

Adenoma-Carcinoma Sequence

Colorectal Pathology Masterclass
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Introduction

- Gastrointestinal tract has a rapid epithelial cell turnover that continues throughout life.
- Intestinal cells are exposed to a hostile environment (toxins and carcinogens contained in digested food).
- Gastrointestinal epithelium has become an important tissue in cancer biology.

Background

- Colonic polyposis syndromes first recognized 200 years ago
- Work on the familial colonic cancer syndromes, including FAP, has led to a number of advances in the understanding of intestinal tumour initiation
- Recognition that many colonic adenomas progress to adenocarcinomas (Morson 1974)
- Adenoma–carcinoma sequence has become established as a stepwise pattern of mutational activation of oncogenes and inactivation of tumour suppressor genes that result in cancer (Vogelstein *et al.* 1988)

Clinical Evidence

- Parallel prevalence of adenomas and carcinomas exists,
- Average age of patients with adenomas being 7 to 8 years younger than that of pts with carcinomas,
- Benign adenomatous tissue found contiguous with resected carcinomas,
- Carinomas in pts with FAP and HNPCC are preceded by adenomas that have the same general histology as found in isolated sporadic carcinomas,

Clinical Evidence (*cont*)

- Anatomic distribution of adenomas and carcinomas is virtually identical,
- Synchronous adenomas are found in 30% of pts who have colorectal cancer,
- Following curative resection of cancer, metachronous adenomas develop in 30%,
- Adenomas >1cm exhibit signs of villous transformation, high-grade dysplasia, multiple acquired genetic alterations and invasive carcinoma.

Adenoma-Carcinoma Sequence

Transition from normal epithelium to adenoma and carcinoma is associated with acquired molecular events, including;

- loss of methyl groups in DNA,
- activated oncogenes, such as K-ras,
- mutation and inactivation of p53 gene.

