CAT gene. The investigated genomic region comprises 1438 bp of the 5'-flanking sequence which was obtained by PCR amplification of genomic DNA by using the following oligonucleotides as primers: 5' -CAATGGTGAGAAATCACTT. Samples were electrophoresed on prerun 4% polyacrylamide gels in Tris-glycine buffer at 200 V for 4 h. Gels were dried and autoradiographed.

DNA Transfections and Chimerical Acetyltransferase Assays—For each transfection experiment, cells were seeded at 2 × 10^5 cells/30-mm dish and transfected 18 h later with 1 μg of the indicated reporter plasmid DNA and 0.5 μg of pRSV-gal (Promega Corp.) using the LipofectAMINE™ Reagent (Life Technologies, Inc.) and following the manufacturer’s indications. Transfected cells were harvested in phosphate-buffered saline after 48 h of hormone exposure for 30 min. DNA transfections were performed by three cycles of freeze-thaw and finally resuspended in 100 μl of buffer A (15 mm Tris-HCl pH 8.0, 60 μm KCl, 15 mm NaCl, 2 mm EDTA, 1 mm dithiothreitol). β-Galactosidase activity was assayed according to Sambrook et al. (1989) in 30 μl of the cell extracts. CAT activity was assayed essentially according to the method of Gorman et al. (1982). TLC plates were run in chloroform/methanol (95:5, v/v), dried, and exposed for autoradiography on Hyperfilm-E (Amersham Corp.) for 16 h. For quantification, radioactivity of the spots on the TLC plates was measured by using the InstantImager eletionic autoradiography system (Packard Instrument Co., Meriden, CT). Stimulation of CAT activity was expressed as fold increase over activity of noninduced transfected cells and was based on at least three independent experiments.

RESULTS

Analysis of Hormonal Regulation of Pepsinogen C Expression in Human Breast Cancer Cells—To evaluate the hypothesis that pepsinogen C expression by human breast carcinomas could be a consequence of hormonal alterations, T-47D breast cancer cells were stimulated with different steroid hormones or synthetic analogs, and the expression of pepsinogen C gene was studied by Northern blot analysis. To this end, and considering that we had previously suggested that androgens could play an important role in the development of breast tumors producing pepsinogen C (Vizoso et al., 1995), T-47D breast cancer cells were first incubated with dihydrotestosterone, and total cellular RNAs were purified and analyzed by Northern blot using a fragment of pepsinogen C cDNA as a probe. As shown in Fig. 1, the addition to the cell culture of 10^-6 M dihydrotestosterone for a period of 48 h induced the accumulation of the 1.5-kilobase pepsinogen C mRNA. Similarly, treatment of T-47 D cells with 10^-5 M concentration of progesterone or the synthetic glucocorticoid dexamethasone, for the same period of time, also induced the expression of pepsinogen C. By contrast, stimulation of these mammary carcinoma cells with estradiol, all-trans retinoic acid, or ethanol (used as vehicle for dissolving the different steroid hormones) did not give any positive signal.

