REVIEW

The genetics of hereditary colon cancer

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The genetic basis of sporadic colorectal cancer has illuminated our knowledge of human cancer genetics. This has been facilitated and catalyzed by an appreciation and deep understanding of the forms of colorectal cancer that harbor an inherited predisposition, including familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome, the hamartomatous polyposis syndromes, and certain other rare syndromes. Identification of germline mutations in pivotal genes underlying the inherited forms of colorectal cancer has yielded many dividends, including functional dissection of critical molecular pathways that have been revealed to be important in development, cellular homeostasis, and cancer; new approaches in chemoprevention, molecular diagnostics and genetic testing, and therapy; and underscoring genotypic–phenotypic relationships.

Colorectal cancer is a common cancer in the United States and worldwide. There are nearly 150,000 new cases annually in the United States (http://www.cancer.org/docroot/stt/stt_0.asp) and ~900,000 cases worldwide (<http://www.who.int/en>). Colorectal cancer-related mortality comprises nearly 55,000 cases annually in the United States (http://www.cancer.org/docroot/stt/stt_0.asp). The lifetime risk of colorectal cancer in the average-risk person, defined as without personal history or family history of colorectal cancer and above the age of 50, is 5%–6%. This increases anywhere up to 20% when there is involvement of first-degree and/or second-degree relatives with colorectal cancer, and reaches a lifetime risk of 80%–100% in hereditary colorectal cancer syndromes, such as in hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP), respectively.

An explosion of information and insights into the molecular pathogenesis of sporadic colorectal cancer dates back to the late 1980s, and since has served as a paradigm for the investigation of cancer genetics in general, and the emergence of novel diagnostics and therapeutics in cancers as well. Much of this was fueled by the identification, characterization, and elucidation of probands and

families with hereditary forms of colorectal cancer. In parallel fashion, an appreciation of the biological underpinnings of colorectal cancer has been transformed through mouse models and delineation of molecular pathways that were predicated upon how these pathways operate to foster different forms of hereditary colorectal cancer.

In assessing the annual cases of colorectal cancer in the United States, it is clear that a distinction should be made for what is truly hereditary and what is in actuality familial. The former connotes a distinct genetic basis that has been defined, whereas the latter comprises an increased predisposition to cancer but without determination, as of yet, as whether there is a hereditary basis with discovery of pertinent tumor suppressor genes that are inactivated in the germline or whether the predisposition is stochastic. In that context, it is estimated that perhaps 20%–30% of all colorectal cancers have a familial basis. A study of 34 kindreds revealed that there is genetic susceptibility to sporadic colorectal adenomatous polyps and colorectal cancer (Cannon-Albright et al. 1988, 1989). Ongoing efforts should be fruitful in deciphering the potential polygenic basis for familial colorectal cancer. These will be achieved through careful selection of families for genome-wide studies. An example is found in the study of nearly 60 kindreds in which siblings less than age 65 had colorectal cancer but without evidence of hereditary colorectal cancer syndromes. This led to genetic linkage to human chromosome 9q22.2-31.2 (Wiesner et al. 2003).

Hereditary colorectal cancer syndromes, especially with an emphasis on biology and genetics and their relationship to phenotypic manifestations, form the basis for this review (Table 1). Approximately 3%–4% of colorectal cancer cases are attributable to HNPCC or Lynch syndrome, and the slight variation is due likely to geography and ethnicity. Nearly 1% of colorectal cancer cases are due to FAP. Less than 1% of cases are due to a panoply of conditions, namely, *MYH*-associated polyposis (MAP), the hamartomatous polyposis syndromes, and hyperplastic polyposis.

FAP

FAP is an autosomal dominant mode disorder that affects one in 13,000 births (Bisgaard et al. 1994). The most compelling feature is the onset and progression of hun-

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Table 1. *Hereditary gastrointestinal polyposis syndromes*

Familial adenomatous polyposis (FAP) (<i>APC</i>)
Attenuated FAP (<i>APC</i>)
Turcot syndrome (nearly two-thirds with germline <i>APC</i> mutation; one-third with germline <i>MMR</i> mutation)
MYH-associated polyposis (<i>MYH</i>)
Hereditary nonpolyposis colorectal cancer (HNPCC) or
Lynch syndrome (<i>MSH2</i> , <i>MLH1</i> , <i>MSH6</i> , <i>PMS2</i>)
Muir-Torre syndrome
Familial colorectal cancer X (genetic basis unknown)
Hamartomatous polyposis syndromes
Peutz-Jeghers (PJ) syndrome (<i>LKB1</i>)
Familial Juvenile Polyposis (FJP) (<i>SMAD4</i> , <i>BMPR1A</i> , <i>ENG</i>)
Cowden's syndrome (<i>PTEN</i>)
Bannayan-Ruvalcaba-Riley (BRR) syndrome (<i>PTEN</i>)
Gorlin's syndrome (<i>PTCH</i>)
Hereditary mixed polyposis syndrome (genetic basis unknown)
Hyperplastic polyposis syndrome (genetic basis unknown)

dreds to thousands of small adenomatous polyps throughout the colon. Such polyps typically trace their emergence to the second decade of life, but have been noted to occur until age 40. Nevertheless, the inevitable course is the development of colorectal cancer unless this distinctive natural history is interrupted by surgical intervention, typically in the form of total proctocolectomy with ileoanal anastomosis (that is, removal of the colon with anastomosis of the terminal ileum of the small bowel with the anal canal via creation of a J-pouch). Certain situations may mandate a subtotal colectomy with ileorectal anastomosis, but the rectal stump or remnant must be monitored for polyp recurrence. Extraintestinal manifestations include gastric fundic polyps, small bowel (especially duodenal) adenomatous polyps, congenital hypertrophy of the retinal pigment epithelium (CHRPE), supernumerary teeth, osteomas, cutaneous lipomas and cysts, thyroid tumors, desmoid tumors, adrenal cortical adenomas, and hepatoblastomas. While many of these features are benign, FAP patients may develop thyroid cancer, gastric adenocarcinoma (<1% lifetime risk), duodenal adenocarcinoma (5%–10% lifetime risk), and/or ampullary adenocarcinoma. Desmoid tumors, which are benign fibroblastic neoplasms (typically intra-abdominal), present a particularly vexing problem due to their proclivity to occur after colectomy and/or to recur after surgical removal of the desmoid tumor itself.

