In this study, we identify and characterize a novel gene, CL-20, that encodes a 17.8-kDa protein with sequence and structural similarity to the growth arrest-specific gene gas3/peripheral myelin protein gene PMP22. The CL-20 protein exhibits a 43% identity with PMP22. The positions of the four lipophilic domains and the N-glycosylation site of PMP22 are conserved in CL-20, suggesting that it also is an integral membrane glycoprotein. The CL-20 gene is located on human chromosome 12 rather than 17 and encodes a 2.8-kilobase mRNA instead of 1.7-kilobase mRNA. These observations indicate that the CL-20 gene is related to but distinct from PMP22. In contrast to PMP22, CL-20 mRNA and protein are induced during squamous differentiation of rabbit tracheal epithelial cells in vitro, and Northern blot analysis and in situ hybridization demonstrated that CL-20 mRNA is most abundant in squamous epithelia. These results indicate that the high expression of CL-20 is closely correlated with squamous differentiation. The differences in tissue-specific expression and regulation between CL-20 and PMP22 suggest different roles for these two proteins. Retinoids, which inhibit squamous differentiation, repress the induction of CL-20. The retinoic acid receptor-selective retinoid SRI-6751–84 is the most effective in suppressing CL-20, suggesting that the activation of the retinoic acid receptor signaling pathway is important in this suppression.

Squamous differentiation can be observed in many tissues including the trachea, bronchi, and skin. The lining of the trachea and bronchi normally consists of a pseudostratified columnar epithelium (1). During vitamin A deficiency or after toxic assault or mechanical injury (2–4), regions of the mucociliary epithelium are replaced by a stratified squamous epithelium. Tracheobronchial epithelial cells also undergo squamous differentiation when cultured in medium deficient in retinoids (5–7). In many respects, squamous differentiation in the tracheobronchial epithelial cells resembles differentiation in epidermal keratinocytes and other squamous differentiating tissues (8). The histologically distinct layers constituting the squamous epithelium (8) exhibit distinctive patterns of expression of specific genes and are evidence that squamous differentiation is a multistage process (5, 9, 10). Early in this differentiation process, cells irreversibly lose their proliferative potential and down-regulate the expression of the cell cycle-associated genes cdc2 and E2F-1 (11, 12). This is followed by the expression of squamous-specific genes such as transglutaminase type 1 (7, 13–15), the cross-linked envelope precursors involucrin, loricrin, and cornin (16–19), cholesterol sulfotransferase (20), and specific keratins (9, 21). These genes have been cloned and are shown to be regulated by a variety of agents including retinoids, which suppress the expression of squamous-specific genes (7–21).

In this study, we describe the isolation and characterization of a cDNA CL-20 that was isolated from a cDNA library prepared from poly(A)- RNA of squamous-differentiated rabbit tracheal epithelial (RbTE)3 cells. The open reading frame (ORF) of CL-20 exhibits substantial sequence similarity to three cDNA sequences, Gas3 (23), SR13 (24), and PMP22 (25–27) encoding the mouse, rat, and human peripheral myelin protein, respectively. The peripheral myelin protein is highly expressed in peripheral nerves (25, 26) and is induced in growth-arrested Balb/c3T3 cells (23). Duplication and mutations in the PMP22 gene have been found to underlie several inherited diseases of the peripheral nervous system (28–33). Although CL-20 exhibits sequence and structural similarities with PMP22, we show that its chromosomal localization, tissue-specific expression, and regulation are very different. Northern blot and in situ hybridization analyses show that high CL-20 expression correlates with squamous differentiation in vitro and in vivo. The latter was supported by observations showing that retinoids, which are potent inhibitors of the expression of several squamous-specific genes, also repress the induction of CL-20.

EXPERIMENTAL PROCEDURES

Cells and Tissue—Primary cultures of RbTE cells were established in serum free Ham's F12 medium supplemented with epidermal growth factor, insulin, transferrin, and antibiotics as previously reported (7). Balb/c 3T3 fibroblasts were grown in Dulbecco's minimal essential medium containing 10% fetal bovine serum. Growth arrest in Balb/c 3T3 fibroblasts was induced by serum starvation or by growth to confluence. Splenic nerves and other tissues were obtained from New Zealand White rabbits and immediately frozen in liquid nitrogen.

