MicroRNA-21 in Colorectal Cancer: “Just Another Brick in the Wall”?  

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MicroRNAs (miRNAs)—small, noncoding RNA strands consisting of 18 to 25 base pairs—have been investigated extensively during the last decade. Initially seen as superfluous material, it has become clear that they play a critical role in translational and posttranscriptional regulation of protein processing. In cancer cells those processes are altered and cancer cells therefore display an irregular miRNA configuration. Many solid tumors have specific patterns of miRNA expression levels, which are used in several commercially available, and, in some cases, Food and Drug Administration approved, diagnostic tests. It is possible to determine tumor origin and, in part, the histologic subtype of solid tumors by its miRNA signature. Evaluating miRNA in tissue and body fluids is therefore an emerging field of biomarker development. MicroRNA 21 (miR-21) is found to be upregulated in a wide range of solid tumors including lung, breast, gastric, colon, and glioblastoma (1), and therefore as a single marker is not specific for colon cancer. Its reported RNA targets include transforming growth factor β (TGF-β), phosphatase and tensin homolog (PTEN), programmed cell death protein 4 (PDCD4), protein sprouty 1 (Spry-1), phosphatase of regenerating liver 3 (PRL-3), and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-xB). Therefore, miR-21 may be involved in the modulation of critical steps in carcinogenesis such as proliferation, apoptosis, and migration (2). It has further been shown that colon cancer cell lines with higher expression levels of miR-21 have an enhanced ability of motility and invasion (3). Slaby and others demonstrated that tissue miR-21 expression is rising with higher Union for International Cancer Control stage (4,5) and therefore represents a marker for clinicopathologic features of the disease. First data have been published to state a role of miR-21 in chemoresistance to gemcitabine in cholangiocellular cancer cell lines (6) and 5-fluorouracil in colon cancer cells (7). Higher miR-21 tissue levels could further be linked to a decreased pathologic tumor response in patients treated with FOLFOX in a neoadjuvant setting for locally advanced colorectal cancer (CRC) (8). Owing to its capability to be secreted by cancer cells, miR-21 has been the first miRNA to be detected in the plasma in patients with diffuse large B-cell lymphoma in 2008 (9). These specifics taken together, miR-21 represents an almost ideal candidate for a diagnostic tool in the diagnosis and treatment monitoring of CRC.

The article by Toiyama et al. (10) in this issue of the Journal confirms previous data showing that miR-21 serum levels are higher in patients with CRC than in healthy controls (2,11). The authors showed that miR-21 levels increased with the stage of CRC. They suggested that miR-21 levels in the serum may be a useful diagnostic tool. MiR-21 serum levels were measured in 186 patients with CRC, 43 patients with advanced adenomas, and 53 healthy controls. The authors showed that miR-21 serum levels were statistically significantly higher in patients presenting with advanced adenomas or CRC compared to healthy controls. A differentiation between advanced adenomas and CRC was not achieved. Within the cohort of patients with CRC, serum levels of miR-21 were statistically significantly higher in metastatic (stage IV) disease than in stage I and II disease. Using a cutoff value determined by the receiver operating characteristic procedure, miR-21 levels had diagnostic and prognostic value. This association remained statistically significant after multivariate analysis adjusting for age, sex, TNM stage, lymph node metastasis, carcinoembryonic antigen level, distant metastasis, and pathologic differentiation.

Several questions remain about the clinical use of miR-21 as a biomarker for CRC. All published miRNA data have been generated from retrospective analyses; therefore, prospective testing in independent control studies is critical for validation. Those studies should further evaluate whether miR-21 can serve as a prognostic or predictive marker in patients with CRC. It is essential to establish standardized techniques to measure serum miRNA levels. The authors tried to address this problem by adding a certain amount of Caenorhabditis elegans miR-39 to a predefined volume of each serum probe, but polymerase chain reaction efficacy of different primer pairs may influence the measurements and the cutoff values. Using miRNA levels derived from tissue specimens, the problem of stromal cell contamination needs to be addressed by microdissection. MiR-21 is also secreted by mucosal cells and in inflammatory bowel disease has been shown to rise with the grade of inflammation (12). The exact mechanism of how miR-21 is involved in carcinogenesis and tumor progression remains unknown. It can be speculated that miR-21 serum levels are elevated in colon cancer as a sign of the inflammatory process of the adjacent healthy tissue. If miR-21 is a confirmed and validated prognostic marker and its mechanism of action in tumorigenesis has been further elucidated, it might even be a druggable target. MiR-21 as a single marker may not be the only useful marker. Other miRNA serum levels such as miR-141 (13) or miR-601 and miR760 (14) have also shown to be of prognostic or diagnostic value. Therefore, it is more likely...
that a miRNA signature has a higher sensitivity and specificity as a biomarker for colorectal cancer. To validate miRNA, the impact of tumor location and the different subtypes of colorectal cancer, such as MIN (microsatellite instability), CIN (chromosomal instability), and CIMP (CpG island methylator phenotype) on miR-21 serum levels need to be tested. For clinicians, it would be of further interest to understand the advantage of using miR-21 as a serum biomarker in the diagnosis and treatment monitoring of CRC in comparison to clinically used protein-based markers such as carcinoembryonic antigen (15). The clinical need to identify patients at high risk for recurrence in stage II disease and to monitor tumor response in stage IV disease should be addressed.

MiR-21 may not be “just another brick in the wall” but rather may be the keystone leading to a molecularly justified, miRNA-based, biomarker era in colorectal cancer.

References

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