Cytogenetic analysis associated FAP with an interstitial deletion on human chromosome 5q21 (Herrera et al. 1986), which was further expanded on by independent genetic linkage analyses to 5q21. Positional cloning verified the gene responsible for FAP to be the Adenomatous polyposis coli (*APC*) gene, a landmark effort (Grodin et al. 1991; Kinzler et al. 1991; Nishisho et al. 1991). The *APC* gene contains 15 exons (ORF of 8538 nucleotides) with exon 15 being the largest coding region (6.5 kb). Sundry studies yielded information that germline *APC* mutations were distributed throughout its 15 exons (especially exon 15, however), and the preponderance of

these were nonsense mutations, resulting in a truncated protein with a broad range of molecular masses less than the predicted 310-kDa (2843 amino acids) wild-type *APC* protein. Some of these germline mutations correlated with phenotypic manifestations, such as CHRPE, the severity of polyposis, and an attenuated form of FAP, designated as attenuated *APC* (AAPC) or attenuated FAP (Fig. 1). Alternative splicing of the *APC* gene 5' to exon 1 generates isoforms that may regulate cell growth and differentiation (Carson et al. 2004); additionally, other exon(s) can be alternatively spliced. Attenuated FAP is highlighted by mutations in either the extreme 5' or 3' ends of the *APC* exons (Spirio et al. 1993), and this may influence potentially the stability of the *APC* protein with markedly delayed onset of and a diminished range of clinical manifestations (e.g., fewer colonic adenomatous polyps in patients in their 50s or 60s). An *APC* mutation (T to A at nucleotide 3920 or *APC* I1307K) was found in 6% of Ashkenazi Jews and ~28% of Ashkenazim with a family history of colorectal cancer (Laken et al. 1997). Interestingly, this mutation creates a small hypermutable region, indirectly causing cancer predisposition (Laken et al. 1997; Syngal et al. 2000). However, this mutation has low penetrance in the general population.

In parallel fashion, often at a feverish pace, the biology of the *APC* protein was unraveled. One critical finding related to the premise that nearly 70% of sporadic (average-risk) colorectal adenomatous polyps harbor somatic *APC* mutations (Powell et al. 1992). Domains of the *APC* protein have been dissected and shown to correlate with functional relationships (Fig. 1). The *APC* protein, together with glycogen synthase kinase-3 β , phosphorylates cytoplasmic β -catenin, thereby leading to β -catenin's degradation (Fig. 1; Su et al. 1993; Korinek et al. 1997; Morin et al. 1997). Most of the β -catenin is bound to E-cadherin to facilitate cell-cell contact through the adherens junctions (Gumbiner and McCrea 1993). However, germline or somatic *APC* mutations render cytoplasmic β -catenin stable, resulting in nuclear translocation, where in concert with T-cell factors (TCF), certain target genes are activated transcriptionally. A partial list of the target genes is *c-myc*, *cyclin D1*, *MMP-7*, *Axin2/conductin* (Leung et al. 2002), and *EphB/ephrinB* (Batlle et al. 2002).

Other functions have been ascribed to the *APC* protein, including participation in transcription-independent-mediated apoptosis that involves caspase's cleavage of *APC* itself (Qian et al. 2007). *APC* is involved also in chromosomal segregation. In this context, *APC* localizes to the ends of kinetochores during mitosis and forms a complex with the checkpoint proteins Bub1 and Bub3 (Kaplan et al. 2001). However, *APC* mutations disrupt microtubule binding and kinetochore-microtubule binding. This may help to explain only partially the chromosomal instability with aneuploidy and enhancement of loss of heterozygosity observed in sporadic colon cancers initiated by *APC* mutations (for review, see Nathke 2006) and also the chromosomal and spindle errors noted in embryonic stem cells homozygous for *ApcMin/+* (multiple intestinal neoplasia) or *Apc1638T* alleles

Figure 1. (A) Wnt signaling and regulation of the APC- β -catenin interaction. Modified from Clevers (2006) with permission from Elsevier (©2006), and from Logan and Nusse (2004) with permission from Annual Reviews (©2004). (B) Schematic depiction of the APC protein with key structural domains that involve critical functions. Certain mutations correlate with phenotypic manifestations (attenuated FAP at the extreme 5' and 3' ends of the APC gene; CHRPE with mutations distal to exon 9; severity of FAP between codons 1250 and 1464, which is a common region for APC mutations in sporadic adenomatous polyps and colorectal cancer).

(Fodde et al. 2001). It should be emphasized that the chromosomal instability observed in colon cancers involves also loss of p53 function and telomere dysfunction.