Isolation of cDNA—The cDNA clone pTG15 has been described previously (13). The CL-20 cDNA clone was obtained by screening a cDNA library prepared from poly(A)+ RNA of Ca2+-treated, squamous-differentiated RbTE cells (custom-made in Lambda Zap by Stratagene) with the 1.2-kb 3'-SstI-HindIII fragment of the cDNA pTG15.

Retinoids—All-trans-retinoic acid was obtained from Hoffman La Roche (Nutley, NJ). The RAR-selective retinoid SRI-6751–84 (6- (5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)l-2-naphthalene-carboxylic acid) and the RXR-selective retinoid SR12217 (4-[2-methyl-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)propenyl] benzoic acid) were provided by Dr. M. Dawson (SRI, Menlo Park, CA) (34).

DNA Sequencing—DNA sequencing of CL-20 and pTG15 was performed in both directions by the dideoxynucleotide chain-termination method.

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The nucleotide sequence(s) reported in this paper has been submitted to the GenBankTM/EMBL Data Bank with accession number(s) U34200.

1 The abbreviations used are: RbTE, rabbit tracheal epithelial; PMP, peripheral myelin protein; Gas, growth arrest-specific; ORF, open reading frame; RAR, retinoic acid receptor; RXR, retinoid X receptor; kb, kilobase(s); bp, base pair(s); PBS, phosphate-buffered saline.
method using a Sequenase v2.0 kit (Amersham) (35) and custom primers (Genomics Facility, North Carolina State University or Research Genetics). DNA and deduced protein sequences were analyzed by the GCG (36) and MacVector (IBI) sequence analysis software packages.

Primer Extension—The oligonucleotide CTGGCTCCCGAGGTTATAAG (see Fig. 1) was radio-labeled with [α-32P]ATP (6000 Ci/mmol, Amersham) using a 5′-end labeling kit from Boehringer Mannheim. The phosphorylated oligonucleotide was purified by NucTrap push column (Stratagene) and Sure Pure TLC (Amersham). Primer extension was carried out with 1 μg of poly(A)−RNA and 0.025 μCi of 5′-32P primer as described (37).

Northern Blot Analysis—Total RNA was isolated from cultured cells and various rabbit tissues using Tri Reagent (Molecular Research Center Inc., Cincinnati, OH) according to the manufacturer’s protocol. Poly(A)+RNA was isolated with the Poly(A) tract 1000 kit (Promega). Northern blot analysis was performed as described previously (18, 38, 39). The plasmid pGas3 MEH8 (23) containing an EcoRI-HindIII fragment encoding gas3 was kindly provided by Dr. C. Schneider (International Center for Genetic Engineering and Biotechnology, Trieste, Italy). Glyceraldehyde-3-phosphate dehydrogenase (pGAD-28) served as a control probe (40).

Chromosomal Localization—A BIOS blot somatic cell hybrid panel was purchased from BIOS Laboratories (New Haven, CT). Briefly, the blot was made from Taq I-digested genomic DNA prepared from different human/hamster or human/mouse hybrid cells. Each cell line contained one or more human chromosome(s) in addition to a complete set of hamster or mouse chromosomes. The human chromosomes contained in each hybrid cell line are listed in Fig. 4B. The cell line 016 is a human/mouse hybrid cell line; all others are human/hamster hybrid cell lines. The blot was hybridized with 32P-labeled CL-20 probe as described for Northern blotting.

In Situ Hybridization Analysis—Tissues were fixed in 4% paraformaldehyde in PBS for 3 h, then washed in PBS and dehydrated through a graded series of ethanol. After incubation in xylene, the tissues were embedded in Paraplast (Monoject Scientific). In situ hybridization analyses were performed as described previously using sense and antisense CL-20 probes (18, 41).

