Classification of Colorectal Cancer Based on Molecular Features

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Editorial

Colorectal cancer (CRC) is a major cause for morbidity and mortality worldwide; it is the fourth most common cancer in men and the third most common cancer in women [1]. CRC is divided into three categories: hereditary, nonhereditary and familial [2,3]. Approximately 15% of CRC cases are considered as a hereditary form which most common contains: Familial adenomatous polyposis (FAP) and hereditary non polyposis colorectal cancer (HNPCC) and MYH-associated polyposis (MAP) [4,5]. CRC develops through multiple pathways leading to DNA repair mechanisms. These pathways can be defined on molecular features: 1) chromosomal instability (CIN), Microsatellite instability (MSI) and CpG island methylator phenotype (CIMP) [6], CIN, or classic adenoma-to-carcinoma pathway, account 65-70% of sporadic CRC, is characterized by an imbalance in chromosome number (aneuploidy), chromosomal genomic amplification, and high frequency of LOH, which has been determined through a series of mutations in tumor suppressor genes or oncogenes, in some pathways including: WNT/APC/B-CAT, RAS, PI3KCA pathway. 18q LOH where the genes Smad2, Smad4 and DCC are located and also loss of 8p and 5q allele correlated with CIN pathway [7-10]. Recently, mentioned hypomethylation of LINE-1 is also associated with the CIN pathway [11]. CIN-positive tumors are generally associated with poor prognosis, distally located and tend to be well- or moderately differentiated [12]. MSI is observed in 15% of CRCs and also most of these tumors are sporadic which is caused by deletion of the DNA Mismatch Repair (MMR) system containing MLH1, PMS2, MSH6, or MSH2 genes. MSI status grouped as: MSI high (MSI-H), MSI low (MSI-L) and MSI stable (MSI-S). MSI tumors present particular clinical features: proximal located, poorly differentiated and intratumoral lymphocytic infiltration and oen presents intense peritumoral invasion and adhesion. It is found in approximately 20-30% of CRC [7]. Clinical features of CIMP CRCs are similar to those associated with MSI [16]. Ogino et al. suggested using eight markers (CACNA1G, p16CDKN2A, CRABP1, IGF2, hMLH1, NEUROG1, RUNX3, and SOCS1) to classify CEC subgroups if 1 to 5 out of 8 markers methylated known as CIMP-low, when none of each markers methylated means CIMP-0, and 6 to 8 out of 8 markers have promoters methylated are - CIMP-high[16]. Hese three CRC pathways are not mutually exclusive, with some tumors exhibiting features of more than one pathway [10]. Based on, simultaneous presence of multiple pathways in tumors, there are five molecular CRC subtypes, with DNA repair mechanisms: 1) CIMP high, MLH1 methylation, MSI high, Braf mutation; (account for 12% of CRC). 2) CIMP high, BRAF mutation, methylation of multiple genes, MSI low or microsatellite stable; (8%). 3) CIMP negative, K-ras mutation, MGMT methylation, CIN, MSI low or microsatellite stable; (20%). 4) CIMP negative, CIN, microsatellite stable; (57%). 5) CIMP negative, MSI high; negative for BRAF mutations (HNPCC) [10]. In conclusion, Molecular classification of CRC is suitable for better understanding of mechanism involved in initiation and development of CRC. Since CRC subtypes have distinct prognosis, chemosensitivity and different survival, these classification can provide a better guide for patient stratification in order to ultimately personalized medicine to improve effective treatments.

References


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