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Unpacking The Essentials Of Genetic Basis Of Colorectal Cancer. A Bird's Eye View For The Trainee.

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ORIGINAL

Abstract

Background: Ever since Bert Vogelstein's landmark paper on "clonal analysis of human colorectal tumours", a seismic body of information has been added for anyone searching for the basics to grapple with. Colorectal cancer management now incorporates molecular studies to determine responses to treatment, prognostication, and identification of hereditary cancers and institute effective surveillance programs. This review aims to answer a few basic questions (1) are there pathways in addition to the adenoma-carcinoma sequence? (2) what are the genetic mechanisms underlying the morphological pathways? (3) how do the classical inherited CRC syndromes fit into the above pathways? And (4) what are the benefits of understanding the molecular basis of colorectal cancers? The two main theories regarding the morphological origins of colorectal cancer are the adenoma-carcinoma sequence and the De-novo origins. The underlying genetic models are the (i) chromosomal instability pathway (CIN), (ii) the microsatellite instability pathway (MSI), and (iii) the CpG Island methylator phenotype (CIMP) pathways. Though unique, the pathways communicate with each other. Hereditary Non-Polyposis Colic (HNPCC) and Familial Adenomatous Polyposis (FAP) the two commonest inherited cancer syndromes show differences in their genetic makeup and behaviour but share the adenoma-carcinoma pathway.

Conclusion: We have moved a long way to improve management by administering tailored treatment based on the genetic profile of colorectal cancer. Therefore, understanding the genetic basis and the main pathways are essential for those in gastrointestinal subspecialties. The review has been made especially with the trainee gastrointestinal surgeon in mind to reiterate the basics.

Introduction

Colorectal cancer (CRC) is the third commonest cancer in the UK. Over 40,000 cases are diagnosed in the UK every year, with a lifetime risk of about 5% in females and 7% in males. As per an update in June 2019 by Bowel Cancer UK, over 90% of these are seen in people over 50 years of age, with 60% of those seen in over 70's. (1). Sporadic CRCs account for 70%, whilst only 5-7% is due to highly penetrant hereditary cancer syndromes. Rest 20 – 30% have some hereditary predisposition (familial). Through complex interactions at genetic and epigenetic levels, CRC presents as a heterogenous disease at the molecular level. (2) The adenoma-carcinoma sequence was the first hypothesis proposed, and to date, there are several epidemiological, pathological, and genetic evidence (albeit indirect) to support this theory. It highlights the gradual development of carcinoma from aberrant crypt focus (ACF) in colonic crypt epithelium through the stages of benign adenoma, dysplasia, carcinoma in situ, and invasive cancer. In a typical adenoma-carcinoma sequence, this transformation is thought to be triggered by the APC (Adenomatous Polyposis Coli)

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gene. (3; 4) Over the last two decades, more information has been made available that influences the prevention, surveillance, and tailored targeted therapy of CRC.

Theories of morphological origins of colorectal cancer. Adenoma Carcinoma sequence and what else?

In adenoma carcinoma sequence, mutation of adenomatous polyposis coli (APC) gene is attributed to be the first step in the oncogenic pathway. About 80% of colorectal adenomas and colorectal cancers carry the mutated APC gene. The adenoma grows, protrudes into the lumen and becomes ulcerated, befitting the description "the mountain route". (5) Familial adenomatous polyposis (FAP) and a majority of sporadic colorectal cancers follow the adenoma- carcinoma sequence which is the prototype of CRC pathogenesis.

Adenomas and risk of cancer. Adenomas may be classified into diminutive (<5mm), small (6mm-1cm) and large(>1cm), and histologically into tubular, tubulo-villous and villous adenomas. Dwelling time of an adenoma is the time taken for an adenoma to change to invasive cancer and this could depend on the size and histology of the adenoma. A diminutive adenoma would take up to 26 years to become cancerous compared to 5years for a large adenoma. Similarly, a tubular adenoma would take about 26 years to turn malignant whilst a villous adenoma would take only 4 years. (5)

