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## EDITORIAL

# Colorectal cancer: From the laboratory to the patient, a now indispensable step<sup>☆</sup>



## Cáncer colorrectal: del laboratorio al paciente, un paso ya imprescindible

Colorectal cancer is the third most common cancer in men and the second in women worldwide, whereas gastric cancer is the fourth most frequent cancer in men and the fifth in women.<sup>1</sup> In both cases, the differences in incidence among diverse geographic areas are very substantial and are clearly associated with dietary and environmental factors. Different Latin American registries show colorectal cancer incidence to be below that of other regions, particularly in the more developed countries.<sup>2</sup> Unfortunately, whereas the incidence of this cancer is decreasing in the Western world, Latin American countries have registered significant increases in colorectal cancer mortality rates within the last few years.<sup>2</sup> The incidence of gastric cancer is particularly elevated in some Latin American countries, such as Chile or Costa Rica, but it is much lower in other regions, such as Mexico or Puerto Rico;<sup>3</sup> *Helicobacter pylori* infection rates and tobacco consumption have been determinants for explaining the majority of these differences. Fortunately, the incidence of gastric cancer is progressively decreasing in Latin America, as in many other parts of the world.

Much has been learned in recent years about the molecular mechanisms involved in the carcinogenic processes of these tumors. This is of the utmost importance, given that such knowledge is revolutionizing therapeutic approaches, enabling targeted treatments that are more efficacious in determined groups of cancers with specific alterations in some pathways instead of others the so-called precision medicine.

Colorectal cancer develops through a process of numerous stages, known as the adenoma-carcinoma sequence, proposed by Fearon and Vogelstein more than two decades ago.<sup>4</sup> During this process, genetic and epigenetic alterations accumulate in genes that are crucial for controlling cell

growth and differentiation. Genomic instability is characteristic of colorectal cancer and affects the entire genome, implying the loss of DNA integrity, which accelerates the process of mutation accumulation. This instability can be chromosomal (CIN) or involve microsatellites (MSI). Tumors with CIN are the most common and present with loss of heterozygosity, frequent cytogenetic alterations, and allelic loss.<sup>5</sup> This process is known as the suppressor pathway of colorectal cancer. Tumors that present with CIN also show inactivation of oncosuppressor genes such as *APC*, *p53*, *DCC*, *SMAD2*, and *SMAD4*. However, the genes that enable this instability are not yet well established. Tumors with MSI develop as a result of the disruption of the DNA mismatch repair (MMR) system. The function of the proteins encoded by the genes of this system (*MLH1*, *MSH2*, *MSH3*, *MSH6*, *PMS2*) is to repair the mismatches between bases that are habitually and periodically produced during DNA replication.<sup>6</sup> When these genes do not function, mutations accumulate along the genome, especially in repetitive nucleotide sequences known as microsatellites. They are located in non-encoding regions and also in gene-coding sequences such as *IGFR2*, *TGFβR2*, *BAX*, or *MSH6* that control important cell mechanisms. In the large majority of cases, the presence of MSI is due to hypermethylation of the *MLH1* promoter gene with the subsequent inactivation of gene transcription and the loss of protein expression.<sup>7</sup> *MLH1* methylation alteration is one of the most solid proves of the involvement of an epigenetic defect in the development of CRC and is responsible for 80% of the cases of MSI.

The use of molecular alterations for guiding chemotherapeutic treatments is now a reality. For example, the epithelial growth factor receptor (EGFR) inhibitor cetuximab is only indicated in the treatment of CRC in patients that do not have tumors with *K-Ras* mutations, because these mutations prevent the drug from responding. In addition, the use of epigenetic targets for developing new chemotherapy treatments is emerging as a strategy with great possibilities, because in principle, epigenetic alterations are potentially

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reversible. Thus the drug would revert the genetic repression of oncosuppressor genes. The most widely studied of these drugs are the demethylating agents that inactivate the DNA methyltransferases (DNMTs). The two DNMT inhibitors, azacitidine and decitabine, are currently approved by the U.S. Food and Drug Administration for use in patients with hematologic diseases, and their use in different cancers, including colon cancer, is being evaluated.

The capacity to systematically evaluate these types of molecular alterations in tumors and progressively incorporate them into the medical routine is of great importance for appropriate patient attention. The study of these mutations has special relevance in the case of cancers diagnosed in Latin America, not only for the importance of the above-mentioned, but also because there is a total absence of molecular data from patients of this region. It is extremely gratifying to finally have contributions such as those of Palacio-Rúa et al. in this edition of the Journal. The authors examined 59 gastric and colorectal tumors for the most commonly described mutations of the *APC*, *p53*, and *KRAS* genes. The number of mutations found was relatively lower than that reported in case series from other areas of the world, which may be due to the fact that the study was limited to the *APC* and *p53* gene regions that usually house the majority of pathogenic mutations. Thus, it cannot be ruled out that some mutations were not detected because they were outside of these regions, but it is also possible, as the authors pointed out, that there is a differential incidence that can depend on many factors that have yet to be identified. At any rate, this study not only confirms the ability to conduct this type of analysis in Latin America, but it also paves the way for a future study with a higher number of cases and expanded coverage of gene regions that will undoubtedly be of tremendous value. The present work already helps to create awareness of the importance of these studies, given

that they have direct implications in the choice of drugs to be used in treating these cancers.<sup>8</sup>

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X. Llor  
*Medical Director, Colorectal Cancer Prevention Program,  
 Co-Director Cancer Genetics and Prevention Program, Yale  
 University School of Medicine, Section of Digestive  
 Diseases Department of Internal Medicine  
 E-mail address: Xavier.llor@yale.edu*