Mouse models that have recapitulated features of FAP have a storied history. Mutagenesis studies revealed that the murine intestinal neoplasia (*Min*) mouse harbors many small intestinal polyps but also large intestinal polyps, although to a smaller extent (Moser et al. 1990). These mice eventually die due to anemia from gastrointestinal (GI) hemorrhage. The gene responsible for this phenotype was identified as the murine homolog of the APC gene (Su et al. 1992). Gene targeting strategies have also led to the widespread use of the *Apc*^{1638N} (Fodde et al. 1994) and *Apc*(Δ 716) (Oshima et al. 1995) knockout mice. The *Apc*^{1638N} mice appear to have a shift of polyps to the colon and certain extraintestinal manifestations that are observed in humans. The *Apc*(Δ 716) mice

have microadenomas preceding mature adenomas in the small intestine. Both mouse models, along with the *Apc*^{Min/+} mice, have proven useful through numerous studies in colorectal carcinogenesis related to the influence or role of environmental factors (e.g., high-fat diet), chemoprevention agents (aspirin, nonsteroidal anti-inflammatory agents, selective Cox-2 inhibitors), diagnosis (evolving proteomics), therapy, and establishment of intersecting pathways through crossbreeding with other mouse models. Particularly illuminating has been the role of COX-2 (Oshima et al. 1996) and the EP2 prostaglandin receptor (Sonoshita et al. 2001) in the background of *Apc* deficiency in the mouse and the manner in which this work has stimulated chemoprevention efforts in the human.

Genetic testing has exploited the notion that the APC gene is subjected to truncating germline mutations. Ini-

tial approaches were based on an in vitro transcription/translation assay to identify truncated APC proteins (Powell et al. 1993), but complete DNA sequencing is now standard. Mutations are detected in 80% of FAP cases. Upon identification of the *APC* mutation in an affected family member, then the specific *APC* mutation can be screened for in at-risk members with very high accuracy. Southern blotting may also unravel uncommon *APC* deletions. Recently, FAP genetic testing has permitted under appropriate circumstances the potential application of this knowledge to preimplantation in vitro fertilization strategies (Motou et al. 2007). Clinical monitoring commences between ages 10 and 12 with flexible sigmoidoscopy or colonoscopy every year, upper endoscopy every 1–2 yr starting at ages 20–25, annual thyroid exam supplemented as needed with ultrasound, and consideration of other modalities to evaluate other organs where cancer(s) may emerge. In aggregate, the genetic and clinical underpinnings of FAP have served as a platform for the dissection of the molecular properties of the *APC* protein and its roles in sporadic colon cancer.

HNPCC (Lynch) syndrome

Originally described in the early 20th century, elaborated on by Henry Lynch (1974), and refined through consensus conferences (Vasen et al. 1991, 1999), this syndrome is marked by an autosomal dominant mode of inheritance, early onset of colon cancer often with a predilection for the right colon, and an 80% lifetime risk of colorectal cancer. The syndrome is noteworthy for a spectrum of extracolonic tumors, such as those originating from the endometrium, ovary, stomach, bile duct, kidney, bladder, ureter, and skin (in this context, referred to as the Muir-Torre syndrome with sebaceous adenomas, basal cell cancers, and keratoacanthomas). The clinical hallmarks of HNPCC syndrome resulted in a classification scheme designated as the Amsterdam I criteria (Vasen et al. 1991), later modified as Amsterdam II to incorporate the importance of the extracolonic cancers (Table 2; Vasen et al. 1999).

An extraordinary amount of work in bacterial and especially yeast genetics paved the way for illuminating translational genetic discoveries in HNPCC (for review, see Fishel and Kolodner 1995). To that end, HNPCC patients have germline mutations in DNA mismatch repair (MMR) genes. In colonic or extracolonic tumors, the wild-type MMR allele is lost through somatic genetic alterations. As a result, DNA replication errors occur in repeat sequences (Aaltonen et al. 1993; Fishel et al. 1993; Ionov et al. 1993), typically in dinucleotide repeats, and are designated as the mutator phenotype. This phenotype can be revealed by PCR-based interrogation of genome-wide microsatellite sequences to evaluate for the possibility of length changes in the microsatellite sequences called microsatellite instability (MSI). The tumor is referred to as MSI-high or MSI-H when two or more markers of the recommended panel by the National Cancer Institute (BAT26, BAT25, D5S346, D2S123, and D17S250 markers) demonstrate MSI, and

Table 2. *Criteria for HNPCC (Lynch) syndrome*

Amsterdam I criteria

At least three relatives with colorectal cancer and the following:

- One should be a first-degree relative of the other two.
- At least two consecutive generations should be affected.
- At least one case of colorectal cancer should be before age 50.
- FAP should be excluded.
- Verification of tumors' histopathology.

Amsterdam II criteria

At least three relatives with HNPCC-related cancers and the following:

- One should be a first-degree relative of the other two.
- At least two consecutive generations should be affected.
- At least one case of HNPCC-related cancer should be before age 50.
- FAP should be excluded.
- Verification of tumors' histopathology.

Original Bethesda criteria

- Individuals with cancer in families that meet the Amsterdam criteria.
- Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers (endometrial, ovarian, gastric, hepatobiliary, or small bowel cancer or transitional cell carcinoma of the renal pelvis or ureter).
- Individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma; one of the cancers diagnosed at <50 yr of age, and the adenoma diagnosed at <40 yr of age.
- Individuals with colorectal cancer or endometrial cancer diagnosed at <50 yr of age.
- Individuals with right-sided colorectal cancer with an undifferentiated pattern (solid/cribriform) on histopathology diagnosed at <50 yr of age.
- Individuals with signet-ring cell-type colorectal cancer diagnosed at <50 yr of age.
- Individuals with adenomas diagnosed at <40 yr of age.

