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Peter Jordan *Editor*

Targeted Therapy of Colorectal Cancer Subtypes

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Targeted Therapy of Colorectal Cancer Subtypes

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Colorectal Cancer Subtypes – The Current Portrait

1

Peter Jordan

Abstract

Colorectal cancer (CRC) is one prominent example for how chemotherapy has been changing by moving from the use of general cytotoxic agents to more tumour-specific drugs. For example, antibody-based drugs neutralize a growth factor receptor protein on the surface of tumour cells. The development of such new therapeutic opportunities requires a more thorough and systematic subclassification of CRC because tumour cells can exploit several alternative genetic pathways for their survival. This chapter gives an overview on CRC subtypes as an introduction to the following book chapters that will describe aspects of specific subtypes, and how these may lead to the development of novel pathway-specific drugs for a more precise therapeutic intervention.

Keywords

Chromosomal instability · Colorectal cancer subtype · Consensus molecular subtype · Microsatellite instability · Oncogene · Polyp · Serrated pathway

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According to the Globocan 2012 data collected by the International Agency for Research on Cancer, cancer of the colon and rectum (CRC) presented in both sexes over 1.35 million cases. This corresponds to the third most common incidence (behind lung and breast cancer) and the fourth cause of cancer mortality worldwide (Ferlay et al. 2015). CRC incidence continues to rise especially in low and middle income countries and is considered one of the clearest markers for rapid societal and economic changes that are associated with cancer development (Arnold et al. 2017). The corresponding life-style and environmental factors contribute significantly to the vast majority of CRC cases, which are designated as sporadic CRC. Nevertheless, hereditary CRC syndromes exist but cause only a small fraction of cases.

Sporadic CRC has been extensively studied and reviewed (Jass 2007; Fearon 2011; Cancer Genome Atlas Network 2012; Brenner et al. 2014; Matos et al. 2016). The majority of the sporadic CRC tumours originates from premalignant precursor lesions known as polyps, which over time progress to clinically relevant tumours. The Fearon-Vogelstein model has provided an initial paradigmatic model for CRC tumorigenesis based on the loss of the tumour suppressor gene APC and stepwise accumulation of mutations in critical genes including KRAS, DCC and TP53 (Fearon and Vogelstein 1990). A persistent activation of the Wnt pathway that regulates the stem

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cell compartment and cell fate along the crypt-villus axis of the colon mucosa emerged as a key driver of CRC.

However, subsequent pathological or molecular analyses have revealed the existence of several CRC subtypes instead of being a uniform disease entity. From the pathologist's perspective, for example, the detected polyps are precursor structures formed as morphologically distinct types and can be divided into either tubular and villous adenomas, or serrated and hyperplastic polyps. The anatomic site of origin further divides tumours into two groups: those found in the distal or in the proximal colon segment. For example, proximally located tumours are usually larger and present a mucinous histology.

On the other hand, molecular analyses demonstrated that tumours can exhibit either widespread chromosomal abnormalities, designated as the chromosomal instability phenotype (CIN), or, instead, a high rate of DNA sequence mutations (the microsatellite instability phenotype, or MSI) caused by deficient DNA mismatch repair. Another molecular feature that distinguishes different tumour groups is the degree of increase in DNA methylation observed in clusters of the CpG dinucleotide found in many gene promoters, a phenotype known as CpG island methylator phenotype (CIMP).

Finally, genotype analyses of tumours detected the presence of typical and sometimes mutually exclusive somatic mutations in specific cancer-related genes, such as the *APC* and *TP53* tumour suppressor genes, or in oncogenes such as *KRAS, PIK3CA* or *BRAF* and contributed to the assignment of CRC subtypes.

By combining the above criteria of pathology and molecular genotyping, sporadic CRC tumours initially formed two main groups. One group included over 70% of the cases and developed tumours, mostly in the distal colon, that appeared to follow an adenoma-carcinoma sequence involving recurrent somatic mutations in the *APC* and *TP53* tumour suppressor genes or in the oncogene *KRAS* (Jass 2007; Cancer Genome Atlas Network 2012; Brenner et al. 2014; Phipps et al. 2015). These cases also exhibit widespread chromosomal abnormalities (CIN), and derive from adenomatous polyps.

A second major group of sporadic CRC included about 15% of patients with tumours occurring preferentially in the proximal colon, presenting a stable chromosome number, but a high rate of DNA sequence mutations, the MSI phenotype. This phenotype develops following the somatic silencing by DNA methylation of the promoter of the *MLH1* gene that encodes a component required for a functional DNA mismatch repair system. The majority of these tumours derive from precursor polyps with a serrated morphology called sessile serrated adenoma (Snover et al. 2005; Bettington et al. 2013) and present activating mutations in the oncogene *BRAF*, but not in *KRAS*.

