Aberrant P-cadherin expression is an early event in hyperplastic and dysplastic transformation in the colon

R G Hardy, C Tselepis, J Hoyland, Y Wallis, T P Pretlow, I Talbot, D S A Sanders, G Matthews, D Morton, J A Z Jankowski

Background: Colorectal adenomatous and, probably, hyperplastic polyp development requires epithelial remodelling and stratification, with loss of E-cadherin expression implicated in adenoma formation. We have shown that P-cadherin, normally expressed in stratified epithelia and placenta, is aberrantly expressed in disturbed epithelial architecture associated with colitis.

Aims: (i) To investigate the role of P-cadherin in colonic polyp formation. (ii) To ascertain whether expression of P-cadherin is independent of or correlated with expression of its associated proteins—E-cadherin, β-catenin, and γ-catenin. (iii) To determine if P-cadherin is functional regarding catenin binding in polyps.

Methods: Expression and localisation of cadherins (E- and P-) and their associated catenins (β- and γ-) were determined in aberrant crypt foci (ACF), in polyps with hyperplastic morphology (hyperplastic polyps and serrated adenomas), and in adenomatous polyps by immunohistochemistry, western blotting, and mRNA in situ hybridisation. Assessment of cadherin-catenin binding was evaluated by co-immunoprecipitation. Adenomatous polyposis coli (APC) mutation was assessed in adenomatous polyps.

Results: P-cadherin was expressed from ACF through to hyperplastic and adenomatous polyps. Alterations in E-cadherin and catenin expression occurred later, with variant patterns in (i) ACF, (ii) hyperplastic polyps and serrated adenomas, and (iii) adenomatous polyps. P-cadherin present in adenomas was functional with regard to catenin binding, and its expression was independent of APC mutational status.

Conclusions: P-cadherin is aberrantly expressed from the earliest morphologically identifiable stage of colonocyte transformation, prior to changes in E-cadherin, catenin, and APC expression/mutation. P-cadherin expression alone does not predict tissue morphology, and such expression is independent of that of associated cadherins and catenins.

P-cadherin is expressed in placenta and stratified squamous epithelia but not in normal colon. P-cadherin null mice develop mammary gland hyperplasia, dysplasia, and abnormal lymphoid infiltration, demonstrating that loss of normal P-cadherin expression leads to cellular and glandular abnormalities. Our group has shown that P-cadherin is aberrantly expressed in inflamed and dysplastic colitic mucosa, with concomitant E-cadherin downregulation. Reduced E-cadherin expression in breast carcinoma and cervical squamous intraepithelial neoplasia is similarly accompanied by aberrant P-cadherin expression. These studies suggest interdependence of expression of E- and P-cadherin in some circumstances. E-cadherin is downregulated in colonic adenomas but expression of P-cadherin has not been studied in these lesions.

We sought to investigate whether P-cadherin was aberrantly expressed during aberrant crypt formation in the colon, and if such expression persisted during polypl development. Subsequently, we analysed if P-cadherin expression was correlated with or independent of alterations in expression and localisation of associated cadherins, catenins, and APC.

Abbreviations: ACF, aberrant crypt foci; APC, adenomatous polyposis coli; LEF, lymphocyte enhancing factor; TCF, T cell factor; PBS, phosphate buffered saline; TBST, Tris buffered saline Tween; DAPI, 4,6-diamidino-2-phenylindole; PTT, protein truncation test.
MATERIALS AND METHODS

Tissue specimens
Formalin fixed paraffin embedded sections of colonic hyperplastic (n=20) and sporadic adenomatous (n=22) polyps were obtained from the archives of University Hospital Birmingham, UK.

Adenomatous polyps were subclassified as follows: tubular (n=11), tubulovillous (n=11), mild dysplasia (n=12), moderate dysplasia (n=5), severe dysplasia (n=5), size <1 cm (n=17), size >1 cm (n=5), right sided (n=4), and left sided (n=18).