Revised Bethesda guidelines

- Colorectal cancer diagnosed in a patient who is <50 yr of age.
- Presence of synchronous or metachronous colorectal or other HNPCC-associated tumors (colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, small bowel, brain, and sebaceous gland adenomas and keratoacanthomas), regardless of age.
- Colorectal cancer with the MSI-high histology (presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) diagnosed in a patient who is <60 yr of age.
- Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 yr.
- Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

MSI-low or MSI-L with one unstable marker, or MSS when no microsatellite loci are unstable. Of note, MSI may be found in ~15% of sporadic colorectal tumors (Thibodeau et al. 1998). Target genes

of MSI include *TGF β IIIR*, *E2F4*, and *Bax*, among others. Germline mutations may be found in *MLH1*, *MSH2*, and *MSH6* MMR genes, and account for perhaps 60%–80% of all detectable germline mutations (Fishel et al. 1993; Parsons et al. 1993; Lynch and de la Chapelle 2003; Vasen and Boland 2005). However, somatic *MLH1* promoter methylation or *MSH2* mutation may be found in MSI-H sporadic colorectal tumors. It is the discovery of MSI that led to the re-evaluation of the Amsterdam classification schema to evolve into the Bethesda, and subsequently revised Bethesda, criteria (Table 2; Boland et al. 1998; Umar et al. 2004). There are also unique histopathological features of MSI-H colorectal cancers, thereby potentially obviating the need for MSI analysis in evaluating whether a family might satisfy the criteria for HNPCC (Jenkins et al. 2007). It has been also advocated that the PREMM (Prediction of Mutations in *MLH1* and *MSH2*) model based on a personal and family history might provide an estimate of the likelihood of finding mutations (Balmana et al. 2006).

The MMR system recognizes and corrects base-pair mismatches and small nucleotide (1–4 base pairs [bp]) insertion/deletion mutations that can occur during DNA replication (Chung and Rustgi 2003; Lynch and de la Chapelle 2003; Edelmann and Edelmann 2004; Vasen and Boland 2005). Eukaryotic MMR mechanisms are more evolved and complex than bacterial MMR. The eukaryotic system, best studied in yeast and in mammalian cells, involves more proteins. These include the homologs of bacterial *MutS* and *MutL*, namely, *MSH* (*MSH1*–*MSH6*) and *MLH* (*MLH1*–*MLH3*)/Post-meiotic segregation or *PMS* (*PMS1*–*PMS2*), respectively. In eukaryotes, *MSH2* and *MSH6* (called MutS α) form a heterodimer and recognize 1-bp mismatches and 1-bp insertion/deletion mutations (Fig. 2). *MSH2* and *MSH3* form a heterodimer (called MutS β) and recognize not only what is recognized by *MSH2*–*MSH6* but expand that capability to recognize 2- to 4-bp insertion/deletion mutations. *MSH4* and *MSH5* participate in the regulation of meiotic recombination (Ross-Macdonald and Roeder 1994). Upon recognition of DNA mismatches, members of the *MLH* and *PMS* gene families are recruited. *MLH1* and *PMS2* (yeast *PMS1*) complex with each other (called MutL α)

and are recruited to form a complex with *MSH2*–*MSH6* or *MSH2*–*MSH3*, and this is mediated via *MLH1*. *MLH1*–*PMS2* trigger a cascade of events that lead to the excision of the DNA strand carrying the mismatched base, which culminates in DNA resynthesis and ligation. The functional significance of *MLH1*–*MLH3* (called MutL γ) and *MLH1*–*PMS1* (called MutL β) in MMR remains to be elucidated. Excision and resynthesis of 1-bp mutations/insertions/deletions in part involve *EXO1*, a 5'–3' exonuclease that binds *MSH2*, *MSH3*, and *MLH1* and functions likely through the *MSH2*–*MSH6* correction system (Tishkoff et al. 1997; Schmutte et al. 2001; Tran et al. 2001).

The identification of exonucleases, apart from *EXO1*, remains to be determined, especially for 2- to 4-bp mutations/insertions/deletions. The potential role of germline *EXO1* mutations and variants in HNPCC has not been conclusive in spite of early notions that they may be important (Wu et al. 2001). *Exo1* deficiency in the mouse has a limited effect on polyp number and size in *Apc(1638N)* mice (Kucherlapati et al. 2007). Collectively, these data would indicate that other exonucleases are involved, but their identification and characterization are the subject of ongoing investigation. Proteins autonomous from exonucleases may be involved in the later stages of DNA repair. Proliferating cell nuclear antigen (PCNA) binds *MLH1*, *MSH3*, and *MSH6* (Umar et al. 1996) and potentially may serve to bridge MMR with DNA replication. Other functions have been attributed to MMR proteins, which include involvement in apoptosis (Chung and Rustgi 2003; Edelmann and Edelmann 2004).

Much work has underscored the development and characterization of mouse models that knock out different MMR genes (Edelmann and Edelmann 2004). *Msh2*^{−/−} mice have reduced life span and a high incidence of lymphomas (T-cell) and small intestinal adenomas and adenocarcinomas with MSI-H in the tumors (de Wind et al. 1995; Reitmaier et al. 1995, 1996; Smits et al. 2000). A subset of the mice has sebaceous gland tumors, reminiscent of Muir-Torre syndrome. *Msh3*^{−/−} mice have a low incidence of late-onset GI tumors with moderate-high MSI (de Wind et al. 1999; Edelmann et al.