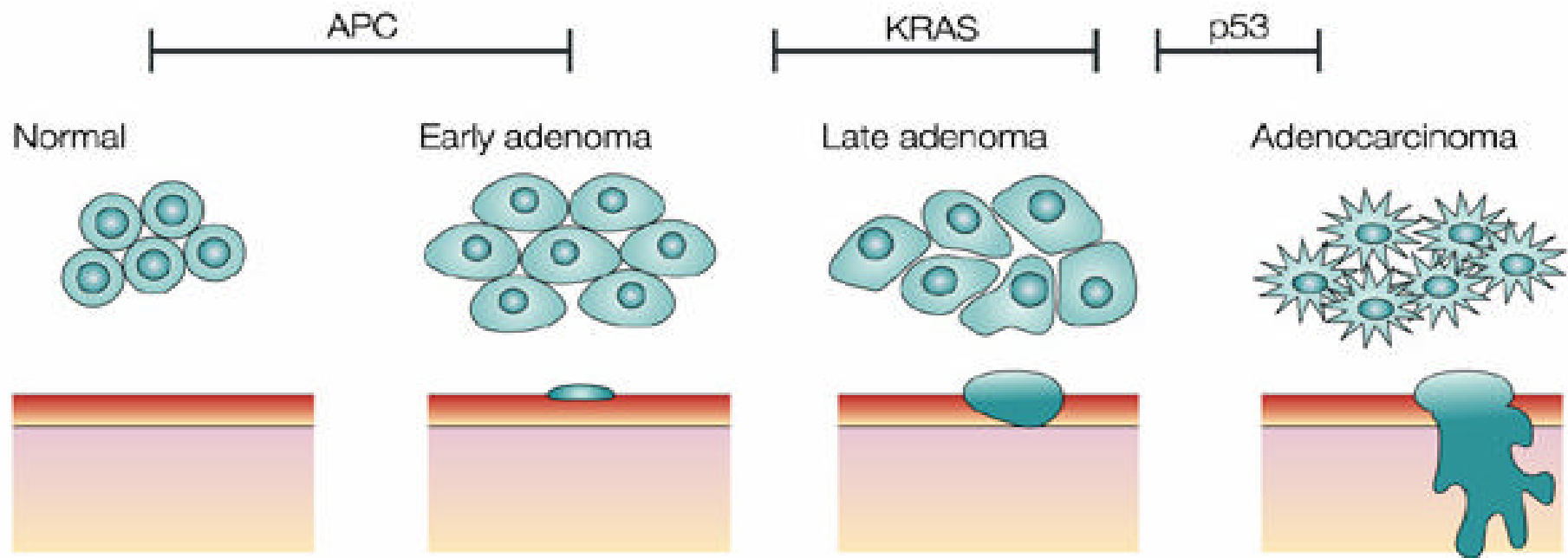


Figure 1

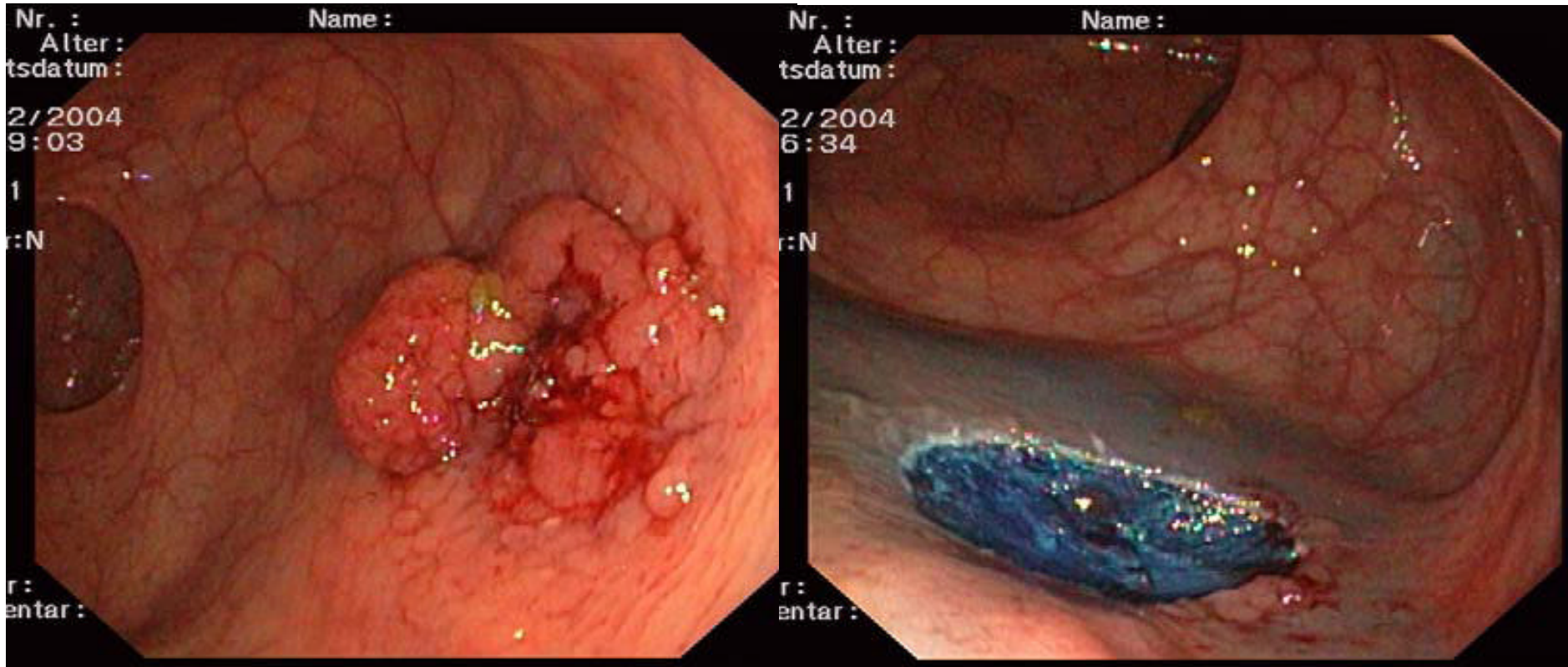


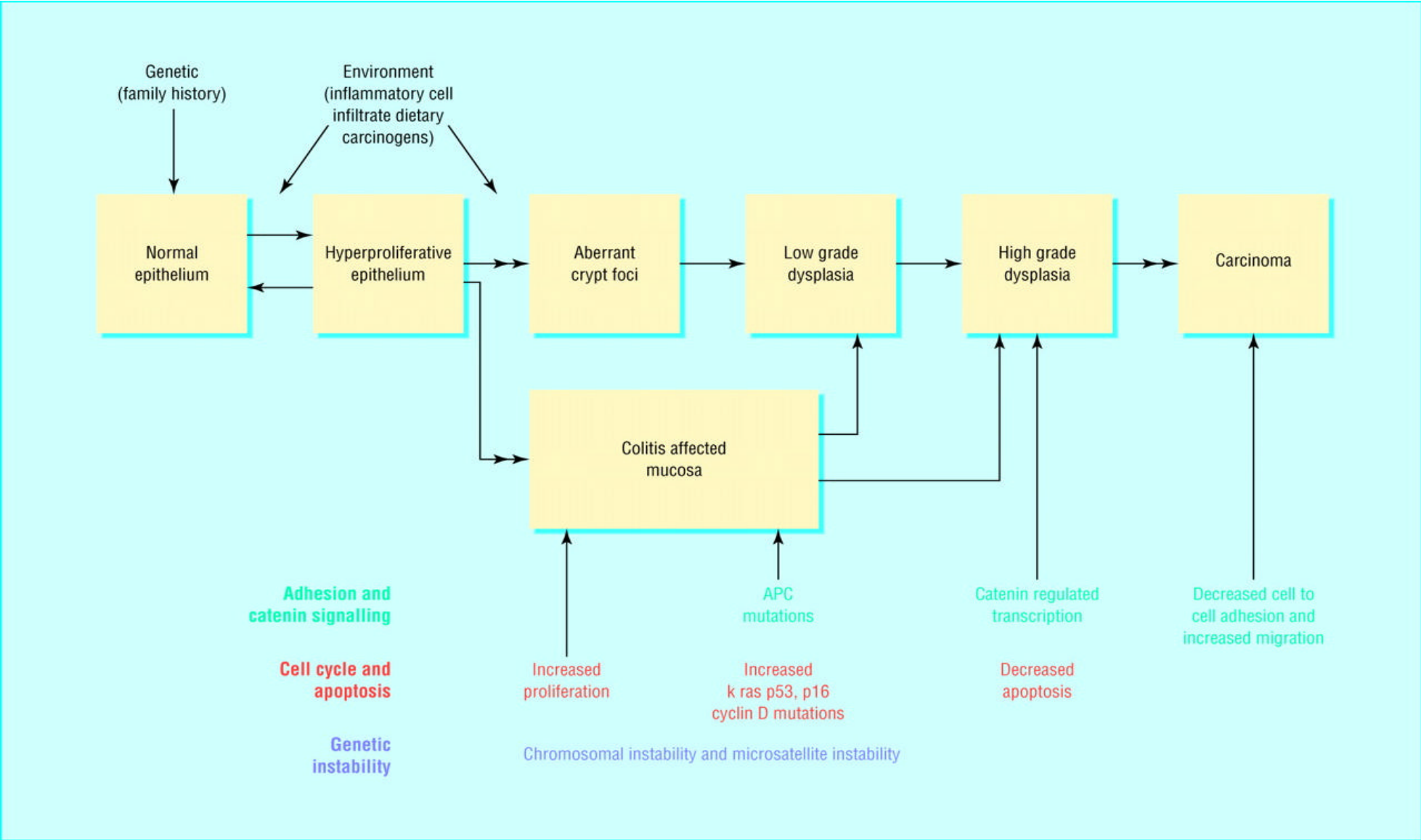
Figure 2: Colorectal polyp and its resection

Colon cancer arises from benign polyps (left) and progress to cancer unless resected (right).

- This tumor progression model deduced from comparison of genetic alterations seen in normal colonic epithelium, adenomas of progressively larger size, and malignancies
- At least 5 to 7 major molecular alterations may occur when a normal epithelial cell progresses to carcinoma.