Formalin fixed paraffin embedded sections of ACF (n=23) were provided from the archives at Case Western Reserve University, Cleveland, Ohio, USA. As most human ACF display some morphological alterations in histological sections, the ACF in this study were designated as follows: those with alterations that were mild and failed to meet the accepted criteria for dysplasia were classified as ACF with atypia and those with alterations that were more severe and met the previously defined criteria for dysplasia were classified as ACF with dysplasia.**

Formalin fixed paraffin embedded sections of serrated adenomas (n=20) were provided from the archives of University Hospital Birmingham and St Marks Hospital, London, UK. Section of formalin fixed normal human skin and colon were used as positive and negative tissue controls for immunohistochemistry, immunofluorescence, and mRNA in situ hybridisation.

Frozen normal colon and adenomatous polytissue stored at −80°C, was gained from the Department of Surgery tissue bank, Birmingham University, UK. These samples were derived from patients undergoing endoscopic bowel examination at University Hospital, Birmingham, UK.

HT 29 colorectal cancer cells were purchased from American Type Culture Collection (Manassas, USA) and maintained in Dulbecco’s Modified Eagle’s medium with 10% fetal calf serum (Life Technologies, Paisley, UK) in a 5% CO2 humidified atmosphere at 37°C. These cells were used as positive cell controls for western blotting and co-immunoprecipitation experiments.

Immunohistochemistry
The streptavidin-biotin indirect immunoperoxidase method was used for immunohistochemistry. Sections (5 µm) were dewaxed, dehydrated, and endogenous peroxidase activity blocked by incubation in 3% H2O2 in methanol for 15 minutes. Microwave antigen retrieval was undertaken for 2× five minutes in 0.01 M trisodium citrate buffer, pH 6. Non-specific immunoreactivity was blocked with 20% normal goat serum in phosphate buffered saline (PBS), pH 7.3, for 30 minutes, and then sections were incubated overnight with primary antibody. Primary antibodies (P-cadherin (IgG1, clone 56), E-cadherin (IgG2a, clone 36), β-catenin (IgG1, clone 14), and γ-catenin (IgG2a, clone 15) were used at a dilution of 1:300 (Transduction Labs, Lexington, Kentucky, USA). The following isotype matched control antibodies to cytokeratins were used in immunohistochemistry. Monoclonal IgG2a mouse antibody to Cam 5.2 was obtained from Becton Dickinson (Mountain View, California, USA) and used at 8 µg/ml. Monoclonal IgG1 mouse antibody to Ber EP4 was obtained from Dako (Copenhagen, Denmark) and used at 2.5 µg/ml. After washing with PBS, sections were incubated with biotinylated goat antimouse/rabbit IgG (Dako) according to the manufacturer’s instructions for 20 minutes. After washing with PBS, sections were incubated with streptavidin-peroxidase conjugate (Dako) for 20 minutes and washed with PBS. Incubation of sections with diaminobenzidine tetrahydrochloride (Sigma, Poole, UK) at 1 mg/ml plus 1 µl/ml H2O2 was used to develop the peroxidase reaction for 10 minutes. Sections were counterstained with haematoxylin and mounted in deplax (Sigma) after being taken through ethanol and xylene, and analysed on a light microscope.

In addition, absorption experiments to test antibody specificity were performed using cell lysates supplied by the manufacturer. Briefly, antibodies were reacted with a 10-fold excess of cell lysate (~100 µg/ml) on a wheel at 4°C for 16 hours. The resulting solution was then used as per protocol for immunohistochemistry. The subsequent specificity of the antibody was determined by the absence of immunoreactivity on appropriate paraffin sections.

Isotype matched antibody controls employed for P-cadherin, E-cadherin, β-catenin, and γ-catenin demonstrated no difference between normal colon, ACF, hyperplastic, adenomatous, or serrated adenomatous polyps (data not shown).

Absorbance controls demonstrated specificity of antibodies by lack of immunoreactivity in control sections: skin for P-cadherin, and normal colon for E-cadherin, β-catenin, and γ-catenin.

Evaluation of immunohistochemistry
Immunostained material was assessed by light microscopy and scored by three independent observers (RGH, JAZJ, DSAS). The number of positive staining samples was noted, as was the percentage of positive crypts per lesion, subcellular localisation of immunoreactivity, and correlation between positive immunoreactivity and tissue phenotype/morphology. Immunoreactivity was compared with that in control sections of colon and skin which had been screened independently and deemed normal by a pathologist (DSAS). The presence of morphologically normal crypts within each section served as additional internal negative/positive controls depending on the antibody used.