Figure 2. DNA MMR system in mammalian cells that perform recognition and editing functions, which have escaped DNA polymerase. A displays the key proteins involved in correction of 1-bp mismatches, whereas B depicts the proteins involved in repair of 2- to 4-bp mismatches (insertions, deletions). The hMSH2/hMSH3 complex can also participate in the repair of 1-bp mismatches. Modified from Chung and Rustgi (2003) with permission from *Annals of Internal Medicine*, and from Edelmann and Edelmann (2004) with permission of Wiley-Liss, Inc., a subsidiary John Wiley & Sons, Inc. (©2004).

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2000). *Msh6*^{-/-} mice develop tumors but with delayed onset compared with *Msh2*^{-/-} mice (Edelmann et al. 1997). However, the tumors in the *Msh6*^{-/-} mice have little or no MSI in their tumors. Interestingly, consistent with the phenotype of *msh6*^{-/-} mice, it was found that a subset of a slightly older cohort of patients with familial non-HNPCC colorectal cancers had germline *MSH6* mutations (Kolodner et al. 1999). As might be expected, *Msh3*^{-/-}, *Msh6*^{-/-} mice develop tumors similar to *Msh2*^{-/-} mice and have evidence of MSI-H (de Wind et al. 1999; Edelmann et al. 2000). *Mlh1*^{-/-} mice behave in a manner similar to *Msh2*^{-/-} mice with reduced life span and a similar spectrum of tumors (Baker et al. 1996; Edelmann et al. 1996). Their tumors display MSI-H. *Msh4* or *Msh5* knockout mice have no tumors. *Pms1* knockout mice have no tumors (Prolla et al. 1998), and *Pms2* knockout mice develop lymphomas and sarcomas but no GI tumors (Baker et al. 1995; Prolla et al. 1998). Collectively, these mouse models emphasize the central importance of *MSH2*, *MLH1*, and *MSH6* in MMR and HNPCC germline mutations and point to potential functional redundancies of the other MMR proteins.

Genetic testing in HNPCC

If a patient's family satisfies Amsterdam criteria, genetic testing should be offered for *MLH1*, *MSH2*, and *MSH6* mutational analysis. However, if there is failure to satisfy the criteria, and with an index of suspicion for HNPCC intact, then tumors, if available, can be obtained for either PCR-based MSI testing or *MLH1*/*MSH2*/*MSH6* immunohistochemistry. Armed with either MSI-H status or lost expression of *MLH1*, *MSH2*, or *MSH6*, then direct genetic testing can be offered and pursued. The options of MSI testing or immunohistochemistry may be equivalent (Pinol et al. 2005), but the precise algorithm may need to be done in accordance with local practice and recommendations. Fulfillment of Amsterdam I criteria, but without evidence of MSI-H status in the tumor(s), prompts the consideration of familial colorectal cancer X syndrome where germline mutations in the known MMR genes do not appear to exist (Lindor et al. 2005). Clinical monitoring of individuals at risk for HNPCC involves colonoscopy every 2 yr starting between ages 20 and 25, and annually above age 40. Women at risk merit annual endometrial aspiration biopsies and transvaginal ultrasonography to visualize the ovaries, commencing between ages 25 and 35 and occurring annually. Other measures need to be individualized. Patients who are gene mutation carriers should receive counseling about subtotal colectomy given the prominence of colon cancer, and for women, prophylactic hysterectomy and bilateral oophorectomies, especially since endometrial cancer is a defining feature of the disease.

MAP

The *MYH* gene on human chromosome 1p33-34 is a base excision repair gene in which germline mutations have

been found in association with multiple colorectal adenomatous polyps (Sieber et al. 2003). These mutations may be missense or nonsense, the latter yielding protein truncation. Two common mutations are Y165C and G382D, accounting for >80% of known mutations. Transmitted in an autosomal recessive inheritance pattern, MAP is defined as involving biallelic inactivation and patients harboring multiple colorectal adenomatous polyps without evidence of FAP or attenuated FAP (Sieber et al. 2003). Monoallelic carriers do not carry an increased risk of colorectal cancer (Balaguer et al. 2007). *Myh* deficiency has been demonstrated to enhance intestinal tumorigenesis in *ApcMin*/+ mice (Sieber et al. 2004). However, analyses of families with FAP have not supported the hypotheses that MYH is a disease modifier in FAP (Plasilova et al. 2004).

Clinical findings of an increased number of polyps may trigger suspicion of either MAP or attenuated FAP in the appropriate setting. However, the polyp number can be quite variable in MAP, and it has been demonstrated that if the number of polyps is used as the sole entry criterion, then nearly 25% of cases may be missed in the general population (Jo et al. 2005). Furthermore, these individuals may have a family history consistent with HNPCC, and thus, *MYH* gene testing may be necessary for patients who meet clinical criteria for HNPCC and who do not have evidence of DNA MMR gene mutations. These patients warrant regular interval screening and surveillance colonoscopy.

Peutz-Jeghers syndrome

Peutz-Jeghers is a hamartomatous polyposis syndrome with an autosomal dominant mode of inheritance. The incidence is about one in every 200,000 births, and onset is in early childhood. Clinically, patients have moderate-large sized, but few hamartomatous polyps, typically in the small bowel but also in the colon and/or in the stomach (Fig. 3). These polyps may enlarge and result in hemorrhage or intussusception with obstruction. However, the pathogenic features are revealed through histopathology with increased smooth muscle bands

Figure 3. (A) Gross view of a polyp in a patient with Peutz-Jeghers. (B) Histopathologic confirmation is required for the diagnosis, depicting the cardinal feature of abundant smooth muscle. Courtesy of P. Russo, MD.

