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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 MYHAssociated polyposis (MAP) [4,5]. CRC develops through multiple pathways leading to dLٔerent phenotypes. Hese pathways may 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 amplLficatLons, and a 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, P53, 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 dLٔerentLated [12]. MSI is observed in 15% of CRCs and also most of these tumors are sporadic which is caused by defection of the DNA Mismatch Repair (MMR) system containing MLH1, PMS2, MSH6, or MSH2 genes. MSI status grouped as: MSI high (MSI-H), MSI low (MSL-L) and MS stable (MSS). MSI tumors present particular clinical features: proximal located, poorly dLٔerentLated a mucinous or medullary histotype and oien presents intense peritumoral and intratumoral lymphocytic LnfiltratLons [13,14]. MSI-high CRC does not respond to -fluorourac\l-based chemotherapies and frequently harbor the BRAF V600E mutation [13,15]. More than 80% of MSI-CRC harbor mutations of the TGF-β Receptor II (TGF-βRII) [15]. In general, the prognosisand survival of MSI-high CRC patients is better than CIN positive CRC patients [14]. He last pathway is characterized by epigenetic alterations, resulting in aberrant hypermethylation of CpG dinucleotide sequences located in the promoter regions of genes involved in cell cycle regulation, apoptosis, angiogenesis, DNA repair, 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 classLficatLon CRC 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 methyled 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 dLٔerent molecular profile and clinicpathological features including: 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 classLficatLons can provide a better guide for patient stratLficatLon in order to ultimately personalized medicine to improve effective treatments.

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