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Clinical relevance of colorectal cancer molecular subtypes

Nuria Rodriguez-Salas[a,*], Gema Dominguez[b], Rodrigo Barderas[c], Marta Mendiola[d], Xabier García-Albéniz[e], Juan Maurel[f], Jaime Feliu Batlle[a,g]

[a] Medical Oncology Department, La Paz University Hospital, Autonoma University of Madrid, Paseo de la Castellana 261, 28046, Madrid, Spain
[b] Department of Medicine, Medical School, Instituto de Investigaciones Biomédicas Alberto Sols, CSIC-UAM, Calle Arturo Duperier, 4, 28029 Madrid, Spain
[c] Biochemistry and Molecular Biology Department, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040 Madrid, Spain
[d] Molecular Pathology of Cancer and Therapeutic Targets Group, La Paz Hospital Research Institute (IdiPAZ), Paseo de la Castellana 261, 28046, Madrid, Spain
[e] Department of Epidemiology, Harvard T.H. Chan School of Public Health and Mongan Institute, Massachusetts General Hospital, Boston, MA, USA
[f] Medical Oncology Department, Hospital Clínic Barcelona, Translational Genomics and Targeted Therapeutics in Solid Tumors Group, IDIBAPS, University of Barcelona, Barcelona, Spain
[g] Affiliated to The CIBER Cancer – Instituto de Salud Carlos III, Madrid, Spain

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ABSTRACT

Colorectal cancer (CRC) is characterized by alteration of critical pathways such *TP53* inactivation, *BRAF, PI3CA* mutations, *APC* inactivation, *KRAS, TGF-β, CTNNB* mutations, disregulation of Epithelial to mesnechymal transition (EMT) genes, *WNT* signaling activation, *MYC* amplification, and others. Differences in these molecular events results in differences in phenotypic characteristics of CRC, that have been studied and classified by different models of molecular subtypes. It could have potential applications to prognosis, but also to therapeutical approaches of the CRC patients. We review and summarized the different molecular classifications and try to clarify their clinical and therapeutical relevance.

1. Introduction

Colorectal cancer (CRC) is the second most common cancer in Europe, with an estimated overall incidence of 447 per 100 000

* Corresponding author at: Medical Oncology Department, La Paz University Hospital, Paseo de la Castellana 261, 28046, Madrid, Spain.
E-mail address: nuria.rodriguez@salud.madrid.org (N. Rodriguez-Salas).

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(Arnold et al., 2015). Most CRCs are sporadic, fewer than 5% of cases occur in patients with inherited predisposition syndromes, although 20%–30% of cases might have a familial predisposition despite the absence of a known germ-line defect. CRC is the second leading cause of cancer death in Europe after lung cancer, even when screening programs and new treatments for the adjuvant and metastatic disease have reduced mortality in the last decade (Holleczek et al., 2015).

CRC is diagnosed at an advanced stage in near 20–30% of patients, and relapse occurs in 40–50% of those diagnosed in early stages. In the last decade the use of different schedules of chemotherapies (oxaliplatin, irinotecan and fluoropyrimidine) combined with targeted biologic therapies (bevacizumab and cetuximab or panitumumab) has considerably improved the median overall survival (OS) for patients with metastatic CRC (mCRC). Nevertheless, the majority of patients with mCRC progress to initial treatment and have to receive second and third line treatments, resulting in a 5-year survival of less than 10%.

Clasically, CRC has been classified by its clinopathological characteristics, but despite similar histologic features and tumor stage, clinical outcomes and drug response are heterogeneous (Souglakos et al., 2009). These differences may be only partly explained by the CRC-initiating molecular events like microsatelite instability (MSI), *RAS* and *BRAF* mutations. MSI (Microsatellite Instability) and the mutational status of *RAS* and *BRAF* help guide clinical management. Both the TNM stage, and in the presence of MSI (Ribic et al., 2003; Popat et al., 2005) inform the administration of adjuvant therapy, and the mutational status of *K/N-RAS* guide the administration of anti-EGFR (anti-Epidermal Growth Factor Receptor) drugs in mCRC. *BRAF* adds prognostic information, but its value in predicting anti-EGFR therapy resistance is unclear (Di Nicolantonio et al., 2008). Nevertheless, these biomarkers do not reflect the complexity of tumor heterogeneity and are not useful for treatment individualization. In fact, the response rate to anti-EGFR monotherapy in *RAS-Wild Type* (WT) patients ranges between 20 and 30%. Other potential biomarkers such us *EGFR* polymorphisms, the number of copies of this receptor, or other antiangiogenesis potential biomarkers such epiregulin, amphiregulin, and mutations of *BRAF, PI3KCA* or *PTEN*, VEGF-isoforms (Vascular Endothelial Growth Factor isoforms), VEGFR-1/VEGFR-2 (Vascular Endothelial Growth Factor Receptor 1 and 2) expression, microvessel density, or circulating endothelial cells (Jayson et al., 2016; Custodio et al., 2013), have not been incorporated into clinical practice due to unconclusive results.