(Fig. 2). There is increased risk for colorectal cancer and, rarely, small bowel cancer (Giardiello et al. 2001). Other phenotypic features include macules with broad but focal distribution: peroral, buccal, periocular, palmar/plantar surfaces, and anogenital surfaces. These macules wane during puberty but persist in the buccal mucosa. Sinus, bronchial, and bladder polyps may also be evident. As patients survive into their third and fourth decades of life, there is increased risk of other cancers (Giardiello et al. 2001): gastric, pancreatic, breast, ovarian, uterine, cervical, and lung, as well as Sertoli cell tumors (males) and sex cord tumors with annual tubules (females). The latter two tumors actually arise in adolescence and young adulthood.

Earlier genetic linkage studies localized the gene locus responsible for Peutz-Jeghers syndrome to human chromosome 19p13.3 (Amos et al. 1997). Shortly thereafter, the actual gene was discovered to be a novel serine-threonine kinase 11 (*STK11*), or *LKB-1* (Hemminki et al. 1998). The tumors associated with Peutz-Jeghers syndrome have 19p LOH or somatic mutations in *LKB1*, consistent with the notion that *LKB1* is a tumor suppressor gene. Mouse models have demonstrated that *Lkb1*^{-/-} is embryonically lethal due to vascular abnormalities in the yolk sac and placenta (Bardeesy et al. 2002; Jishage et al. 2002). *Lkb1*^{+/-} mice develop the expected polyps in the GI tract with some predilection for the stomach. As these mice age, they develop liver cancers (Miyoshi et al. 2002; Nakau et al. 2002). Interestingly, *Lkb1* may be haploinsufficient in polyps (Miyoshi et al. 2002; Nakau et al. 2002); however, *Lkb1* LOH has been found also to occur in the epithelium of some of the polyps arising in the *Lkb1*^{+/-} mouse (Bardeesy et al. 2002). When *Lkb1*^{+/-} mice are crossed into a *p53*-deficient background, the mice develop hamartomatous polyps at a faster rate and also evolve to contain hepatic adenomas and liver cancers (Takeda et al. 2006). The hepatic adenomas have evidence of *Lkb1* LOH, suggesting that *p53* loss may stimulate *Lkb1* LOH (Takeda et al. 2006). *Lkb1* deficiency prevents culture-induced senescence without concordant loss of *Ink4a/Arf* or *p53* (Bardeesy et al. 2002). *Lkb1*^{-/-} mouse embryonic fibroblasts do not undergo transformation by activated *Ha-Ras* either alone or with known cooperating transformation-associated oncogenes (Bardeesy et al. 2002).

The biological properties of *LKB1* have emerged in recent years, with evidence of unexpected functions in the process. One original theme was that *LKB1* is important in regulating cell proliferation and growth, perhaps in part through induction of apoptosis. To that end, ectopic *LKB1* overexpression in cells leads to G1 cell cycle arrest (Tiainen et al. 1999). Phosphorylation of *LKB1* (Ser 431) by PKA or p90 ribosomal S6 is essential for suppression of cell growth (Collins et al. 2000; Sapkota et al. 2001). *LKB1* is needed for brahma-related gene-1-induced growth arrest (Marignani et al. 2001), and *LKB1* plays a role in *p53*-dependent apoptosis (Karuman et al. 2001). These initial findings have been supplanted by the discoveries that *LKB1* controls cellular polarity (as its Par4 homologs in model organisms) (Martin and St. Johnston 2003) and also cellular metabolism (Woods et al. 2003; Shaw et al. 2004a,b). Seminal studies have enlightened a role for *LKB1* as being involved as a sensor for energy stress and nutrient deprivation (Fig. 4). *LKB1* binds and activates AMP (α , β , γ subunits) (Shaw et al. 2004b) and related kinases to induce AMP kinase (AMPK), which, in turn, regulates the gene product of *TSC2* or tuberlin. Tuberlin facilitates the generation of Rheb-GDP from Rheb-GTP. Rheb-GTP activates mTOR, which is critical in the regulation of protein synthesis, cell growth, and proliferation through the phosphorylation of S6K1 and rS6 and the inhibition of 4E-BP1 that allows the liberation of eIF4E. Germline *LKB1* mutations and somatic *LKB1* alterations result in the down-regulation of tuberlin, up-regulation of Rheb-GTP, and induction of mTOR (Shaw et al. 2004a). Indeed, the hamartomatous polyps of *Lkb1*-deficient mice display enhanced activation of downstream effectors of mTOR (Shaw et al. 2004a). It is tempting to speculate that mTOR inhibitors that exist (e.g., Rapamycin), or those in development, might be useful as chemopreventive or therapeutic measures in patients with Peutz-Jeghers syndrome.

Patients suspected to have PJS are candidates for genetic testing with evaluation for germline *LKB1* mutations. Those identified patients, or patients at risk, should undergo periodic upper endoscopy, colonoscopy, and small bowel follow-through X-ray series; and meticulous attention to the risk of various cancers (especially pancreatic cancer) is required as the patients reach their third decade of life and beyond.

Figure 4. The *LKB1* tumor suppressor gene pathway in the regulation of energy and nutrients. Modified from Shaw et al. (2004a), with permission from Elsevier (©2004).

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Figure 5. (A) A gross view of a polyp in a patient with FJP. (B) Histopathologic confirmation is required for the diagnosis, depicting the cardinal feature of cysts in the epithelia of the polyp(s). Courtesy of P. Russo, MD.