Subsequent studies unravelled further heterogeneity within these two groups of tumours. For example, some 8% of sporadic cases have a mutation in *BRAF* but are not MSI. Another 10% have mutation in *KRAS* but occur in the proximal colon and derive from a type of serrated polyp called traditional serrated adenoma (Jass 2007; Phipps et al. 2015). In addition, many adenomatous-derived polyps in the distal colon lead to carcinomas with CIN, but without the presence of mutated *KRAS*.

Although this heterogeneity precluded a simple genotype-phenotype correlation of CRC, it laid the foundation for subtype-specific therapeutic approaches. For example, the stimulation of tumour cell proliferation through the epidermal growth factor receptor (EGFR) and its downstream signalling along the mitogen-activated protein kinase (MAPK) pathway, has led to the development and clinical approval of therapy using the anti-EGFR antibodies cetuximab and panitumumab. In clinical practice only around 10% of cases respond to anti-EGFR therapy (Bardelli and Siena 2010; Misale et al. 2014), while others are *a priori* resistant due to mutually exclusive mutations in either *KRAS (30%), NRAS (2%),* or *BRAF (15%)* that all operate in the EGFR pathway (Zhao et al. 2017). Such mutations revealed to be alternative mutational events and occur early during tumour development, given they can be detected in microdissected premalignant polyps or aberrant crypt foci (Yang

et al. 2004; Beach et al. 2005; Rosenberg et al. 2007; Velho et al. 2008; Carr et al. 2009; Sandmeier et al. 2009; Boparai et al. 2011; Kim et al. 2011). Another example are inhibitors of the *BRAF* kinase activity that have the potential to target some 10–15% of CRC cases (Obaid et al. 2017).

Besides the MAPK pathway, the activation of the phosphatidylinositol 3-kinase (PI3K) pathway has therapeutic potential. Mutations in exon 20 of the *PIK3CA* gene were found to associate significantly with the MSI pathway, while exon 9 mutations E542K and E545K are overrepresented in *KRAS* mutant tumours (Zhao and Vogt 2010; Whitehall et al. 2012; Day et al. 2013).

More recently, genome-wide techniques have allowed determining the gene expression signatures of colorectal tumours. The subsequent bioinformatic clustering of the expression profiles provided yet another approach for the identification of CRC subtypes. Several studies have been published with partly overlapping conclusions (Perez Villamil et al. 2012; Schlicker et al. 2012; De Sousa E Melo et al. 2013; Sadanandam et al. 2013; Marisa et al. 2013; Budinska et al. 2013; Roepman et al. 2014), but have eventually resulted in the definition of at least 4 consensus molecular subgroups (CMS) (Guinney et al. 2015).

These expression signatures overlap in part with some of the previous genotypic or phenotypic CRC subtype characterization. For example, the MSI_BRAF subtype from the serrated pathway corresponds fully to the unique CMS1 gene expression profile and both classification schemes determined that roughly 15% of all sporadic CRCs belong to this group.

By contrast, the major group of 70% of the CRC cases CRC with recurrent mutations in the *APC*, *TP53* and *KRAS* genes and CIN has been subdivided into three distinct CMS profiles. CMS2 joins tumours with *APC* mutations, CIN and frequent gene amplification or deletion, while CMS3 features mutation in *KRAS* and a mixed status of MSI and CIN. Interestingly, this group revealed major changes in metabolic reprogramming of tumour cells. Finally, CMS4 unites tumours with CIN and a high degree of mesenchymal characteristics and activation of the TGFβ pathway. Concerning this subtype, subsequent studies emphasized the contribution of stromal-cell gene expression to the CMS definitions (Calon et al. 2015; Isella et al. 2015, 2017). This could imply that clinically meaningful CRC gene signatures are being obscured by the presence of abundant stromal cell-derived signals. Alternatively, if this CMS4 turns out to be a therapeutically meaningful classification, then progression of this CRC subtypes might be strongly influenced by microenvironmental cues from the tumour stroma. A comparison of the most relevant characteristics of each CMS is given in Fig. 1.1.

