An update on the molecular pathology of the intestinal polyposis syndromes

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Abstract

The intestinal polyposis syndromes are characterised by multiple polyps of the large bowel, increased risk of colorectal cancer and a variety of extra-colonic manifestations. Most are caused by high-penetrance germline mutations in genes that affect signalling pathways (Wnt, BMP or mTOR) or the repair of base substitution mutations. However, there are exceptions to these rules: Lynch syndrome usually presents with few polyps; and hyperplastic (serrated) polyposis currently has no known genetic cause. Polyp morphology also varies considerably between, and sometimes within, syndromes. Patients with the same germline mutations can have very different disease severities and features, perhaps as a result of modifying genes or simply chance. Although clinical features and histopathology will continue to have an important role, molecular testing is best placed to classify these diseases and hence inform patient management. As more genes are identified, this classification is likely to improve and enable better individual cancer prevention based on the mutated gene, the specific germline mutation, modifier genes and non-genetic factors.

Keywords colorectal cancer; DNA repair; genetics; polyposis; Wnt and BMP signalling

Introduction

The colorectal polyp is accepted as being the precursor lesion for most cancers of the large intestine. These polyps usually take the form of conventional adenomas or a variety of lesions with serrated morphology, some of which take a sessile form. However, there also exist a small number of rare, inherited conditions in which there is a primary, high-penetrance predisposition to intestinal polyps caused by a single faulty gene. In some of these polyposis syndromes, the primary predisposition is to conventional adenomas and in others it is to serrated lesions, yet in other inherited polyposes, polyps are seen that very rarely have any counterpart in the general population. Furthermore, in most of the polyposis syndromes, polyps are not confined to the large bowel, and there also often exist specific extra-intestinal features that can help in the diagnosis of these conditions. Almost without exception, the risk of colorectal carcinoma is increased in the polyposis syndromes, but the risk of other specific extra-colonic cancers is also raised in most cases, albeit rarely to a lifetime risk as high as that of colorectal cancer.

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In this short review, I shall take a tour through the molecular pathology of the major, known polyposis syndromes (Table 1), focussing on recent new findings.

Familial adenomatous polyposis (FAP)

FAP is caused by germline mutations in the APC gene (chromosome 5p22.1) which encodes a protein with a major isoform of 2843 amino acids. The protein is multi-functional, but its main role seem to be to provide a scaffold for the phosphorylation of the Wnt pathway effector, β-catenin which is subsequently degraded.[1] With very few exceptions, pathogenic *APC* mutations are protein-truncating or -ablating mutations that disrupt the scaffold. The great majority of pathogenic mutations occur before codon 1580, and thereby remove critical "SAMP" repeats that bind β-catenin. Simple base substitution mutations are almost all non-pathogenic, although splice-site mutations can be. Classical FAP is a disease of 100s—1000s of adenomatous polyps throughout the colorectum, although an attenuated disease variant — caused by germline mutations in the ends of the gene or the alternatively spliced exon 9 — also exist and patients develop fewer polyps, typically 10—100. In addition, there exist more subtle associations between polyp burden and *APC* mutation location.[2] As well as colorectal adenomas and CRC, FAP patients are at increased risk of duodenal polyps and carcinoma, gastric polyps, intra-abdominal desmoids and congenital hypertrophy of the retinal pigment epithelium (CHRPE), and also have modestly increased risks of thyroid cancer, hepatoblastoma, adrenocortical carcinoma and brain tumours.

APC is a prototypical tumour suppressor gene and FAP polyps generally start to grow after "second hits" inactivate the wildtype allele,[3] although many FAP polyps are polyclonal, comprising cells with different, independent second hits.[4] The APC mutations are thought to provide a very modest selective advantage to the adenoma cell, but this is sufficient to cause thousands of polyps given the huge number of crypts in the colorectum.[5] Hundreds or more adenomas generally occur in the teens, but few progress to CRC before the age of 30. In most cases, colectomy or more extensive surgery is required to control the disease, but this leaves considerable morbidity and risk of death from duodenal carcinoma or desmoid disease.[6]

Despite the hypothetical constitutive Wnt activation that bi-allelic inactivation of APC causes, the level of β-catenin in FAP polyps is not always obviously raised and the protein is not always present in the nucleus where it can effect transcription.[7] Although the epithelium is *APC*-mutant, it is possible that the wildtype mesenchyme can partly constrain the growth of FAP polyps through production of homoeostatic growth signals, or that the Wnt increase potentially delivered by *APC* mutation is buffered by cell-intrinsic mechanisms. Nonetheless, when CRCs occur in FAP, they have generally followed a classical pathway in which *APC* mutations are followed by mutations in genes such as *KRAS*, *SMAD4* and *TP53*, probably accompanied by a grossly abnormal chromosome complement (CIN).