Tubular adenomas comprise 70-80% of the total colorectal adenomas with a less than 5% chance of harbouring an invasive cancer. Tubulo- villous adenomas constitute about 15%, and about 20-25% of them would have invasive cancer. Villous adenomas on the other hand comprise only 5 to 10% of all the adenomas but has a 40% risk of harbouring invasive cancer. Adenomas more than 2cm in size also have a 40% risk of hiding an invasive component. (6)

The De-novo pathway. About a decade after the adenoma- carcinoma was described, Japanese and European studies reported that colorectal cancers could arise from flat, and flat depressed lesions without any adenomatous component. This was also referred to as the "direct route" as opposed to the "mountain route" for adenoma- carcinoma sequence. (5) A large population-based study from France proposed that ulcero-infiltrative colorectal cancers could arise de-novo as they showed no adenomatous elements. Such tumours are relatively less in left colon and rectum (17%), whilst it could account for up to 40% of the tumours in the right colon (7). Japanese researchers put forward the terminology of Non Polypod Growth (NPG)- cancer for those less than 10mm in diameter which showed early submucosal, venous and lymphatic invasion. Such tumours were all in advanced stages and nearly 80% of them showed no adenomatous elements supporting the theory of de-novo carcinogenesis (8).

The three models of the genetic basis of colorectal cancers

Three genetic models have been identified. They are, 1.Chromosomal Instability (CIN) pathway, 2.the Microsatellite Instability (MSI) Pathway, and 3.the CpG Island Methylator phenotype (CIMP) or serrated adenoma pathway (9). Each model has its representative morphological pathway; however, they are not mutually exclusive.

1.The Chromosomal Instability (CIN) pathway underlies the adenoma-carcinoma sequence. The classical example of this pathway to carcinogenesis is Familial Adenomatous Polyposis (FAP). Mutation in Adenomatous Polyposis Coli (APC) gene which is a tumour suppressor located on chromosome 5q21 is the initiating mechanism. APC mutation is found in 80% of FAP adenomas and 65 to 70% of sporadic colorectal cancers. This is followed in sequence by activation of Kirsten Rat Sarcoma Virus (KRAS) proto-oncogene which induces cell proliferation. Wild-type (not harmful) KRAS is a tumour suppressor gene, but once mutated it transforms into an oncogene. 30 to 50% of colorectal cancers harbour KRAS gene. (10) Further deactivation of, TP53 coded on

chromosome 17p13 and Deleted in colorectal cancer (DCC) gene coded on 18q leads to fully invasive cancer (9).

TP53 gene is the master tumour suppressor which checks defective proliferative signals, sequesters damaged DNA, and induces apoptosis of defective cells. Mutated P53, results in the accumulation of defective cell lines. Mutated P53 is found in up to 75% of colorectal cancers and is a major factor inducing changes from adenoma to invasive cancer (9).

Deleted in colorectal cancer gene (DCC) gene is a conditional tumour suppressor found in up to 70% of advanced colorectal cancers. Loss of heterozygosity (LOH); i.e. deletion of one of the alleles of the chromosome on 18q renders it defective (9). The hallmark of the CIN pathway is a progressive loss of chromosomes in regulator genes resulting in increasing genomic instability as opposed to microsatellite instability described below.

2. Microsatellite Instability Pathway (MSI) Pathway Also known as the mutator pathway results from abnormal levels of unstable microsatellite nucleotides in the genome. Microsatellites, also known as short tandem repeats (STR's) are oligonucleotide chains of up to six base pairs that are formed as a part of DNA replication. Due to DNA replication errors, faulty base pairs or deletion of base pairs occur resulting in point mutations or insertion-deletion loops (frame shift mutations). Such defective nucleotides could be present in up to 6% of the total genome. However, they are picked up and rectified by the Mismatch Repair (MMR) proteins coded by the Mismatch Repair (MMR) genes. The MMR genes have been identified on chromosomes 2p and 3p and they are, MLH1 (Mut L Homolog 1), MSH2 (Mut S Homolog 2), MSH6 (Mut S Homolog 6) and an endonuclease enzyme coded by PMS2 on chromosome 7. Defects in any of the above genes cause a defective protein expressed by the respective gene resulting in unchecked accumulation of unstable microsatellites which earns its name MSI pathway (11). The number of unstable microsatellites can be measured using immunohistochemical studies in colorectal cancer specimens. MSI tumours could be classified into high (MSI-H), low (MSI-L), and stable (MSS) if the MSI > 30%, 10 to 29%, or none respectively (12). In short there are two mechanisms of introducing MSI which are (1) mutation and (2) hypermethylation of MMR genes (13)