We next investigated if the effect of steroid hormones on

1 The abbreviations used are: 5-bp, base pair(s); CAT, chloramphenicol acetyltransferase; PCR, polymerase chain reaction; RT, reverse transcription; pep, pepsinogen; HRE, hormone responsive elements.
pepsinogen C mRNA induction was only circumscribed to T-47D cells or could be extended to other human breast cancer cell lines. For this purpose, a series of cell lines, varying in their hormonal receptor status as well as in their invasive and metastatic ability, were stimulated with 10^{-6} M dihydrotestosterone for 48 h, and the expression of pepsinogen C gene was examined by RT-PCR in order to increase the sensitivity of detection. In this experiment, RT-PCR omitting the reverse transcriptase step was used as a control of RNA-dependent amplification. In addition, the quality of the studied RNAs was checked by PCR amplification of the reversed transcribed RNAs using a pair of primers (5'-CGGGCAGTACAACAAAGCCA, and 5'-CAGACCGTAGATCTGGAAAG) that directed the amplification of a 219-bp segment corresponding to the cDNA sequence of the human cysatin C gene, a housekeeping gene expressed in all the tissues studied so far (Freije et al., 1991). As illustrated in Fig. 2A, a 350-bp fragment of the human pepsinogen C CDNA was amplified from RNA of T-47D, MFM-223, SK-BR-3, and ZR75-1 breast cancer cell lines treated with 10^{-6} M dihydrotestosterone but not from MDA-MB-231, MDA-MB-435, and Hs-578T cell lines, subjected to the same hormonal treatment. A possibility to explain this variability in the androgen-mediated induction of pepsinogen C mRNA in different breast cancer cells could be that these cells differ in their androgen receptor status. To evaluate this possibility, we undertook the analysis of androgen receptor expression in all of them, by using RT-PCR amplification with oligonucleotides deduced from the sequence reported for this receptor (Lubahn et al., 1989). In fact, and as shown in Fig. 2B, a perfect correlation was found between androgen-induced pepsinogen C expression by breast cancer cell lines and androgen receptor status in these cells. Similar results were obtained in the case of glucocorticoids and progesterone induction of pepsinogen C expression by breast cancer cells. Thus, cells expressing glucocorticoid and progesterone receptors responded to the respective hormonal treatments by synthesizing pepsinogen C, whereas cells defective in any of these receptors failed to produce this protein upon treatment with the respective hormones (data not shown). Taken together the obtained results indicate that, according to our previous proposal (Vizoso et al., 1995), the observed extragastric expression of pepsinogen C is a consequence of the ability of this gene to respond to a variety of hormonal stimuli, including androgens, glucocorticoids, and progesterone.

**Functional Characterization of the Promotor Region of the Human Pepsinogen C Gene**—To investigate further the molecular mechanisms involved in the hormonal regulation of pepsinogen C gene expression by breast cancer cells, we undertook the functional characterization of the promoter region of this gene, with a special interest in looking for the putative hormone-responsive elements (HRE) that could mediate the above observed hormonal stimulation. For this purpose, a genomic region comprising 1438 bp of the 5'-flanking region of the pepsinogen C gene (Hayano et al., 1988) was obtained by PCR amplification of human lymphocyte DNA and cloned in front of the chloramphenicol acetyltransferase reporter gene. A computer search of the nucleotide sequence corresponding to this promoter segment revealed that in addition to the previously identified TATA box (at -91, with ATG being +1), several consensus or imperfect half-sites of the HRE (Evans, 1988; Beato, 1989) were found dispersed along the sequence (Fig. 3A). To determine if some of these elements were important for hormonal induction of the pepsinogen C gene in breast cancer cells, the construct was transfected to T-47D cells, and CAT activity was assayed in transfected cells treated with steroid hormones or synthetic analogs (Fig. 3B). As shown in the figure, CAT activity was detected after induction of T-47D-transfected cells with dihydrotestosterone and dexamethasone, the effect of both hormones being additive. The range of detectable stimulatory effect of these hormones was 10^{-8} to 10^{-6} M. Similar results were also obtained when the transfected cells were treated with progesterone, while undetectable or very weak CAT activity was observed after induction with vehicle alone or estradiol (Fig. 3B and data not shown). In addition, the CAT activity induced by dihydrotestosterone was inhibited by addition of the pure antiandrogen flutamide, at the same concentration (10^{-6} M) although higher concentrations of flutamide were usually required to completely abolish the effect of dihydrotestosterone. By contrast, dexamethasone induction of the pepsinogen C promoter construct was not altered by the presence of the antiandrogenic compound. According to these data, it seems likely that the action of dihydrotestosterone and dexamethasone is mediated via androgen and glucocorticoid receptor mechanisms.
Characterization of a Hormone Response Element in the Pepsinogen C Promoter—In order to delineate the cis-acting regions responsible for this hormonal regulation, constructs containing smaller promoter fragments were generated by endonuclease restriction or PCR amplification and assayed for hormonal induction in T-47D breast cancer cells. As shown in Fig. 5, induction of CAT activity was detected after dihydrotestosterone treatment approximately in the same extent in the −440 element, −440 to −459, whose sequence AGAACTATTTGTTCC was closely related to the consensus sequence established for HRE (Evans, 1988; Beato, 1989; Fabre et al., 1994). This region could then be one of the cis-acting elements responsible for the differences in hormone induction of the −640 and −440 constructs. To test this possibility, an additional recombinant plasmid was generated, the −640DEL plasmid, in which those 20 bases were deleted from the −640 construct. Fig. 5 also shows the CAT activity induced by dihydrotestosterone stimulation of T-47D cells transfected with the additional recombinant plasmid. It was observed that CAT activity strongly decreased in the cells transfected with the constructs lacking this putative HRE (plasmid −640DEL). These results suggest that the region between −444 and −459 of the pepsinogen C promoter likely contains one cis-acting element responsible for the hormonal stimulation of this gene by androgens.