Antibodies—The peptide VSDDNASVGWRNCTS (CL-20-PEP3) was synthesized and purified by the Protein Chemistry Laboratory (University of North Carolina, Chapel Hill). The peptide was cross-linked to KLH using an immunoconjugation kit from Pierce and injected subcutaneously into New Zealand White rabbits as described (41).

Immunoblot Analysis—RBTE cells were rinsed with cold PBS containing 0.5 mM EDTA and scraped directly into SDS-sample buffer. All samples were heated for 5 min (95°C) and stored at −70°C. Proteins (25 μg) were separated on precast, 10–20% polyacrylamide gradient gels (Integrated Separation Systems, Natick, MA) and transferred to Immobilon-P membrane (Millipore) using a Polyblot (American Bio-technics, Hayward, CA) semidry electrophoretic transfer system. Membranes were then incubated in blocking buffer (5% w/v) nonfat dry milk in PBS containing 0.05% Tween 20 overnight at 4°C and subsequently for 1 h at room temperature with primary antibody in blocking buffer. Immunoreactivity with anti-CL-20-PEP3 (1:50 dilution) was carried out with 125I-protein A as described previously (42).

RESULTS

Cloning Analysis of CL-20—The cDNA clone pTG15 is one of five clones that were isolated after screening of a cDNA library prepared from poly(A)+ RNA of squamous-differentiated RBTE cells with a degenerate oligonucleotide mixture encoding the active site of transglutaminases (13). We showed that the degenerate oligonucleotides had at best a 78% homology with a region on the noncoding strand of pTG15 and concluded that pTG15 did not encode a transglutaminase (13). We have subsequently demonstrated that pTG15 hybridized to two mRNAs, 2.8 and 4.4 kb in size. The smaller of these mRNAs is differentially expressed during squamous differentiation of cultured RBTE cells while the larger is faintly detectable regardless of the state of differentiation (not shown). A 1.22 kb SstI HindIII 3′-fragment of pTG15 (Fig. 1A) hybridized strongly and exclusively to the 2.8-kb mRNA, while a 0.82 kb SstI 5′-fragment of pTG15 (Fig. 1A) hybridized to the low abundance 4.4-kb mRNA (not shown). The 3′-fragment was used to rescure the cDNA library to isolate the full-length cDNA for the differentially expressed mRNA. 1 of the 23 clones isolated, designated CL-20, contained an insert of about 2.8 kb. The full insert, as well as a 0.3-kb PstI-EcoRI fragment from its 5′-end (not shown), hybridized strongly and exclusively to a 2.8-kb mRNA, which was differentially regulated during squamous differentiation of RBTE cells (Fig. 1B). These results indicate that the CL-20 cDNA represents the differentially expressed 2.8-kb mRNA and suggest that the 3.6-kb insert of pTG15 is likely to be a chimeric cDNA (Fig. 1A). The latter is supported by the presence of an EcoRI site within the pTG15 insert at the junction of the 3′-CL-20 sequence and the 5′-unrelated sequence, as linkers for this enzyme were used in the construction of the cDNA library. The differentially expressed CL-20 mRNA was present at low levels in undifferentiated RBTE cells but greatly elevated upon squamous differentiation.

Nucleic Acid Sequence Analysis—The insert of CL-20 was sequenced in both directions. The sequence is shown in Fig. 2. A putative translation initiation site was evident 174 bases from the 5′-end of the cDNA. The open reading frame terminated with a stop codon 480 nucleotides downstream from the initiation codon, indicating that CL-20 encodes a protein of 160...
amino acids. CL-20 contains a large 3'-untranslated region of about 2.0 kb that contains six AUUUA instability elements. Primer extension demonstrated four potential start sites 8–12 base pairs upstream of the end of the cDNA (the strongest being at 12 base pairs) as noted in Fig. 2.

