

Supplementary Figure 1. Laser-capture microdissection of SRCs from an eHDGC. Four μm paraffin sections on untreated slides were deparaffinized, rehydrated with ethanol, stained with 0.1% crystal violet acetate (Sigma-Aldrich, St Louis, Missouri), dehydrated and left in Xylene. Individual SRCs were dissected from dried sections with an Arcturus LM200 laser-capture facility (Molecular Devices, Sunnyvale CA) at 7.5 μm spot size, 90 mW power and 800 μs duration, captured using CapSure Macro LCM caps (Molecular Devices), and immediately emerged in lysis buffer. The figure shows an example of SRCs before (left) and after (right) dissection. The section was stained with Periodic Acid Schiff solution instead of crystal violet for better visualization of SRCs.

Supplementary Figure 2. Histopathology of SRCCs in MNU-treated *cdh1^{+/-}* mice. *A*, Gastric antral murine intramucosal SRCC (left two panels). The magnified panel shows the typical cellular composition of murine SRCC, with typical signet-ring cell morphology dominating the luminal part and less differentiated cancer cells deeper in the mucosa. For comparison, a human intramucosal SRCC from a *CDH1* mutation carrier (eHDGC) is shown in the right two panels. *B*, a large murine SRCC with macroscopic sessile polyp appearance in the distal gastric antrum. Magnifications to the right show SRCs with cytoplasmic mucin, and also SRCs with intracytoplasmic lumens. *C*, mucin stain (Alcian Blue and Periodic Acid Schiff) of a murine SRCC, TNM stage T2 (muscularis propria invasion). Magnifications show intramucosal SRCs with intracytoplasmic mucin and intracytoplasmic lumens(1,2) and invasive carcinoma in the muscularis propria (3). The HE stain (4) shows the poorly differentiated morphology of invading cancer cells (here at the muscularis mucosae layer). The corresponding macroscopic appearance (circle) of the murine T2 SRCC in the glandular stomach is shown in the lower right panel. *D*, tubular adenomas were induced by MNU in both *cdh1^{+/-}* and wt mice. A large tubular adenoma (left panel), and magnified views (middle and right) showing crowded neoplastic glands between non-neoplastic pits and glands. Neoplastic glands have a high nuclear to cytoplasmic ratio and mucin depletion compared to the adjacent non-neoplastic glands.

The lower middle panel shows the corresponding mucin stain (Alcian Blue and Periodic Acid Schiff), demonstrating mucin depletion in the dysplastic glands and retention of apical cytoplasmic mucin in the non-neoplastic glands. *E*, a small tubular adenoma composed of mucin-depleted, crowded glands surrounded by non-neoplastic glands. The magnification (lower panel) shows nuclear enlargement, overlapping, and chromatin irregularity.

Supplementary Figure 3. Histopathology of tubular adenomas in MNU-treated *cdh1^{+/-}* mice. *A*, tubular adenomas were induced by MNU in both *cdh1^{+/-}* and wt mice. A large tubular adenoma (left panel), and magnified views (middle and right) showing crowded neoplastic glands between non-neoplastic pits and glands. Neoplastic glands have a high nuclear to cytoplasmic ratio and mucin depletion compared to the adjacent non-neoplastic glands. The lower middle panel shows the corresponding mucin stain (Alcian Blue and Periodic Acid Schiff), demonstrating mucin depletion in the dysplastic glands and retention of apical cytoplasmic mucin in the non-neoplastic glands. *B*, a small tubular adenoma composed of mucin-depleted, crowded glands surrounded by non-neoplastic glands. The magnification (lower panel) shows nuclear enlargement, overlapping, and chromatin irregularity.

Supplementary Figure 4. The apparent cellular origin of murine SRCCs. Samples were stained with an antibody against Mucin 6 (NCL-MUC-6, 1:10, Novocastra, Bucks, UK), a specific marker of mucous neck cells. A GS-II stain is shown below for comparison. Note the expression in the neck region of normal gastric epithelium and in adjacent cancer cells.

Supplementary Figure 5. Normal E-cadherin expression in tubular adenomas. Reduced E-cadherin expression is specific to murine SRCCs (left) and not observed in tubular adenomas (right). The right panel shows the same area as the β -catenin stain in Figure 4B.