Circulating Biomarkers of Colorectal Cancer

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Colorectal cancer (CRC) is one of the most common neoplasms worldwide. It is the second most frequently diagnosed malignancy in women and third in men. It is estimated that more than one million people worldwide develop CRC every year. In addition, this carcinoma is the second leading cause of cancer death in Europe, ranking fourth in males and third in females.

Keywords: biomarker ; colorectal cancer ; tumor

1. Introduction

The challenges facing medicine in the future lie in the establishment of new diagnostic strategies based on novel and accurate tumor biomarkers that will improve the early detection of malignant diseases, such as CRC, and facilitate differentiation between CRC and CA. A growing number of publications focus on the molecular and cellular mechanisms involved in the development, progression and metastasis of this malignancy. The design of epigenetic and genetic panels of biomarkers useful in CRC diagnosis constitutes a reasonable strategy in the clinical management of CRC [1][2][3]. There are three main mechanisms that are currently considered to be responsible for CRC pathogenesis. The first one is the suppressor pathway, or the pathway of chromosomal instability, which is associated with the accumulation of mutations leading to oncogene activation (*KRAS*) and suppressor gene inactivation (*TP53, DCC, SMAD4, APC*), and consequently to neoplastic transformation [4][5]. The second pathway is the accumulation of errors during DNA replication due to the presence of mutations in the genes responsible for its repair (*MLH1, MSH2, MSH6, PMS2, MLH3, MSH3, PMS1* and *Exo1*) [6]. The third mechanism is related to aberrant hypermethylation [7].

Many recent reports have focused on *RAS*, *BRAF* (Raf murine sarcoma viral oncogene homolog B) and *HER2* (human epidermal growth factor receptor 2 gene) mutations as predictive factors of mCRC patients who receive chemotherapy [8][9]. A study by Zheng investigated the frequency and prognostic role of *HER2* and *BRAF* gene mutations in CRC patients. The authors concluded that *HER2* amplification significantly correlates with greater bowel wall invasion and a more advanced TNM stage, while *HER2* amplification is an independent prognostic factor for worse disease-free survival [8]. Moreover, a statistically significant correlation for the RAS mutation and overall survival was also proved, whereas RAS mutation and liver metastasis were found to be independent factors for shorter overall survival of CRC patients in multivariate analysis [9].

A greater understanding of the pathways involved in CRC development will facilitate the establishment of diagnostic and prognostic biomarkers for this malignancy. In recent years, DNA and RNA markers in blood have been investigated as a potential diagnostic tool in CRC. It has been indicated that the analysis of biomarkers, such as DNA, RNA or proteins in the blood, accelerates the development of diagnostic tools in molecular biology. These techniques are characterized by greater sensitivity and enhanced cost-effectiveness, and may be employed in clinical practice [1].

2. DNA-Based Biomarkers

A variety of DNA markers have been assessed in plasma, including *APC, KRAS, p53, MLH1, HLTF, TMEF2, NGFR*, and *SEPT9* [1]. A study by Diehl et al., which utilized the detection of mutations by beads, emulsification, amplification and magnetics (BEAMing) assay, found that APC mutations in plasma samples were detected with a sensitivity of 73%, which, however, was limited to 9% in patients with CA [10]. Furthermore, some authors have demonstrated that the hypermethylation of *Septine 9* (guanosine triphosphatase class gene) is related to CRC development [11][12] and is found in 58–96% of CRC patients, and in only 18% of CA subjects with specificities of 86–100% [11][12][13][14].

3. RNA-Based Biomarkers

Some clinical investigations have revealed that the transcriptome of plasma and peripheral blood also offers potential diagnostic biomarkers [15][16]. A plasma biomarker panel including *BANK1, BCNP1, CDA, MGC20553* and *MS4A1* may discriminate patients with CRC from healthy subjects with a sensitivity and specificity of 88% and 64%, respectively [15][16]. Other molecular biomarkers provide a source of miRNAs [17][18][19]. Elevated miR92 levels have been detected in the plasma of patients with CRC compared with healthy individuals [20]. Moreover, statistically higher levels of miR92a and miR29a have been found in patients with CRC and CA in comparison to healthy controls [21].

4. Plasma Proteins

The development of new technologies in proteomics, such as chromatographic techniques based on mass spectrometry (MS) assays, surface-enhanced laser desorption/ionization time-of-flight (SELDI-TOF)-MS, and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) MS, allows for the identification of large-scale protein patterns. These methods allow for the identification of peptide patterns that discriminate patients with CRC from healthy individuals with a sensitivity and specificity of 90% [22]. However, they are not specific to CRC [23]. Some authors have evaluated the significance of epithelial cell adhesion molecules, p53, p62, CEA, HER-2/neu, Ras, topoisomerase Ⅱ-alpha, histone deacetylase 3 and 5, ubiquitin L3, tyrosinase, tropomyosin, and cyclin B1 as biomarkers for CRC. These stable biomarkers can be detected by immunoassays and are absent in healthy individuals, and therefore might be promising biomarkers for further research [1][24][25][26]. Moreover, some clinical investigations have assessed the combined ELISA analysis of MAPKAPK3 and ACVR2B in patients with CRC and healthy controls, with a sensitivity of 83% and a specificity of 74% [25][27].

Although there is still insufficient evidence supporting the use of biomarkers, such as genetic and epigenetic biomarker panels in CRC diagnosis, it appears to be a reasonable strategy for the medicine of the future [1]. However, what should also be taken into consideration is that CRC cells are able to enter blood via blood vessel invasion, where they circulate and release detectable biomarkers in the plasma or circulating phagocytes. Furthermore, such vessel invasion occurs more frequently in the advanced stages of CRC [28][29][30].

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