Comparison of the Amino Acid Sequence and Structure between CL-20 and PMP22—Searching the data base (GCG FastA on the combined nucleic acid database) with the ORF of CL-20 revealed substantial sequence similarity to three cDNA sequences Gas3 (23), SR13 (24), and PMP22 (26) encoding the peripheral myelin protein from mouse, rat, and human, respectively. These PMP22 genes exhibit a high degree of conservation, 86% identity, at the protein level. In contrast, CL-20 exhibits a 43% identity (65% similarity) to PMP22 (Fig. 3A), suggesting that CL-20 encodes a distinct but related gene.

In addition to the amino acid sequence homology, CL-20 exhibits structural similarities with PMP22. Examination of the Kyte-Doolittle hydrophilicity profile indicates that like PMP22, CL-20 contains four hydrophobic domains (Fig. 3B), suggesting that CL-20 encodes an integral membrane protein. In particular, the second hydrophobic domain (amino acids 64 through 89) is highly homologous between CL-20 and PMP22 (Fig. 3A) with 18 of the 26 amino acids being identical. CL-20 contained two potential N-glycosylation sites, amino acids 35 and 43, the latter being conserved between the two proteins (Fig. 3A).

Chromosomal Localization of Human CL-20—To determine the chromosomal localization of human CL-20, TaqI-digested DNA from a panel of hybrid DNA cell lines was examined by Southern analysis with a 32P-labeled probe for CL-20. As shown in Fig. 4, the human-specific pattern of CL-20 hybridization was strongly detected in the hybrid cell line 683 and weakly in line 756 but not in other cell lines. Since both of these cell lines contain human chromosome 12 but no other cell line does, CL-20 must be on human chromosome 12. PMP22 has been localized previously to human chromosome 17 (27, 32), which is not present in either cell line positive for human CL-20. These observations confirm that CL-20 is a novel gene that is distinct from PMP22.
Tissue-specific Expression of CL-20—To examine the tissue-specific expression of CL-20, we analyzed the level of CL-20 mRNA in different tissues by Northern blot analysis. As shown in Fig. 5, CL-20 mRNA was most highly expressed in the squamous-differentiated epithelia of the tongue and the esophagus and at low levels in lip (Fig. 5A). After long exposure, CL-20 mRNA was also detectable in the ovary, uterus, prostate, testis, and lung but not in brain and kidney (Fig. 5B). The localization of CL-20 mRNA was examined by in situ hybridization using sections from rabbit esophagus and tongue. In both the squamous epithelium of the esophagus and tongue, CL-20 mRNA was localized in suprabasal layers, predominantly in the granular layer (Fig. 6). Little CL-20 mRNA was present in the undifferentiated basal layers. These findings are in agreement with our in vitro data showing induction of CL-20 mRNA in squamous-differentiated RbTE cells (Fig. 1B) and support the conclusion that high expression of CL-20 in several tissues is associated with squamous cell differentiation.

Comparison of the Regulation of CL-20 and PMP22—Since CL-20 and PMP22 are structurally related proteins, we examined whether they have some functional similarities as well. PMP22 is highly expressed in peripheral nerve (29, 30). We therefore investigated the expression of CL-20 in the sciatic nerve. Total RNA isolated from rabbit sciatic nerve was examined by Northern analysis using radiolabeled probes for PMP22 and CL-20. Both the 2.8-kb CL-20 and the 1.8-kb PMP22 mRNA were found to be expressed (Fig. 7A). PMP22 expression has been reported to be repressed after nerve injury and to increase after regeneration (24); however, nerve injury and regeneration had little effect on the expression of CL-20 mRNA (not shown). In addition, PMP22 (Gas3) expression has been shown to be greatly increased in Balb/c3T3 cells upon growth arrest induced by either serum starvation or confluence (23). CL-20 mRNA was detectable in proliferating Balb/c 3T3 cells; however, in contrast to PMP22, its expression was not significantly changed when cells became growth arrested (Fig. 7B). Northern blot analysis showed that PMP22 mRNA was undetectable in squamous-differentiating RbTE cells (not shown).