Aberrant crypt foci

- Earliest lesions in the development of adenomas are dysplastic aberrant crypt foci.
- The morphogenesis of adenomas is controversial with "top-down" and "bottom up" mechanisms proposed in the literature.
- Strong evidence that both top-down morphogenesis and bottom-up histogenesis occur during adenoma development, and the mechanisms are not mutually exclusive.



Top-down Morphogenesis

- Epithelium composed of genetically altered cells located in the superficial portions of the mucosa,
- abnormal cells spreads laterally and downward to form new crypts,
- these connect to pre-existing crypts and eventually replace them.

Bottom-up Histogenesis

- transformation takes place among the stem cell population at the crypt base,
- transformed stem cell replicated,
- monoclonal conversion produces the monocryptal adenoma,
- which expands early by crypt fission and later by overgrowing adjacent crypts.

Molecular Pathways

At least 2 major pathways by which these molecular events can lead to colorectal cancer.

- Chromosomal instability (85%),
- Microsatellite instability (replication error) (15%).

Chromosomal Instability

Key changes include:

- widespread alterations in chromosome number (aneuploidy),
- detectable losses at the molecular level of portions of chromosome 5q, chromosome 18q, and chromosome 17p;
- mutation of the K-ras oncogene.

Chromosomal Instability (*cont*)

- Among the earliest events is deletions of the APC gene, this is a consistent finding.
- Not every tumour acquires every mutation.
- Order in which mutations are acquired is not consistent.

Chromosomal Instability (*cont*)

- Type of mutations may influence the rate of tumour growth or type of pathologic change,
- Rate of adenoma to carcinoma progression appears to be faster in microsatellite unstable tumours ,
- Mucin production characteristic.

Microsatellite Instability

Key characteristics:

- largely intact chromosome complement,
- acquisition of defects in DNA repair,
- mutations that may occur in important oncogenes are allowed to persist.

Microsatellite Instability (*cont*)

At the molecular level:

- numerous nucleotide substitutions and insertion/deletion mutations in repeated nucleotide sequences (microsatellites).
- carcinoma results from inactivation of both alleles of a nucleotide mismatch repair gene, usually hMSH2 or hMLH1.

Microsatellite Instability (*cont*)

- Germline mutation of a mismatch repair gene causes hereditary non-polyposis colorectal cancer syndrome.
- Most sporadic cases result from transcriptional silencing of the hMLH1 mismatch repair gene by promoter methylation.

Microsatellite Instability (*cont*)

Microsatellite instability carcinomas have distinctive clinical-pathologic features;

- right-sided location,
- poor differentiation,
- unusual histologic types (mucinous, medullary and signet-ring cell histology),
- expansile growth pattern,
- numerous tumour-infiltrating lymphocytes,
- prominent peri-tumoural lymphoid nodules, (Crohn's-like lymphoid response).