	CMS1	CMS2	CMS3	CMS4
Frequency	14%	37%	13%	23%
Tumour location	proximal	distal	proximal or distal	distal
Precursor polyp	sessile serrated	adenomatous	serrated or adenomatous	adenomatous
DNA sequence stability	MSI	MSS	MSS or MSI	MSS
DNA methylation	CIMP-H	no CIMP	CIMP-L	no CIMP
Chromsome number	stable	CIN	stable or CIN	CIN
Mutated genes	BRAF	APC, TP53	KRAS	
Pathway signature	immune activation	WNT and MYC	metabolic deregulation	TGF-β, mesenchymal

Fig. 1.1 Comparison of the pathological, molecular and genomic features that distinguish the four consensus molecular subtypes (CMS) of colorectal tumours defined by gene expression-based clustering. *CIMP* CpG island methylator phenotype, *-H high*, *-L* low, *MSI* microsatellite instability, *MSS* microsatellite stability, *CIN* chromosomal instability

It should be noted that despite of the progress of using genome-wide and unbiased gene expression signatures for the CMS classification, a group of 13% of all sporadic CRC cases could not be accommodated into the 4 CMS groups due to a mixture of features observed in the other 4 groups. This may indicate several properties: either further criteria are required to define this group, or these tumours are heterogeneously composed of different clones, or transition can occur between CMS signatures during tumour progression.

Altogether, this heterogeneity among sporadic CRC cases implies that a standardized therapeutic approach does not exist for patients; however, it also provides an opportunity for the identification of subtype-specific therapeutic targets or strategies.

In this book, a collection of review articles presents major CRC subtypes and how they can be distinguished by molecular analyses. They also highlight how this knowledge may guide the development of therapeutic strategies with higher precision and efficiency, thus reducing harmful side effects and increasing therapeutic efficacy.

In particular, the second chapter by Matos and Jordan describes the subgroup characterized by proximal colon location, mutation in the oncogene *BRAF* and microsatellite instability.

Then, Aguilera and Serna-Blasco elaborate on the *KRAS*-mutant CMS3 subtype in the distal colon and its changes in cell metabolism.

Chapters 4 and 5 are devoted to alterations in the phosphatidylinositol (PI)-dependent signalling pathway that affects more than one CRC subgroup. Fernandes et al. describe the role of the oncogenic lipid kinase PI3K and targeted therapeutic strategies, whereas Kotelevets et al. focus on the antagonizing phosphatase and tumour suppressor PTEN.

Chapter 6 reviews CRC subtype CMS2, which is characterized by recurrent mutations in the canonical Wnt signalling components, and presents the perspectives for using targeted therapy.

The more mesenchymal tumour cell properties that distinguish the highly invasive CMS4 subtype are addressed in Chap. 7 by Georges et al., together with the role of tumour budding and of the microenvironment.

Chapters 8 and 9 present important aspects of the targeted treatment approach through anti-EGFR therapy. Martins et al. describe first the clinical challenges encountered in the treatment of patients with anti-EGFR therapy. Finally, Pereira and Rodrigues elaborate on the development of miRNA-based strategies to improve the response to EGFR-directed therapy in patients.

Altogether, the book presents the main aspects of our current knowledge on heterogeneity in colorectal cancer, a prerequisite for the development of novel targeted therapy approaches.

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2 Targeting Colon Cancers with Mutated *BRAF* and Microsatellite Instability

Paulo Matos and Peter Jordan

Abstract

The subgroup of colon cancer (CRC) characterized by mutation in the *BRAF* gene and high mutation rate in the genomic DNA sequence, known as the microsatellite instability (MSI) phenotype, accounts for roughly 10% of the patients and derives from polyps with a serrated morphology. In this review, both features are discussed with regard to therapeutic opportunities. The most prevalent cancer-associated *BRAF* mutation is BRAF V600E that causes constitutive activation of the pro-proliferative MAPK pathway. Unfortunately, the available BRAF-specific inhibitors had little clinical benefit for metastatic CRC patients due to adaptive MAPK reactivation. Recent contributions for the development of new combination therapy approaches to pathway inhibition will be highlighted. In addition, we review the promising role of the recently developed immune checkpoint therapy for the treatment of this CRC subtype. The MSI phenotype of this subgroup results from an inactivated DNA mismatch repair system and leads to frameshift mutations with translation of new amino acid stretches and the generation of neo-antigens. This most likely explains the observed high degree of infiltration by tumour-associated lymphocytes. As cytotoxic lymphocytes are already part of the tumour environment, their activation by immune checkpoint therapy approaches is highly promising.

Keywords

Alternative splicing · BRAF · Microsatellite instability · RAC1b · Serrated polyp pathway

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2.1 Introduction

As described in the introductory Chap. 1, sporadic colorectal cancer (CRC) is not a homogenous disease entity but presents with distinct subtypes that differ in molecular and pathological criteria. One defined subgroup comprises about 10–15% of the patients and displays a high mutation rate in the genomic DNA sequence,

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