Fig. 4. Human chromosomal localization of CL-20. A, Southern analysis of Taq-digested DNA from a panel of hybrid human/hamster or human/mouse cell lines with the 32P-labeled 2.8-kb CL-20 probe. Open arrows indicate hamster-specific DNA fragments hybridizing to human-specific DNA fragments. B, somatic cell hybrid panel specifying the human chromosome(s) present in the hybrid cell lines. ● indicates 5–30% of cells contain given human chromosome; ○ indicates >30% of cells contain given human chromosome; D indicates the presence of multiple deletions in the respective human chromosome. Shaded columns indicate the two hybrid cell lines, 683 and 756, exhibiting a human hybridization pattern with the CL-20 probe in Southern analysis. Shaded row indicates human chromosome 12 that contains the CL-20 gene.
These results indicate that CL-20 is regulated differently from PMP22 and suggest that CL-20 is playing a biological role that is distinct from that of PMP22.

Suppression of CL-20 Expression by Retinoids—The results above indicate that induction of CL-20 mRNA expression is closely correlated with squamous differentiation. Retinoids have been reported to block squamous differentiation of tracheobronchial epithelial cells and other cell types and suppress the expression of several squamous cell-specific genes (5, 9). To study the sensitivity of the expression of CL-20 to retinoids, we treated RbTE cells with retinoic acid, the RAR-selective retinoid SRI-6751–84, and the RXR-selective retinoid SR11217 just before parallel, untreated cultures began to differentiate. Fig. 8 shows that treatment of RbTE cells with these retinoids repressed the induction of CL-20 mRNA. A 50% inhibition of the expression of CL-20 mRNA could be observed at a concentration of $10^{-11}$ M of the RAR-selective retinoid. The retinoid SR11217 was less potent in inhibiting CL-20 mRNA expression with $10^{-8}$ M of SR11217 being as effective as $10^{-11}$ M.

**DISCUSSION**

CL-20 represents a novel gene related to PMP22 (22–24). The similarity between the two proteins is both at the level of the amino acid sequence as well as the structure. The amino acid sequence of CL-20 exhibits a 65% similarity and a 43% identity with PMP22. The sequence of peripheral myelin protein is highly (about 86%) conserved across species. The homology of CL-20 with PMP22 is much smaller, suggesting that it represents a novel gene, related to but distinct from PMP22. In addition to their amino acid sequence homology, CL-20 and PMP22 show structural similarities. Like PMP22, CL-20 contains four hydrophobic domains. Likely, these genes encode membrane proteins (23, 33). Recently, a structural model of PMP22 has been proposed in which the four hydrophobic domains span the membrane either as a $\beta$-sheet or as an $\alpha$-helix (33). CL-20 may have a similar structure. The second hydrophobic region of CL-20 and PMP22 is the most highly conserved (69% identity) and may point at a functionally important domain that is shared between these two proteins.

CL-20 contains two potential N-glycosylation sites, one of
lyzed by immunoblot analysis using a rabbit antiserum against HNK-1. These epitopes have been shown to be commonly
recognized by several antibodies including HNK-1, L1, J1, myelin associated glycoprotein, and P0 (43-48). HNK-1 antibodies have been reported to be able to inhibit aggregation and cell adhesion, indicating that this carbohydrate is functionally important (47-51).

Another feature shared by CL-20 and PMP22 is the presence of a relatively long 3’-untranslated region containing several AUUUUA instability motifs. A modulatory role in mRNA degradation under specific physiological conditions has been suggested for this motif (52). CL-20 and the gas genes may be differentially regulated with regard to mRNA stability between cell types and during differentiation or growth arrest. Interestingly, regulation of gas3 expression during growth arrest of 3T3 cells is largely through an increase in the stability of its mRNA (28). However, possible involvement of these instability elements in the regulation of CL-20 has yet to be determined.

Polyadenylation of CL-20 mRNA appears to be signalled by a non-consensus motif. The region within 30 base pairs upstream of the poly(A) sequence in the cDNA contains three sequences (AATATA, TATAAA, and AATAGA) with one base mismatch to the consensus polyadenylation signal sequence, which is normally highly conserved (52). TATAAA has been observed previously to function as a polyadenylation signal in hepatitis B viruses (53). In that system, efficient use of the TATAAA signal for polyadenylation is conferred by upstream elements. Both the non-consensus polyadenylation signal and the presence of the AUUUUA motifs hint at post-transcriptional controls being involved, under some conditions, in the regulation of CL-20.