Immunofluorescence
Tissue sections were blocked in 5% normal goat serum in 1% bovine serum albumin in PBS for 20 minutes and reacted with primary antibodies. Antibodies used were mouse anti-P-cadherin and E-cadherin (Transduction) used at 1:300, and rabbit polyclonal anti-β-catenin (Sigma) used at 1:200. Sections were washed with PBS and incubated for one hour with secondary antibody. Texas Red linked antimosue IgG1 and FITC linked antimouse IgG2a (Sigma) were used at a 1:800 dilution, and FITC linked antirabbit IgG (Stratagene, Luton, UK) was used at a dilution of 1:200. Nuclei were stained with 4,6-diamidino-2-phenylindole (DAPI; Sigma) at a concentration of 0.1 µg/ml for one minute. Sections were washed in PBS, allowed to air dry, and mounted in immunofluorescence mounting medium (Sigma). Sections were analysed on an Olympus BX40 fluorescence microscope.

Western blotting
Adenomatous polyp biopsies taken from a ~80°C tissue bank were defrosted on ice. The mucosa was dissected from the adherent connective tissue and cut into two approximately equal parts. One half was homogenised in protein lysis/sample buffer (0.0675 M Tris, pH 6.7, 2% sodium dodecyl sulphate, 5% β-mercaptoethanol, 10% glycerol, 0.001% bromophenol blue) and heated to 100°C for five minutes; the other was homogenised in immunoprecipitation buffer (20 mM Heps, 1% Triton X-100, 150 mM NaCl, 1 mM EDTA, 100 mM NaF). Residual insoluble debris from both aliquots was removed by centrifugation at 13 000 rpm for five minutes. Briefly, protein lysis samples were separated on an 8% sodium dodecyl sulphate-polyacrylamide gel electrophoresis gel and proteins were transferred onto Hybond PVDF nitrocellulose membranes (Amersham, High Wycombe, UK). Membranes were blocked overnight at 4°C in 10% Marvel in Tris buffered saline Tween (TBST), and incubated with the following primary antibodies and antigens at concentrations of 1:100 (P-cadherin rabbit polyclonal; Santa Cruz, Santa Cruz, USA), 1:200 (E-cadherin rabbit polyclonal; Santa Cruz), 1:4000 (β-catenin; Sigma), and
1:200 (cyclin D1, mouse IgG2a, clone DCS-6; Sigma) in TBST for one hour. Blots were washed extensively with TBST and probed with antimouse or rabbit horseradish peroxidase conjugated secondary antibody (Amersham) at a concentration of 1:10 000 for 30 minutes. After extensive washing in TBST, ECL reagent (Amersham) was used according to the manufacturer’s instructions.

Co-immunoprecipitation
Adenoma samples lysed in immunoprecipitation buffer were precleared with 1% w/v protein-A sepharose (Sigma) for 30 minutes at 4°C. Supernatants were then incubated with polypropylene and rabbit horseradish peroxidase conjugated secondary antibody (Amerham) at a concentration of 1:10 000 for 30 minutes. After extensive washing in TBST, ECL reagent (Amersham) was used according to the manufacturer’s instructions.

mRNA in situ hybridisation
Sections (7 μm) were cut from normal colon and skin, and hyperplastic and adenomatous colorectal polyps, and mounted onto silanated slides. A 784 base pair cDNA fragment of P-cadherin was generated by digesting human P-cadherin cloned into the EcoRI site of pBR322 (a gift from S Hirohashi, National Cancer Centre Research Institute, Tokyo, Japan) with BlnI. This cDNA was random prime labelled to a specific activity of approximately 1×10⁶ cpm/μg 35S dCTP using a kit (Promega, Southampton, UK), as previously described. Protein products were resolved by 15% sodium dodecyl sulphate-polyacrylamide gel electrophoresis and bands visualised by autoradiography.