The major remaining scientific and clinical challenges in FAP include gaining a full understanding of how *APC* mutations cause tumours, especially whether functional consequences other than Wnt activation are important, and developing effective therapies against desmoids, which are benign, yet very

A summary of the colorectal polyposis syndromes

Condition	Gene	Colonic features	Extra-colonic features	Polyp morphology	Mechanism
Familial adenomatous polyposis (FAP)	APC	Multiple polyps, carcinoma	Duodenal polyps and cancer, gastric polyps, intra-abdominal desmoids, Gardners', CHRPE, thyroid cancer, hepatoblastoma	Classical adenoma	Wnt activation
MUYTH-associated polyposis (MAP)	MUYTH	Multiple polyps, carcinoma	Duodenal polyps and cancer, gastric polyps	Classical adenoma Possibly serrated polyps	Defective base excision repair
Polymerase proofreading-associated polyposis (PPAP)	POLE POLD1	Multiple polyps, carcinoma	Duodenal polyps and cancer, endometrial cancer, possibly other cancers	Classical adenoma	Defective polymerase proofreading repair
Juvenile polyposis (JPS)	SMAD4 BMPR1A	Multiple polyps, carcinoma	Duodenal polyps, gastric polyps. AV malformations with SMAD4 mutations	Juvenile-type (smooth, lobulated, cystic)	BMP inhibition
Hereditary Mixed Polyposis (HMPS)	GREM1	Multiple polyps, carcinoma	None known	Several different types and mixed morphology Hyperplastic polyps and serrated adenomas predominate	BMP inhibition
Cowden syndrome (CS)	PTEN	Multiple polyps Carcinoma risk unclear	Many	Hamartomas, juvenile-like	AKT activation
Peutz–Jeghers syndrome (PJS)	LKB1 (STK11)	Multiple polyps, carcinoma	Polyps elsewhere in gastrointestinal tract Risk of several other cancer types "Freckling" of lips, buccal mucosa and other skin sites	PJS-type (arborizing, smooth muscle core)	mTOR activation
Hyperplastic polyposis (HPPS)	Not known	Multiple polyps, carcinoma	None known	Hyperplastic polyps (often large, proximal colon), serrated and conventional adenomas	Not known
Multiple adenomas (MAs)	Not known Polygenic in some cases	Multiple polyps, carcinoma	None known	Classical adenomas, sometimes with serrated lesions	Not known

Table 1

difficult to eradicate with surgery, and the cause of very dangerous side-effects owing to their size and effects on nearby organs.

DNA repair deficiencies: Lynch syndrome, polymerase proofreading-associated polyposis and MUTYH-associated polyposis

These conditions have related causes in a compromised ability to repair mispaired bases or small insertion-deletion mutations, often arising from DNA replication errors. Lynch syndrome (LS) results from defective DNA mismatch repair (MMR). A germline MMR mutation in *MSH2* (chromosome 2p21, including deletions overlapping with the *EPCAM* gene), *MLH1* (chromosome 3p21.3), *MSH6* (chromosome 2p16.3) or *PMS2* (chromosome 7p22.1) causes MMR inactivation once a second hit occurs. LS is typified by CRC, endometrial cancer and lower, risks of other cancers (gastric, ovarian, skin (Muir–Torre syndrome), small bowel, uroepithelial, and others),[8] but usually there is no true polyposis; however, a few LS patients do develop multiple serrated polyps or adenomas,[9] for reasons that are not well understood, but may include the action of modifying genes. MMR acts after normal DNA replication to "mop up" spontaneous mutations that have eluded other repair mechanisms after a cell replicates its DNA. It is relatively more effective against small insertions or deletions, and here its loss causes the phenomenon of "microsatellite instability" (MSI) in short repeat tracts. It has been shown that the colons of LS patients contain multiple crypts that have lost MMR after second hits, but – in contrast to FAP – these crypts do not generally turn into a tumour and LS cases overall have a very modest excess of polyps.[10] However, when tumorigenesis does occur, it appears to be very rapid in LS, with endoscopically-visible lesions having a short life before progression, again in contrast to FAP.