Role of gastrin

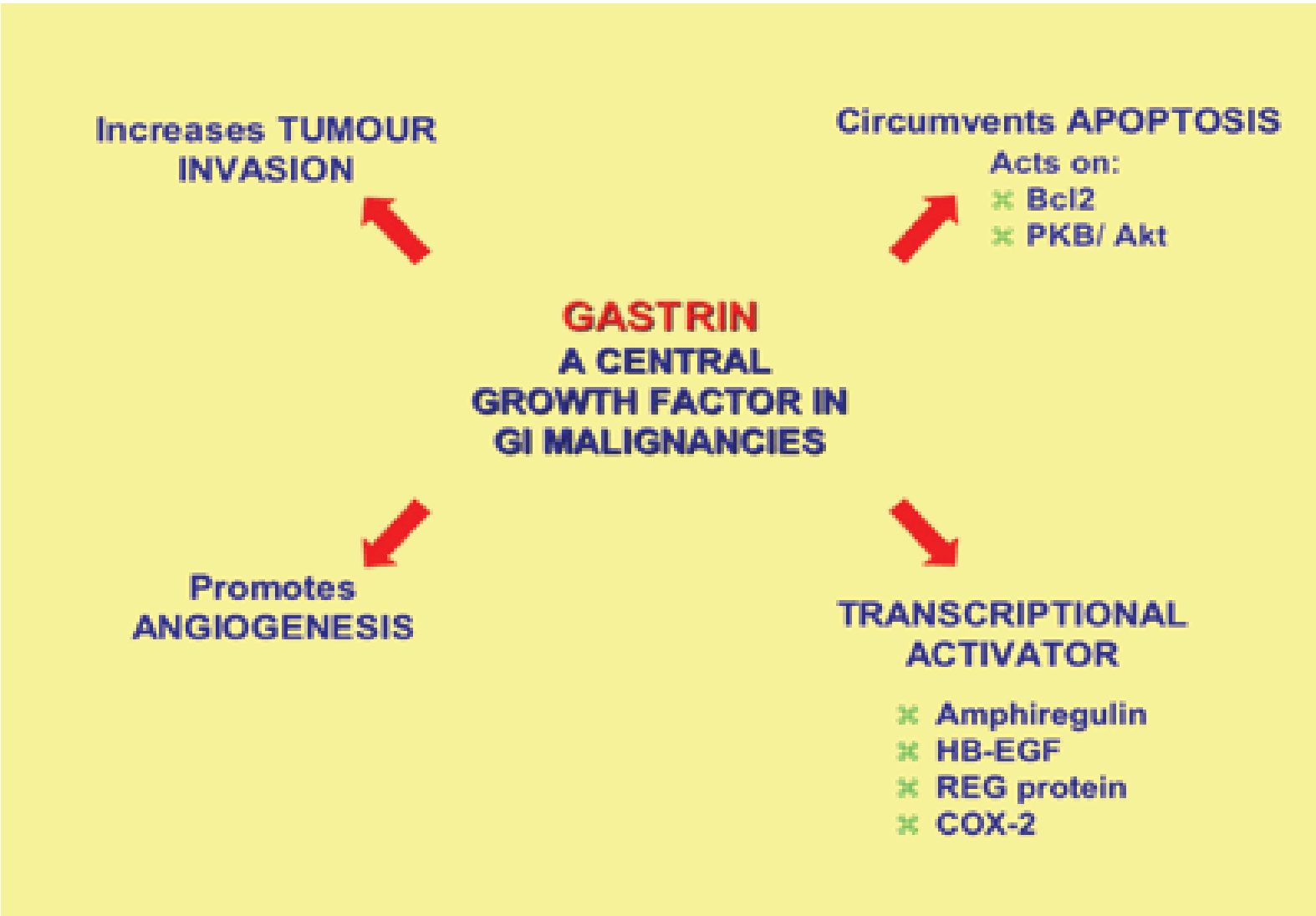
- Gastrin and the gastrin/ cholecystokinin (CCK-2) receptor genes exhibit tightly coordinated expression within the normal gastric mucosa.
- When aberrantly expressed,
 - gastrin gene can impart anti-apoptotic activities,
 - gastrin/ CCK-2 receptor can activate the transcription of a number of factors including ligands of the epidermal growth factor (EGF) receptor and matrix metalloproteinases (MMPs).

Role of gastrin

- However administration of precursor gastrin molecules does not induce tumourigenesis in the in vivo models studied so far,
- A parallel carcinogenic stimulus is required to promote tumourigenesis,

Role of gastrin (*cont*)

- Studies suggest that carcinogen treatment (azoxymethane) results in mutational events which may:
 - induce up-regulation of receptors mediating the effects of precursor gastrin molecules,
 - or result in de novo expression of novel receptor isoforms imparting altered sensitivity to precursor gastrin molecules.
- Gastrin gene expression has been shown to be activated following an APC mutation.



Anti-gastrin antibodies

- Possibility of employing antibodies to neutralize the effects of gastrin in cancer has been evaluated,
- Hormone has multiple ligands acting in a variety of ways as well as multiple isoforms of the CCK-2 receptor,
- Identification of effective antibody difficult.
- The use of immunogens, to produce antibodies to neutralize gastrin species before their interaction with receptors possible solution.

Conclusion

- Progression from normal mucosa to carcinoma known to involved step wise genetic events,
- 2 major pathways involved,
- Gastrin and its receptors may have significant role in adenoma-carcinoma sequence,
- Potential role for anti-gastrin therapy in the future.