Juvenile polyposis

Familial Juvenile Polyposis (FJP) is an autosomal dominant disorder in which 10 or more juvenile polyps are observed in the GI tract. It affects one in 100,000 births, and the phenotypic manifestations are found in childhood to adolescence. The polyps, as with the polyps in PJ syndrome, may bleed or obstruct (Fig. 5). The establishment of these hamartomatous polyps as juvenile polyps is predicated on histological interpretation and confirmation of microcysts in the epithelia (Fig. 5). They are found in the colon, but also other parts of the GI tract. There is an increased risk of colon cancer (Giardiello et al. 2001). While reports of gastric, small bowel, and pancreatic cancers are found in the literature, it is unclear if these are true associations with juvenile polyposis. It is important to bear in mind that juvenile polyps can be sporadic.

Germline mutations in *BMPR1A* (bone morphogenic protein receptor 1A), *SMAD4*, or *ENG* (endoglin, an accessory receptor for TGF- β) are reported in FJP (Howe et al. 1998, 2001; Sweet et al. 2005), suggesting that the TGF- β pathway is critical in the pathogenesis of FJP. Conditional inactivation of *Bmpr1a* in mice impairs normal intestinal homeostasis with an expansion of the stem and progenitor cell populations, eventually leading to intestinal polyposis resembling FJP (He et al. 2004). Inhibition of BMP signaling by transgenic expression of noggin results in the formation of numerous ectopic crypt units (Haramis et al. 2004). These changes phenocopy the polyps observed in FJP (Haramis et al. 2004). Targeted disruption of *Smad4* was pursued by crossbreeding the conditional *Smad4* knockout mice and transgenic mice expressing Cre-recombinase under T-cell-specific promoters (Kim et al. 2006). The T-cell-specific homozygous *Smad4* knockout mice developed normally, but life span was shortened. There is thickened mucosa of both the large and small intestines with polyps as well as rectal prolapse. Histology revealed ef-

acement of villus architecture and expansion of the stromal compartment containing cystic lesions lined by columnar epithelial cells and plasma cell infiltrates in the intestine (Kim et al. 2006). In contrast, conditional *Smad4* deletion in the intestinal epithelia does not yield intestinal tumors. This highlights the importance of the inflammatory response in the stromal compartment in the regulation of epithelial tumorigenesis.

Genetic testing involves the exploration of germline mutational analysis of *BMPR1A*, *SMAD4*, or *ENG*, recognizing that a subset of FJP patients do not harbor these mutations. Clinical monitoring is similar to that recommended for PJS, but the risk for extracolonic cancers is not observed as noted.

Cowden's syndrome

Cowden's syndrome has an autosomal dominant mode of transmission and affects one in 200,000 births. Hamartomatous polyps may be found throughout the GI tract, and these polyps are of a diverse nature: juvenile, lipomas, lymphoid, ganglioneuromas, and inflammatory. The lifetime risk of colon cancer may approach 10%, but this remains controversial. Cutaneous manifestations are of paramount importance in the diagnosis of Cowden's syndrome. These include acral verrucous papules, the classic trichilemmomas of the face (in particular, eyes, nose and mouth; this distribution is reminiscent of the macules in Peutz-Jeghers), and fibromas of the oral mucosa, gingiva, and tongue (Fig. 6). About two-thirds of patients have a thyroid goiter, and there is a 10% lifetime risk of thyroid cancer. About 75% of the women have fibrocystic breast disease and fibroadenomas, and the lifetime risk of breast cancer is nearly 50%, with typically early-age-onset breast cancer. Soft tissue and internal tumors are present, such as lipomas, neurofibromas, uterine leiomyomas, and meningiomas. Cowden's syndrome involves germline *PTEN* mutations, which is a negative regulator of PI3K and AKT (Fig. 4; Liaw et al. 1997). *Pten* deficiency in the mouse causes a multitude of tumors, including in the thymus, endometrium, liver, prostate, and GI tract, although the GI tract neoplasms are associated with lymphoid tissue (Podsypanina et al. 1999).

An association between Lhermitte-Duclos disease (cerebellar dysplastic gangliocytoma) and Cowden's syndrome has been advocated. Bannayan-Ruvalcaba-Riley

Figure 6. Cutaneous manifestations of Cowden's syndrome: papules (A) and trichilemmomas (B). Courtesy of C. Eng, MD.

(BRR; also called Bannayan-Zonana) syndrome is allelic to Cowden's syndrome (Arch et al. 1997; Marsh et al. 1997). Comprising lipomas, pigmented macules of the penis, and macrocephaly, BRR also harbors germline *PTEN* gene mutations (Arch et al. 1997; Marsh et al. 1997), as is observed with Cowden's. Clinical suspicion merits *PTEN* genetic testing in at-risk Cowden's families with careful screening for thyroid and breast lesions, along with that for GI polyps.

Other hamartomatous polyposis syndromes

Hereditary mixed polyposis syndrome was defined as a potentially new entity through the investigation of large kindred with mixed hamartomatous and hyperplastic polyps, and genetic linkage to human chromosome 6q (Thomas et al. 1996; Whitelaw et al. 1997). Other potential gene loci have been noted, namely, on chromosomes 15q13-14 (Jaeger et al. 2003) and 10q23 (Cao et al. 2006), although the latter might represent a variant of juvenile polyposis since loss of *BMPR1A* function was noted in one of the families. Thus, in the consideration of this syndrome, it would appear that the clinical features and types of polyps are important to define, and more studies are needed to establish the genetic underpinnings. Other conditions have involvement of their cognate polyps in different anatomic sites of the GI tract and include neurofibromatosis type I, multiple endocrine neoplasia type 2b, and the Gorlin syndrome (also referred to as the Gorlin-Goltz syndrome or the nevoid basal cell carcinoma syndrome). In each of these aforementioned conditions, the GI tract is one of multiple sites of involvement and not the cardinal feature.