Hereditary Non-Polyposis Colorectal Cancer (HNPCC) accounts for 3 to 5% of CRC's and is a classic example of the MSI pathway. MSI is seen in 15-20% of sporadic CRC and 90% of HNPCCs. Histology of Colorectal cancers with microsatellite instability shows high lymphocytic infiltration and lymphoid aggregation (Crohn's like), poor differentiation (medullary), and mucinous differentiation on histology (14).

3. CpG island methylator phenotype (CIMP) pathway. Cytosine-phosphate- Guanine bonds reside in CpG islands in the genome. Such islands are seen in up to 50% promoter regions on human chromosomes. Hypermethylation of CpG islands could inactivate Mismatch repair genes, resulting in MSI. It may also cause the silencing of Tumour suppressor genes involved in various other cancers. (15) This hypermethylation-mediated carcinogenesis by CIMP is called the alternate pathway or "serrated pathway" in which sessile serrated adenomas transform into serrated adenocarcinoma. At this point, it should be noted that CIMP is the main promoter of MSI in CRC.(16) Depending on the presence of CIMP cancers could be classified into CIMP high (CIMP1), CIMP low (CIMP2), and CIMP negative. CIMP high tumours tend to have BRAF mutations and poorer prognosis.(16) The most common genetic alterations and their relative presence in colorectal cancer are given in Table 1.

Serrated adenocarcinomas vs conventional adenocarcinomas. Arising from serrated adenomas, serrated carcinomas constitute 7% of all CRC's. Serrated polyps are of mainly four types, hyperplastic polyps (80 to 90%), sessile serrated adenomas (10 to 25%), Traditional serrated adenomas (1 to 2%), and Mixed polyps (up to 4%). Altogether the serrated adenomas constitute 10 to 25% of all colonic polyps. Hyperplastic polyps and Traditional Serrated adenomas are more common in the left colon whilst the sessile serrated polyps are common in the right colon. (17)

Interactions of the different pathways at a molecular level in the pathogenesis of hereditary and sporadic CRC's. Researchers have shown that the CIN and MIS pathway communicate and may coincide in colorectal cancer pathogenesis. (18; 19) It is now understood that APC- beta-catenin

Table 1. Genes and their relative presence in CRC. APC-adenomatous polyposis Coli, DCC-Deleted in colorectal cancer, MMR Mismatch Repair. KRAS and BRAF are the two oncogenes, whilst APC, DCC and P53 are tumour suppressor genes. MMR mismatch repair gene. *Loci of the main genes MLH1, MSH2. (3; 6)

Genes	Gene Lcous	Relative Presence In Colorectal Cancer Specimens
APC	5q22	30% to 80% of sporadic and 75% of FAP's
DCC	18q21	70% of all CRC's
MMR	2p21, 3p21-23 *	15% to 20% sporadic and 95% of HNPCC's
P53	17p13	50% to 75% of all CRC's
KRAS	12p12	35% to 50% of all CRC's
BRAF	7q34	10% of all sporadic CRC's

pathway contributes to carcinogenesis in up to 65% of HNPCCs. (20)The CIMP route accounts for 15% of sporadic colorectal cancers. (21) CIMP is also responsible for MSI sporadic CRC's. HNPCC follows the classical adenoma-carcinoma sequence although the underlying genetic abnormality is MSI. The precursor lesion in HNPCC cancers are adenomas with varying amounts of villous elements. In the case of sporadic MSI high CRC's, the precursor lesions are serrated adenomas with high CIMP status. In summary, CIN accounts for about 65 to 75%, CIMP 20 to 30%, and MSI about 5% of CRC's. It should be noted that a major chunk of the MSI-positive cancers (sporadic) is promoted by CIMP route (22; 23). (Figure 1)

Inherited syndromic and familial non-syndromic colorectal cancers. Sporadic colorectal cancers account for up to 70% of all colorectal cancers. Some have a familial tendency (non-syndromic) but may not have the characteristics of inherited cancer syndromes. This could account for about 25% of colorectal cancers. Ture inherited colorectal cancers (syndromic) account for less than 6% of the total. (2) (Figure 2)