Here we review the current knowledge about the most important issues in molecular characteristics of CRC and the proposed classifications in molecular subtypes with the objective of translate it to clinical practice and treatment selection.

2. Molecular basis of colorectal cancer

CRC is a heterogeneous disease in terms of its clinical manifestations, molecular characteristics, sensitivity to treatments and prognosis. CRCs arise invariably from benign precursor polyps and show a progressive stepwise accumulation of genetic and epigenetic changes that are the main forces for tumor development. The molecular changes associated to tumor progession in CRC are primarily attributable to genomic instability, that enables the accumulation of somatic aberrations, and can act through three major pathways: microsatellite instability (MSI) (Ionov et al., 1993), chromosomal instability (CIN) and CpG island methylator phenotype (CIMP) (Pino and Chung, 2010). These changes may occur, either individually or in combination, resulting in the growth of tumors with different clinical and pathological features (Bardi et al., 2004).

Epigenetic mechanisms maybe as significant as gene mutations in cancer but are less well understood. Various covalent histone modifications and methylation of cytosine residues in DNA represent prominent modes of gene regulation (Plass et al., 2013). CRC shows 8%–15% lower total DNA methylation than normal tissue (Goelz et al., 1985), even in precursor adenomas (Feinberg et al., 1988). The most studied epigenetic events in the CRC are CpG island methylation and histone modifications, although there are other different ways that also contribute to epigenetic modifications, such as nucleosomal occupancy and remodeling, chromatin looping, and noncoding RNAs expression. A distinct subset of CRCs shows coordinate hypermethylation of many CpG-rich promoters, conferring the CpG island methylator phenotype (CIMP), with transcriptional attenuation of tumor suppressor genes.

Other factors that contribute to tumor heterogeneity are the order in which mutations appear, genetic polymorphisms, the polyclonal composition of the tumor, and the impact of tumor microenvironment (extracellular matrix, suporting stromal cells and immune cells). These interactions depend on the genetic composition of the normal non-neoplastic cells, so the biological behavior of aparently similar tumors, can vary depending on the genetic characteristics of the person on which it develops. In addition, the phenotypic manifestation of these genetic/genomic variations can be modified by external influences such as diet, hormonal changes, comorbidities, etc. It should be noted that a single molecular alteration may not have great clinical significance, but the set of molecular alterations themselves can change the phenotype and the aggressiveness of the tumor (Hanahan and Weinberg, 2011). Finally tumor and microenvironment heterogeneity and diversity in the evolution in CRC may be partly responsible for the differences in responses to treatments (De Smedt et al., 2015).

Extensive investigations have been made about the host immune response against cancer and demonstrated the prognostic impact of the immune cell infiltrate in tumors. A methodology named 'Immunoscore' has been defined to quantify the cancer immune infiltrate in CRC. This score has been demonstrated to be a prognostic factor superior to the AJCC/UICC TNM classification. Evaluation of lymphocyte populations with antitumour immune responses (CD3, CD8 and CD45RO), both in the core of the tumor and in the invasive margin of tumors, are a clinically useful prognostic marker in colorectal cancer limited or extensive disease (Galon et al., 2014, 2016).

3. Critical pathways in colorectal tumorigenesis

Most investigators divide CRC biologically into those with microsatellite instability (MSI; located primarily in the right colon and frequently associated with the CpG island methylator phenotype (CIMP) and hyper-mutation), and those that are microsatellite stable but chromosomally unstable, also called non-hypermutated tumors. Together they show common alteration of critical pathways. These include *TP53, BRAF, PI3CA* and *APC* inactivation, *KRAS, TGF-β*, *CTNNB,* Epithelial-to-mesnechymal transition (EMT) genes and *WNT*-signaling activation, *MYC* amplification, and others (Cancer Genome Atlas Network, 2012). (Fig. 5). This molecular events allows loss of control of cell growth, increases cell- proliferation and cell-survival, inhibits apoptosis, disturbs control of cell methabolism, promotes invasion, promotes epithelial to mesenquimal-transition, angiogenesis, alters the relationship with environment and the inmune-system, promotes intestinal-crypt disorganization, etc.

Ras-family G-proteins transduce growth factor signals and are aberrantly activated in a wide variety of cancers. *KRAS* is mutated in about 40% of CRC (Bos et al., 1987) and *NRAS* in 5%–8%. Mutations in both genes cluster in codons 12 or 13, and less frequently at