RESULTS
P-cadherin is expressed prior to disturbances in E-cadherin, catenins, or APC—expression in ACF
P-cadherin was expressed in 15/23 (65%) ACF. P-cadherin expression status was similar in ACF with only atypia (9/13 or 69%) versus ACF with dysplasia (6/10 or 60%). Such expression was both membranous and cytoplasmic in subcellular localisation, and was confined to histologically abnormal crypts. Staining was typically of greater intensity in the superficial localisation, and was confined to histologically abnormal crypts. Staining was typically of greater intensity in the superficial localisation, and was confined to histologically abnormal crypts. Staining was typically of greater intensity in the superficial localisation, and was confined to histologically abnormal crypts. Staining was typically of greater intensity in the superficial localisation, and was confined to histologically abnormal crypts. Staining was typically of greater intensity in the superficial localisation, and was confined to histologically abnormal crypts.

Table 1 Pattern of cadherin and catenin expression in aberrant crypt foci with atypia and dysplasia, categorised by P-cadherin expression status

<table>
<thead>
<tr>
<th>Pattern of cadherin and catenin expression</th>
<th>n</th>
<th>E-cadherin membranous</th>
<th>β-Catenin cytoplasmic</th>
<th>γ-Catenin cytoplasmic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACF: atypia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-cadherin+9</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>P-cadherin–9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ACF: dysplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-cadherin+9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>P-cadherin–9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
| P-cadherin expression status was similar in ACF with only atypia (9/13 or 69%) versus ACF with dysplasia (6/10 or 60%). Such expression was both membranous and cytoplasmic in subcellular localisation, and was confined to histologically abnormal crypts. Staining was typically of greater intensity in the superficial localisation, and was confined to histologically abnormal crypts. Staining was typically of greater intensity in the superficial localisation, and was confined to histologically abnormal crypts. Staining was typically of greater intensity in the superficial localisation, and was confined to histologically abnormal crypts. Staining was typically of greater intensity in the superficial localisation, and was confined to histologically abnormal crypts. Staining was typically of greater intensity in the superficial localisation, and was confined to histologically abnormal crypts.
positive and negative samples. γ-Catenin cytoplasmic translocation occurred in one sample, a dysplastic P-cadherin negative ACF. No nuclear γ-catenin was seen in any sample.

ACF with atypia and dysplasia thus showed similar patterns of cadherin and catenin expression (table 1), with an initial disturbance in P-cadherin expression in many cases.

**Universal P-cadherin expression in lesions with hyperplastic morphology**

All hyperplastic polyps (n=20) and serrated adenomas (n=20) showed extensive P-cadherin immunoreactivity in hyperplastic regions of both lesions (fig 2A–C) and dysplastic regions of serrated adenomas, by both immunohistochemistry and immunofluorescence (fig 3A, B). This immunoreactivity was seen to be both membranous and cytoplasmic in nature.

**Figure 2** Cadherin and catenin expression in hyperplastic colonic polyp. (A, B) P-cadherin was extensively expressed along membranes of cells in hyperplastic crypts, as demonstrated by immunohistochemistry (magnification ×60, ×200). (C) Immunofluorescence image using FITC labelled E-cadherin and Texas Red labelled P-cadherin hyperplastic crypt demonstrating (i) membranes staining purely for E-cadherin (green), (ii) membranes where P-cadherin and E-cadherin were colocalised (orange), and (iii) cytoplasmic P-cadherin immunoreactivity (red) (magnification ×200).

**Figure 3** Cadherin and catenin expression in serrated adenomatous colonic polyp. (A) P-cadherin was expressed along membranes and in the cytoplasm of areas displaying serrated architecture (magnification ×100). (B) Magnified (×200) photograph from boxed section of (A) showing membranous and cytoplasmic P-cadherin expression. (C) E-cadherin shows maintained membranous expression in all areas (magnification ×200). (D) β-catenin nuclear immunoreactivity (arrowed) in crypts with serrated architecture (magnification ×100).