The Gorlin syndrome has an autosomal dominant mode of transmission with multiple basal cell carcinomas; epidermoid cysts; "pits" on the palms and soles; odontogenic keratocysts; jaw, rib, and vertebral abnormalities; ovarian fibromas; short metacarpals; and hyper-telorism. There is increased risk of medulloblastoma, and to a lesser extent, fibrosarcoma of the jaw. The underlying genetic basis is attributable to germline *PTCH* gene (chromosome 9q22.3) mutations, which is critical in sonic hedgehog signaling. One is struck by the overlap between some features of Gorlin syndrome with FAP (e.g., epidermoid cysts, jaw abnormalities), Turcot syndrome (medulloblastoma with germline APC mutations), and Muir-Torre syndrome (basal cell cancers with MSI). This raises the possibility of functional interactions between aberrant wnt signaling and sonic hedgehog signaling in some of the hereditary polyposis syndromes, or that MSI may be detectable in tumors with aberrant sonic hedgehog signaling. Of note, MSI has been detected in some sporadic basal cell carcinomas (Sardi et al. 2000).

Hyperplastic polyposis

While long-standing dogma had consigned hyperplastic polyps to incidental occurrences, there has emerged over time a more rigorous histopathological classification of a

subset of hyperplastic polyps as serrated polyps and an appreciation that hyperplastic polyposis predisposes to colorectal cancer, albeit without a clear inheritance pattern. The most common types of hyperplastic polyp or serrated polyp are solitary and benign and are not viewed as being subject to malignant transformation, at least directly. These include microvesicular, goblet-rich, and mucin-poor subtypes (Table 3; Fig. 7). The other types include sessile serrated adenoma (SSA), traditional serrated adenoma (TSA), and mixed polyps (TSA and tubular adenomas) and have replaced older nomenclatures (Table 3; Fig. 7). All these polyps tend to be flat and diminutive and, thus, may escape recognition at the time of colonoscopy. Magnification chromoendoscopy with indigo carmine may enhance their detection, especially in the context of patients undergoing screening or surveillance due to personal or family history of polyps. This new classification is gaining acceptance but as of yet does not have universal acceptance, in part due to lack of liberation from older nomenclatures and in part due to definition of dysplasia in classic adenomas versus SSAs. SSAs, TSAs, and mixed polyps may progress to cancer. This was appreciated initially in individuals, and even families, with large hyperplastic or serrated polyps, often in the right colon, designated as hyperplastic or serrated adenomatous polyposis. Synchronous colorectal cancers can occur in such settings.

The molecular pathway(s) responsible for the progression of SSAs, TSAs, and mixed polyps to colon cancer deviates from the conventional chromosomal instability pathway observed in the majority of sporadic colon cancers that emerge from adenomatous polyps. Rather, there is evidence of MSI with hypermethylation of *MLH1* as part of global hypermethylation or a CpG island methylator phenotype (CIMP) (Park et al. 2003). It is conceivable that SSAs may be the precursors of MSI-H sporadic colon cancers. Apart from this consideration, SSAs harbor mutations in the *BRAF* gene, often V600E (Spring et al. 2006). Similarly, *BRAF* mutations are observed in MSI-H colon cancers (Tanaka et al. 2006) but are uncommon in MSS colon cancers or in sporadic adenomas. Thus, when encountered, SSAs, TSAs, and mixed polyps should be resected endoscopically since the time interval to colorectal cancer, and the frequency in which this occurs, is not known currently. Nor is it defined whether these types of polyps may, in turn, have their own intermediate lesions before evolving into colon cancer. Interestingly, *BRAF* mutations may be found in microvesicular and goblet cell-rich subtypes of serrated polyps, raising the intriguing possibility that they

Table 3. *Hyperplastic or serrated polyps*

Common subtypes
Microvesicular
Goblet-rich
Mucin-poor
Sessile serrated adenoma (SSA)
Traditional serrated adenoma (TSA)
Mixed polyps (TSA and tubular adenomas)

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Figure 7. (A) Classic hyperplastic polyp. (B) TSA. (C) SSA. Courtesy of G. Lauwers, MD.

may progress to SSAs in the correct milieu (Lauwers and Chung 2006).

Summary and future perspectives

The hereditary forms of colorectal cancer have served to illuminate our understanding of the sporadic counterpart, but also provided a critical basis to understand principles of cancer genetics in general. Investigation of hereditary colorectal cancer has had, and continues to have, vast translational applications. These include, but are not limited to, chemoprevention, risk stratification and genetic testing, molecular diagnostics, accompanying genetic mouse models, and even more likely in the future, targeted therapeutics. This industrious amount of information to date has made evaluation of patients who have familial colorectal cancer, not defined by the known hereditary forms of colorectal cancer, imperative and increasingly compelling. Such genetic discoveries and insights will lead to new definitions and classifications of subsets of families. Some of these may be inevitably in the continuum with known hereditary forms (especially HNPCC or Lynch syndrome), but others, perhaps the majority even, may be quite distinctive. These in turn will inform us once again about the molecular pathogenesis of sporadic colorectal cancer, and likely other cancers as well, and basic cellular processes, and lead to further translational applications. An ideal scenario would be to risk-stratify the general population based on family history and presence or absence of germline genetic mutations and polymorphisms to shape clinical monitoring measures.

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