Lynch syndrome: it is the most common inherited CRC syndrome. There is a 60-80% lifetime risk of Hereditary nonpolyposis colorectal cancer and a 40-60% chance of endometrial cancer. . HNPCC does not show as many polyps as in FAP, and cancers could arise from polyps and flat lesions in HNPCC. If a CRC or Lynch syndrome-related cancer develops in a young person, it should trigger MSI testing (revised Amsterdam and Bethesda criteria) Screening should start by age of 20 years, and then 1 to 2 yearly. If CRC develops in such individuals, subtotal colectomy with the restoration of intestinal continuity and 2 yearly surveillance is indicated. (14; 24)

Familial Adenomatous Polyposis (FAP). This autosomal dominant condition is caused by germline mutation in APC (Adenomatous Polyposis Coli) gene on 5q21. Up to a thousand polyps develop with a 100% risk of developing CRC by the age of 50. There is a 12% chance of duodenal adenocarcinomas. Attenuated FAP (AFAP) on the other hand is characterized by 30 to 100 polyps, more proximally located, appearing later in life, and has a 70% lifetime risk of CRC. Gardner's syndrome refers to FAP with epidermoid cysts, dental cysts, and desmoid tumours. Surveillance colonoscopy should start from age of 12 years and then 1 to 2 years. If the individual develops >20 adenomas or adenomas >1cm, total proctocolectomy is indicated with Ileal pouch-anal anastomosis. If the rectum is preserved, mucosal stripping is indicated followed by regular pouch surveillance. Upper GI endoscopy using a side viewing endoscope is recommended every 1 to 3 years to look for duodenal and periampullary lesions, starting from 20 to 25 years of age. (25; 26; 27)

Other rare syndromes like MUTYH-associated polyposis (MAP), Peutz- Jeghers, Juvenile polyposis, and Hyperplastic polyposis are given in Table 2.

Hyperplastic Polyposis (HPP). This is a rare condition characterized by multiple or large (>1cm) polyps dispersed anywhere in the colon. WHO guidelines for diagnosis are one of the following: (i) > or = to 20 hyperplastic polyps anywhere in the colon, (ii) > or= to 5 hyperplastic polyps proximal to the sigmoid with at least two of them more than or equal to 10mm, and (iii) any number of