**Figure 4** Cadherin and catenin expression in adenomatous colonic polyps and bifurcating gland. (A) E-cadherin showed downregulation at membranes in dysplastic crypts (arrows) (magnification ×100). (B) P-cadherin was expressed along membranes and in the cytoplasm of dysplastic crypts but not in more morphologically normal crypts (centre) (magnification ×100). (C) P-cadherin mRNA (black grains) was seen throughout this dysplastic crypt with some serrated features (magnification ×100). (D) P-cadherin mRNA grains largely absent from RNase treated serial section of a crypt seen in fig 3C (magnification ×100). (E) Immunofluorescence image using FITC labelled E-cadherin and Texas Red labelled P-cadherin dysplastic crypt demonstrating (i) membranes staining purely for E-cadherin (green), (ii) membranes where P-cadherin and E-cadherin are colocalised (orange), and (iii) cytoplasmic P-cadherin immunoreactivity (red) (magnification ×200). (F) Immunofluorescence image using FITC labelled β-catenin, Texas Red labelled P-cadherin, and 4,6-diamidino-2-phenylindole (DAPI) stained nuclei showing colocalised cytoplasmic β-catenin and P-cadherin in a dysplastic area of a crypt (yellow), with nuclear β-catenin reactivity in the same dysplastic areas (arrows) (magnification ×200). (G, H) Bifurcating dysplastic gland showing extensive cytoplasmic and membranous P-cadherin staining (G) (arrows) with coexisting cytoplasmic and nuclear β-catenin localisation (H) (arrows) (both magnification ×100). (I) γ-Catenin was translocated from the membrane to the cytoplasm and nucleus in dysplastic crypts (arrows) (magnification ×100).
P-cadherin expression in the colon

Table 2 Pattern of cadherin and catenin expression in tubular and tubulovillous adenomas, categorised by P-cadherin expression status

<table>
<thead>
<tr>
<th>Adenomas</th>
<th>E-cadherin membranous (reduced)</th>
<th>β-catenin cytoplasmic/nuclear</th>
<th>γ-catenin cytoplasmic/nuclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular adenomas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-cadherin+</td>
<td>9</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>P-cadherin−</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Tubulovillous adenomas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-cadherin+</td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>P-cadherin−</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

adenomas (fig 4I) but γ-catenin translocation from the membrane was present only in P-cadherin positive tubulovillous adenomas (n=8). As with β-catenin, γ-catenin translocation was seen in both P-cadherin positive and negative crypts. No nuclear γ-catenin localisation was seen in bifurcating glands.

Table 2 summarises expression patterns of cadherins and catenins in adenomas.

**P-cadherin is functional as regards catenin binding, and its expression is independent of APC mutation in adenomas**

To assess whether P-cadherin was functional with regard to catenin binding, we examined whether aberrantly expressed P-cadherin formed complexes with β-catenin in adenomas by co-immunoprecipitation. In all instances where β-catenin was efficiently immunoprecipitated from adenomas, both P-cadherin and E-cadherin co-immunoprecipitated (fig 6), demonstrating that β-catenin binds to both P-cadherin and E-cadherin in these adenomas. Absence of bands on probing with anti-cyclin D1 (which does not bind cadherins or catenins) confirmed the absence of non-specific binding (data not shown).

Data obtained in hyperplastic polyps suggest that P-cadherin expression is independent of APC status. To test this hypothesis, PTT analysis of APC was carried out in four adenomas shown to express P-cadherin immunohistochemically. Of the four adenomas analysed, three showed a

---

**E-cadherin (fig 3C), β-catenin, and γ-catenin maintained their normal basolateral membranous localisation in all samples except for one serrated adenoma which demonstrated nuclear β-catenin (fig 3D).**

Hyperplastic polyps and serrated adenomas defined by hyperplastic morphology therefore demonstrated analogous patterns of cadherin and catenin expression.

**Expression of P-cadherin is independent of E-cadherin and catenin expression and localisation in adenomatous polyps**

Our analysis of adenomatous polyps (n=22) demonstrated decreased membranous E-cadherin (fig 4A) and β-catenin expression, with an increase in cytoplasmic/nuclear β-catenin expression, localised to dysplastic areas.

Immunohistochemical and immunofluorescence data demonstrated P-cadherin expression in crypts with both mildly, moderately, and severely dysplastic phenotypes in 18/22 (82%) adenomas. The percentage of crypts demonstrating P-cadherin immunoreactivity varied from 25% to 100% among adenomas, with no trends on comparing tubular and tubulovillous examples, or polyp site or size. As with hyperplastic polyps, this expression was both cytoplasmic and membranous in nature (fig 4B). In situ hybridisation demonstrated P-cadherin mRNA in dysplastic crypts (fig 4C) but not in RNase treated negative control serial sections (fig 4D). P-cadherin expression did not correlate with position along the crypt axis. No obvious phenotype characterised adenomas that did not express P-cadherin.