Comparison of the regulation of the CL-20 and PMP22 genes indicates a number of differences. In contrast to PMP22, the expression of CL-20 is closely associated with squamous differentiation. This is indicated by the relatively high level of CL-20 mRNA expression in squamous tissues in Northern blot analysis. Moreover, in situ hybridization studies showed that in the squamous epithelium of the esophagus and tongue, CL-20 mRNA is expressed at very low levels in the basal layer containing undifferentiated cells but becomes highly expressed in the differentiated, suprabasal layers. The association of CL-20 expression with squamous differentiation is confirmed in cultured RbTE cells in which CL-20 mRNA and protein are present at low levels in undifferentiated cultures and are dramatically induced in squamous-differentiated cells. No expression of PMP22 could be detected in squamous-differentiated cells. On the other hand, expression of PMP22 is particularly high in Schwann cells and growth-arrested Balb/c 3T3 cells (23). Both PMP22 and CL-20 are expressed in peripheral nerve, but while the former is down-regulated upon injury and up-regulated upon regeneration (24, 29, 54), the latter is not. Likewise, while PMP22 is greatly induced when Balb/c 3T3 cells become growth arrested (23), CL-20 mRNA is expressed at low levels, and its expression is not significantly altered during growth arrest.

Retinoids are important regulators of differentiation in tracheobronchial epithelial cells (5). They promote mucociliary differentiation and are potent inhibitors of squamous differentiation. The latter is indicated by the suppression of the induction of several squamous-specific genes such as transglutaminase type I and cornin (18, 55, 56). In this study, we demonstrate that retinoids suppress the expression of CL-20. This inhibition is observed both at the protein and mRNA levels. It is likely that many of the effects of retinoids on gene expression in tracheobronchial epithelial cells are mediated either directly or indirectly by the nuclear retinoid receptors RAR and RXR (57). The RAR-selective retinoid was very potent in suppressing CL-20, suggesting that the activation of the RAR-signaling pathway is important in this suppression. Preliminary data indicated that CL-20 mRNA is extremely stable which is conserved in PMP22. Although the exact carbohydrate structure has not yet been established, human PMP22 binds the monoclonal antibody HNK-1, which recognizes specific epitope(s) composed of sulfated carbohydrates (43-45). Preliminary observations have indicated that CL-20 may also bind HNK-1. These epitopes have been shown to be commonly present on several proteins that play a role in cell adhesion.

\[2\] K. W. Marvin and A. M. Jetten, unpublished observations.
in squamous-differentiated RbTE cells (t½ > 16 h) and that retinoid treatment has no significant effect on the half-life of this mRNA, suggesting that retinoids regulate the expression of this RNA at the transcriptional level.

Squamous differentiation is a multi-stage process in which irreversible growth arrest occurs early and is followed by the expression of squamous cell-specific genes (5). The induction of CL-20 expression could be related to either of these two stages of differentiation. However, retinoids, which have been shown not to block irreversible growth arrest but to suppress the induction of these genes occurs later during squamous differentiation both in vitro and in vivo. Although the structural similarity of CL-20 and PMP22 argues for a similarity in function, the differences in the same gene (33). The peripheral hypomyelination in the CMT1A cases, is associated with allelic point mutations in the same gene (33). The peripheral hypomyelination in the trembler mouse also correlates with a point mutation in the same gene (33). The peripheral hypomyelination in the trembler mouse also correlates with a point mutation in the same gene (33).

In summary, CL-20 encodes a novel gene that is related to but distinct from PMP22. The gene, although detectable in several non-squamous tissues including peripheral nerve, is highly induced during squamous differentiation both in vitro and in vivo. Although the structural similarity of CL-20 and PMP22 argues for a similarity in function, the differences in tissue-specific expression and regulation suggest that their precise roles are distinct.

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