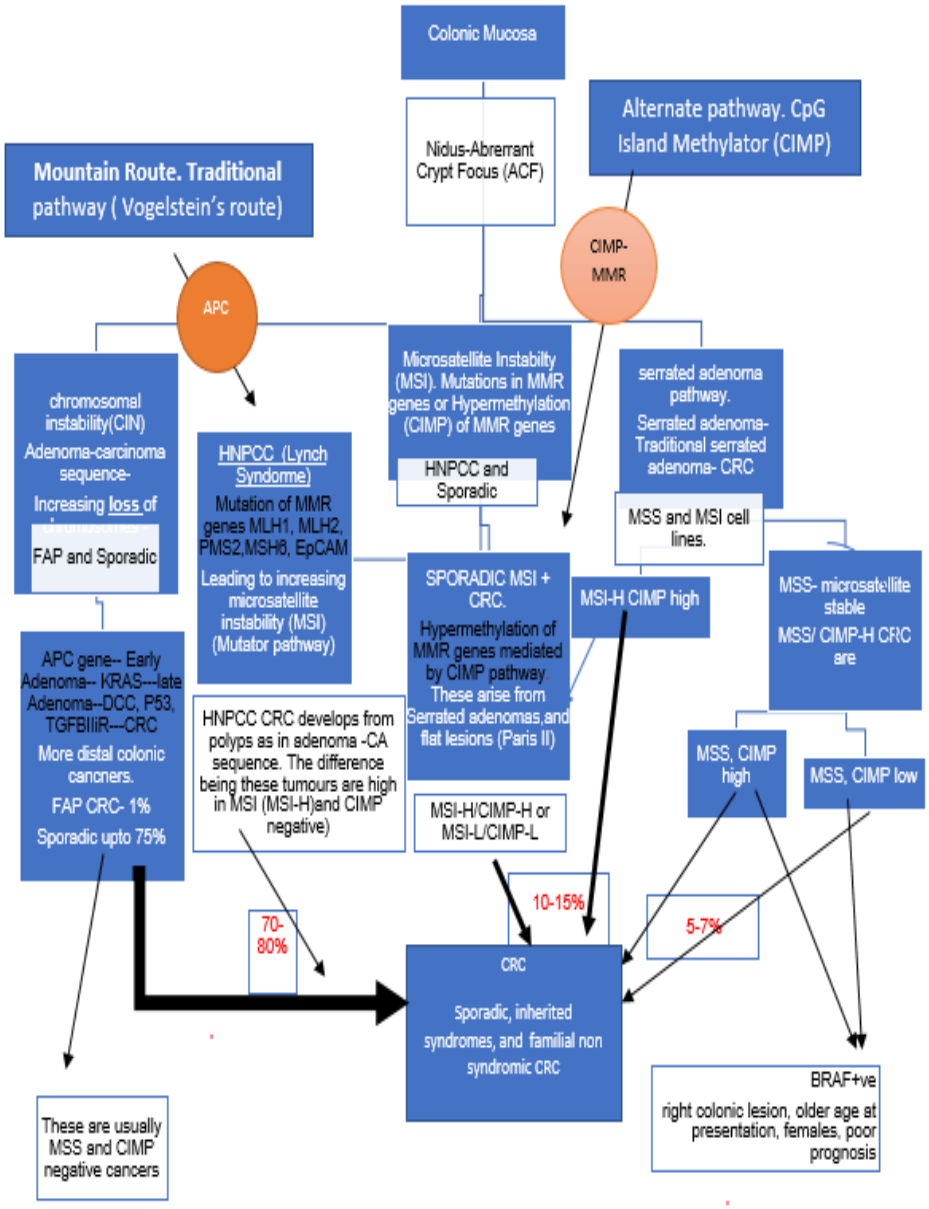

Figure 1. Interaction of the different pathways

Table 2. Inherited Syndromes in colorectal cancer

Syndrome/ main characteristics/ genetic defect	Lifetime Cancer Risk by organ	Other non-malignant features
Lynch syndrome. Non- Polyposis (fewer than FAP) Autosomal dominant MLH1, MSH2, MSH6, PMS2	Colon 50–80% Endometrium 40–60% Stomach 11–19% Ovary 9–12% Hepatobiliary tract 2–7% Upper urinary tract 4–5% Pancreatic 3–4% Small bowel 1–4% CNS (glioblastoma) 1–3%	Keratoacanthomas, sebaceous adenomas
Familial adenomatous polyposis: Autosomal dominant APC gene	Colon 100% Duodenum/periampullary 4–12% Stomach <1% Pancreas 2% Thyroid 1–2% Liver (hepatoblastoma) 1–2% CNS (medulloblastoma) <1%	100's to 1000's of colonic polyps Gastric fundic gland and duodenal adenomatous polyposis CHRPE, epidermoid cysts, osteomas Dental abnormalities Desmoid tumors
Attenuated FAP Autosomal dominant APC gene	Colon 70% Duodenum/periampullary 4–12% Thyroid 1–2%	Up to 100 colonic polyps Upper GI polyposis similar to FAP
MUTYH-associated polyposis: Autosomal recessive MUTYH gene Peutz-Jeghers syndrome: Autosomal dominant STK11 gene	Colon 80% Duodenum 4% Breast 54% Colon 39% Pancreas 11–36% Stomach 29% Ovaryb21% Lung 15% Small bowel 13% Uterine/cervixc 9%	Colonic polyps similar to AFAP Duodenal polyposis Mucocutaneous pigmentation GI hamartomatous (Peutz-Jeghers) polyps
Juvenile polyposis syndrome: Autosomal dominant SMAD4, BMPR1A Hyperplastic polyposis: Inheritance unknown Unknown genetics	Colon (SMAD4)gene 39% Stomach, pancreas, and small bowel 21% Colon > 50%	Features of HHT Congenital defects Hyperplastic polyps, sessile serrated polyps, traditional serrated adenomas and mixed adenomas