In many dysplastic crypts, P-cadherin was coexpressed with E-cadherin but in some dysplastic crypts only P-cadherin or E-cadherin was expressed (fig 4E). In a few severely dysplastic crypts, there was generally a lack of either P-cadherin or E-cadherin expression.

To support the immunohistochemistry and immunofluorescence data, western blots of adenoma and normal colon samples were run. Bands corresponding to P-cadherin (120 kDa) and E-cadherin (120 kDa) were demonstrated in adenomas but only E-cadherin was present in normal colon (fig 5).

In all adenomas analysed, β-catenin was translocated from the membrane to the cytoplasm/nucleus in most dysplastic crypts (fig 4F). This translocation occurred in both P-cadherin positive and negative crypts. P-cadherin expression and β-catenin cytoplasmic/nuclear localisation were also seen in all glands undergoing bifurcation (n=5) (fig 4G, H).

Cytoplasmic and nuclear translocation of γ-catenin was identified in both P-cadherin positive and negative tubular

---

**Figure 5 Western blot of HT 29 colorectal cell line (positive control), human normal colon, and colorectal adenomas for (A) P-cadherin (120 kDa) and (B) E-cadherin (120 kDa). E-cadherin was expressed in normal colon whereas P-cadherin was not. Both P-cadherin and E-cadherin were expressed in all adenomas analysed.**

**Figure 6 Western blot of HT 29 colorectal cell line (positive control) and colonic adenomas for (A) β-catenin (92 kDa), (B) P-cadherin (120 kDa), and (C) E-cadherin (120 kDa). β-catenin primary immunoprecipitation with subsequent immunoblotting for β-catenin, P-cadherin, and E-cadherin. Both P-cadherin and E-cadherin co-immunoprecipitated with β-catenin in the adenomas analysed.**

---

www.gutjnl.com
Most adenomatous colonic polyps studied displayed a very high incidence of aberrant P-cadherin expression. A small number of adenomas did not express P-cadherin however. Possible explanations for this include: (i) P-cadherin expression occurred during evolution of the adenoma but this expression was transient and had been lost when the polyp was biopsied. (ii) Other proteins involved in stratified epithelial formation can substitute for P-cadherin in polyp formation. (iii) P-cadherin is a more labile antigen than the other cadherins and catenins that were expressed in these lesions.

Our novel demonstration of γ-catenin nuclear translocation in adenomas raises the question of whether γ-catenin is leading to targeted gene transcription in these lesions. Previous reports support a role for γ-catenin in oncogenesis. The transcription targets of γ-catenin are uncertain, and it is unclear therefore whether γ-catenin is involved in adenoma growth in the manner that β-catenin appears to be.

In conclusion, we have demonstrated aberrant P-cadherin expression from the earliest stage of abnormal crypt morphology, before alteration in E-cadherin, catenins, and APC occur, with persistence throughout polyp development. P-cadherin expression appears to be independent of expression of associated cadherins, catenins, and APC, and is unable to determine tissue morphology alone. Subsequent challenges will be to dissect the molecular mechanisms leading to aberrant P-cadherin expression and to elicit their downstream effects. In this manner manipulation of such molecules may become possible, leading to the prospect of therapies designed to reverse or prevent colorectal polyp development and progression.

ACKNOWLEDGEMENTS

This work was funded by a Research Training Fellowship from the Wellcome Trust to Robert Hardy, and in part by a Public Health Service grant CA66725 from the National Cancer Institute to Theresa Pretlow.

REFERENCES

P-cadherin expression in the colon

Aberrant P-cadherin expression is an early event in hyperplastic and dysplastic transformation in the colon

R G Hardy, C Tselepis, J Hoyland, Y Wallis, T P Pretlow, I Talbot, D S A Sanders, G Matthews, D Morton and J A Z Jankowski

Gut 2002 50: 513-519
doi: 10.1136/gut.50.4.513

Updated information and services can be found at:
http://gut.bmj.com/content/50/4/513

These include:

References
This article cites 38 articles, 21 of which you can access for free at:
http://gut.bmj.com/content/50/4/513#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Colon cancer (1547)
- Cancer: small intestine (189)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/