To verify the functional activity of the 15-bp HRE identified in the promoter region of pepsinogen C gene, this element was incorporated either as a single copy or as several copies into the plasmid pBLCAT2, containing a minimal thymidine kinase promoter upstream from the CAT gene, and the CAT activity was measured in transfected androgen-stimulated cells. Fig. 6 shows the results obtained in transfected T-47D cells with the
**DISCUSSION**

The present study was undertaken to evaluate the possibility that expression of human pepsinogen C, an aspartic proteinase mainly involved in the digestion of proteins in the stomach, was under hormonal control in breast cancer cells. In this work, we provide evidence that the expression of this gene is up-regulated by androgens, glucocorticoids, and progesterone in different breast cancer cell lines, including T-47D, MFM-223, SK-BR3, and ZR75-1. By contrast, the expression of the pepsinogen C gene was not significantly stimulated in any of these cell lines by estrogens, anti-estrogens, or by retinoid derivatives like all-trans-retinoic acid. This is the first report showing that hormonal treatments alter the steady state levels of the human pepsinogen C mRNA and provides a molecular basis to explain previous observations indicating that this proteinase is produced by a specific type of breast carcinoma, characterized by a high differentiation grade and a favorable clinical evolution (Vizoso et al., 1995).

The finding that the gene encoding pepsinogen C is induced by different steroid hormones, but not by estrogens, makes this protein interesting as a marker of hormone action in breast cancer cells. Thus, it is generally assumed that breast cancer is a consequence of a hormonal imbalance with estrogens playing a major stimulatory role in the proliferation of breast cancer cells (Davidson and Lippman, 1989). In fact, a significant percentage of human breast carcinomas (up to 50%) are initially responsive to anti-estrogen therapy (Santen et al., 1990). According to these data, the role of estrogens in mammmary tumor cell growth has been extensively studied, and a number of estrogen-induced proteins have been identified in breast cancer cells (Dickson and Lippman, 1987; Rochefort et al., 1987; May and Westley, 1988). These proteins include growth factors such as insulin growth factor-1, transforming growth factor-α and-β, or proteolytic enzymes like cathepsin D, which may account in part for the mammmary tumor cell growth and invasive properties of the tumor cells. By contrast, knowledge on the functional role of other steroids in the development and progression of breast cancer is limited. Therefore, the finding of proteins like pepsinogen C, produced by breast cancer cells under hormonal stimuli other than estrogens, but not by the normal resting mammmary gland, opens the possibility to study the mechanisms by which these hormones could contribute to the develop-
opment and progression of those carcinomas with ability to produce and secrete this gastric proteolytic enzyme. Of special interest in this regard is the finding that the pepsinogen C pattern of hormone responsiveness is similar to that of genes encoding apolipoprotein D and Zn2+-glycoprotein that are also up-regulated by androgens, glucocorticoids, and progesterone in breast cancer cell lines but not by estrogens (Simard et al., 1992; Haagensen et al., 1992; López-Boado et al., 1994). These data strongly suggest that all these three genes share some hormonal regulatory mechanisms that could be responsible for their enhanced expression in a subset of breast carcinomas as well as for the striking accumulation of their encoded proteins in pathological breast fluids, like those obtained from women with gross cystic disease of the breast (Mazoujian and Haagensen, 1990; Balbín et al., 1990; Sánchez et al., 1992b).