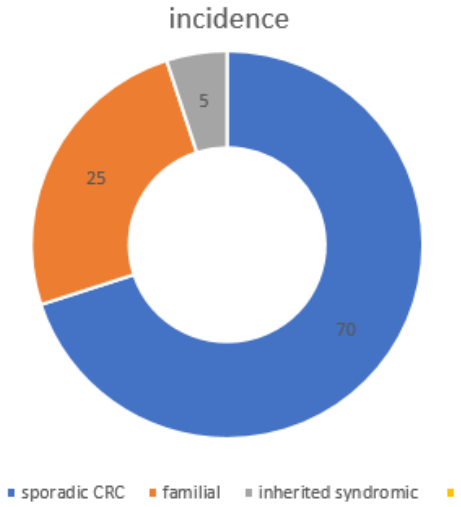

Figure 2. Epidemiology of colorectal cancers

hyperplastic polyps with a first degree relative with HPP. The risk of CRC with HPP is about 40%. (25; 28; 29)

Familial Non-Syndromic colorectal cancer (high risk), type X. About 2% of CRCs, meet the Amsterdam criteria for Lynch syndrome but 40%-70% of them do not show the classical MSI. They show no extracolonic manifestations and the CRC appears a decade later than in Lynch syndrome. This unknown genetic cause is labelled "type X". (25; 30; 31)

Familial colorectal cancer (common risk). This refers to those at higher risk due to, (i) first-degree relatives with CRC diagnosed over 50 years of age conferring a 2 to the 3-fold risk and (ii) those with a first-degree relative who had CRC below 45 years or two first-degree relatives with CRC at any age, conferring 3 to 6 fold risk. (25; 30) The genetic basis of such familial risk CRC could be due to multiple, low-level, less penetrant genetic abnormalities as suggested in genome-wide association studies (32).

RAS oncogenes and their significance. KRAS (Kirsten Rat Sarcoma Virus) is a proto-oncogene causing cell growth. The wild KRAS protein (natural) has intrinsic policing to cause growth phase arrest, and apoptosis. However, when mutated(non-wild), it transforms into an oncogene. (10)

BRAF which is the B homolog of rat sarcoma virus, is part of the mitogen-activated protein kinase pathway, a role it shares with KRAS. About 10% of CRCs show BRAF which signifies poor prognosis and resistance to anti-EGFR treatment (33; 34).

Discussion

Routine MSI/ MMR for CRCs help to identify those with a likelihood of having Lynch syndrome. Universal screening is cost-effective in the prevention of colonic and endometrial cancers in family members (35). BRAF mutation in MSI rules out Lynch syndrome (34). MSI high tumours are usually right-sided and have better prognosis (14).

Up to 50% of CRCs show KRAS mutations (non-wild). Mutant KRAS and BRAF reduce progression-free and overall survival. It also imparts resistance to anti-EGFR therapy with Cetuximab and Panitumumab. Wild KRAS is essential for successful anti-EGFR chemotherapy.(36) Although rare, a combination of BRAF and KRAS adversely affects prognosis and shows a poor response to anti-EGFR therapy (37). Mutated BRAF in MSS CRC is associated with poorer outcomes compared to MSI CRC. Anti-BRAF treatments are undergoing trials along with anti-EGFR therapy in CRC with BRAF mutations. Targeted therapy for pathways leading on from BRAF is also being

trialed. (38)

Circulating tumour DNA (ct DNA) in the blood of CRC patients could guide targeted therapy and response to it. ctDNA following surgical resection indicates a high risk for recurrence and the need for adjuvant treatment. (39) Many more potential biological markers including tumour sidedness of primary tumour, immunocyte infiltration, stromal content, etc are being studied. (38)

Issues with genetic results of unknown significance, and those showing a high penetrance gene without a phenotype pose a clinical dilemma along with carriers of fewer penetrant genes. Hence, pre and post-test counselling is essential.(40)

Conclusion

It is imperative to understand the genetic pathways and their clinical significance. Research in molecular biology and the repertoire of assays and targeted therapies are set to grow. This asks for informed involvement in discussions at CRC multidisciplinary meetings.

Conflict Of Interest

All authors declare no conflict of interest of any kind.

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