In the case of pepsinogen C, and on the basis of the above results showing a close correlation between hormonal inducibility of its expression and receptor status of the breast cancer cells, it seemed likely that these regulatory mechanisms could be mediated by interaction of the respective nuclear receptors with cis-acting DNA sequences presumably present in the promoter region of the pepsinogen C gene. The results presented in this work are consistent with this hypothesis. Thus, after functional analysis of the proximal promoter region of this gene, we have identified a 15-bp cis-acting sequence that plays a major role in the observed pepsinogen C gene induction by steroid hormones in breast cancer cells. The importance of this element as a functional HRE was confirmed by the observation that it can function both in the context of the pepsinogen C promoter and as a separate element when cloned in front of the thymidine kinase promoter. Furthermore, its precise deletion was sufficient to diminish to a great extent the response of the remaining pepsinogen C promoter. In addition, gel mobility shift binding assays confirmed the specific binding of nuclear factors, including the four major guanine/cytosine contact points (Scheiderer et al., 1986; Tsai et al., 1988; Zilliacus et al., 1995). It should be also mentioned that this HRE found in the pepsinogen C gene, as most functional HREs previously characterized, does not have complete dyad symmetry with respect to the two 6-bp elements, which is consistent with studies indicating that the steroid hormone receptors are not binding to the two half-sites in an equivalent manner (Luís et al., 1991). When the nucleotide sequence of this functional HRE was analyzed in more detail, it was found to be remarkably similar to two HREs (AGCAAGTattTGCTCT and AGCAAGTattTGCTT, in the complementary strand) that have been shown to confer a specific androgen responsiveness to the genes coding for prostate-specific antigen and glandular kallikrein, two members of the kallikrein subfamily of serine proteinases that are expressed at high levels in human prostate (Riegelman et al., 1991; Young et al., 1991; Wolf et al., 1992; Murtha et al., 1993). This observation, together with the fact that pepsinogen C is also present in human prostatic tissue (Szeczi et al., 1995), suggests that androgens could be the most relevant steroid involved in its production in both normal and pathological conditions, including breast cancer. Furthermore, recent studies have shown that prostate-specific antigen, widely assumed to be an exclusive prostatic protein, is also produced by certain human breast carcinomas, and it is induced by androgens in T-47D breast cancer cells (Monne et al., 1994; Yu et al., 1994). These results provide an interesting parallelism between these two proteolytic enzymes and extend previous observations establishing a pathological connection between human prostate and mammary tissues, based on the finding of common proteinases overproduced in tumors from both sources and showing a similar pattern of hormone responsiveness in cultured cell lines (Sánchez et al., 1992a,b; Simard et al., 1992; López-Boado et al., 1994; Yu et al., 1994). Nevertheless, the possibility that in vivo expression of pepsinogen C may be under multihormonal control cannot be ruled out. In fact, in addition to androgen receptors, glucocorticoid and progesterone receptors have also been found in breast carcinomas and in normal tissues producing pepsinogen C such as prostate and stomach (Allegre et al., 1979; Polimeni et al., 1994; Wu et al., 1994). Furthermore, glucocorticoids like hydrocortisone enhance pepsinogen C expression in stomach mucosa of developing rats (Ishihara et al., 1989; Ichinose et al., 1990; Tsukada et al., 1994). In any case, and despite the similarity in their response elements, androgens, glucocorticoids, and progesterone display distinct physiological activities; it seems clear that additional factors, including tissue availability of appropriate steroids and their receptors or synergistic interaction between steroid receptors and other transcription factors, must be involved to provide the required specificity (Schüle et al., 1988; Tsai and O'Malley, 1994). A detailed analysis of these possibilities will contribute to the precise elucidation of the relative importance of the in vivo hormonal factors controlling pepsinogen C production in normal tissues and in those conditions like breast cancer in which this gastric protease may be useful as a biochemical marker of tumors with specific patterns of hormone responsiveness.

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