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REVIEW PAPER

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The role of new biomarkers for the diagnosis and treatment of colon cancer

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ABSTRACT

Introduction. Colorectal cancer may be benign or malignant. According to the World Health Organization and CDC, it is the second most common cancer worldwide, after lung cancer. The mortality of colorectal cancer has been dropping for more than 20 years due to the improvements in screening techniques and treatments.

Aim. The aim of this article is to discuss the role of new biomarkers for the diagnosis and treatment of colon cancer.

Material and methods. This article is a review done in regards to discuss the role of new biomarkers for the diagnosis and treatment of colon cancer.

Analysis of the literature. A review is discussed the role of new biomarkers for the diagnosis and treatment of colon cancer using current literature.

Conclusion. The screening tests based on diagnostic new biomarkers may cause faster detection of cancer and risk factors, and provide prognostic information in order to adjust individual therapy.

Keywords. colon cancer, diagnosis, treatment

Introduction

Nowadays colon cancer takes a third position among neoplastic disease in the USA. The overall 5-year survival rate is approximately 65%, higher for localized disease (90%) than metastatic disease (14%).[1] Morbidity is predicted to increase in incidence by 60% by 2030.[2] American Cancer Society recommend commencement screening for all average-risk adults at 45 years old. Family history, other cancers, and advanced colon polyps are strong risk factors that must take into account earlier diagnostic.[3] Conventional colonoscopy contains about 25% of false-negative results.[4] Colorectal carcinogenesis is long-term process. Tumor arise from adenomatous polyps that gradually progress to dysplasia and eventually to carcinoma about 5-15 years.[5] By auto- and paracrine secretion of cytokines, chemokines, proteins

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and growth factors, cells create optimal conditions for progression and act as a suppressor on immune mechanisms. Thus, in order to assess the cause of expansive tumor growth and spread, it is necessary to determine cancer biomarkers, which are a more sensitive marker than traditional clinical-histopathological grading.[6,7]

Aim

We investigated the feasibility of an increase in research towards the better understanding of the role of new biomarkers for the diagnosis and treatment of colon cancer.

Material and methods

All materials are based on data base such as Pubmed, Science Direct and Medline.

Analysis of literature

NAA10

NAA10 is a orthologous gene of arrest-defective 1 (ARD1), which was first identified in *Saccharomyces cerevisiae* 30 years ago. NAA10 is located on chromosome Xq28 and composed of eight exons, protein consists of 235 amino acid in humans.[8] Ren et al. proved increased mRNA and protein expressions of NAA10 in colon cancer. Also Jiang et al. and Yang et al. reported high expression levels of NAA10 in patients with this tumor, which might suggest the potential role of NAA10 as a prognostic biomarker for colon cancer. Moreover Jiang group demonstrated that, of 106 patients with high level of NAA10, 74 died of cancer.[9] The NAA10 analysis also concerned other, neoplasms such as breast, lung and bone cancer.[10]

Transmembrane 4 L six family 1 (TM4SF1)

Transmembrane 4 L six family 1 (L6-Ag, TAL6, L6) and was a highly expressed surface protein of colon, lung, breast tumors. human lung, breast, colon, and ovarian carcinomas, discovered in the 90s. The TM4SF1 gene is located on chromosome 3. Many studies have shown that TM4SF1 plays an indispensable role in promoting cancer cell proliferation and migration through a series of signaling pathways.[11] Otsuka et al. proved that TM4SF1 expression was higher in metastatic cancer-derived tumors than in primary tumor-derived cells from a single colorectal cancer patient.[12] Park et al. found that TM4SF1 was upregulated in colon cancer tissues and cell lines and was positively correlated with lymph node metastases.[13]

S100 protein

All chemokines, chemokines and growth factors, demonstrating pleiotropic effects, affect almost every stage of the creating and spread of colorectal cancer. S100 is a Ca2 + ion-binding protein, having EF-hand motifs (regulatory domain, hand-domain), a factor involved in the processes of translating changes in Ca2 + ion levels into a specific cellular response by binding to specific proteins - annexin, a cytosolic phospholipase A2, endoplasmic reticulum proteins and myosin.[14] Many proteins of the S100 family have been identified, which are involved in growth and progression (S100Ab and S100A9). S100A1B and S100BB are present in melanoma, thyroid cancer, clear cell kidney cancer and colon diseases.[15] The expression is low in benign polyps while the S100 increases in the inflammatory tissue from which the tumor grows.[16] Scientist proved that S100 secretion in colon cancer positively correlates with the clinical stage of the disease, progression, metastasis effect and evidence of early or late relapse. Zeng et al. showed a high S100A10 levels was associated with advanced-stage colon cancer. Also noticed that high expression of S100A1 was correlated with poorer overall survival and disease-free survival and that overexpression of S100A2 and S100A11 was associated with weak colon cancer disease-free survival, indicating that S100A1, S100A2 and S100A11 are potential prognostic markers.[17]

Cyclin A2

Cyclins are proteins that regulate the cell division cycle by binding and activating cyclin-dependent kinases. Cyclin A2 is an established regulator of cell proliferation and has been used for molecular diagnostics as a proliferation marker. A number of studies have investigated the role of cyclin A2 on cancer development in vitro and in vivo. Guo et al. generated mice deficient for cyclin A2 in colonic epithelial cells. Colons of these animals showed severe inflammation and mucosal remodeling leading to low- and high-grade dysplasia. In result cyclin A2 deletion promoted the development of dysplasia and adenocarcinomas in a murine colitis-associated cancer model. Adenocarcinomas were only detectable in cyclin A2–deleted mice, but not in controls. In next steps researchers explored the status of cyclin A2 expression in clinical samples at the mRNA and protein levels and found higher expression in tumors of patients with stage 1 or 2 compared with those of patients with stage 3 or 4 colon cancer. High *level of cyclin 2* is associated with a better prognosis in patients. Based on the analysis, a conclusion can be drawn that cyclin A2 is a candidate for a prognostic marker for cancer.[18] Li et al. proved that cyclin A2 and Cyclin B1 were also expressed higher in adenocarcinoma t. Cyclin genes were highly related to the drug sensitivity of some drugs, which might provide guidance for clinical treatment. In conclusion, cyclin genes are new a and unusually promising biomarkers for the diagnosis and prognosis of colon cancer.[19]

IL-6

It has also been shown that IL-6 plays a key role in the development of tissue neoplasms due to their chronic

inflammation, being the basic link between inflammation and carcinogenesis with TNF-α and the nuclear factor NF-κB.[20,21] A strong release of IL-6 occurs in cases of uterine, lung, colorectal, kidney, breast, pancreatic and ovarian cancer.[22,23] The correlation between the concentration of this cytokine has been proven, and unfavorable prognosis - serum levels increase in proportion to the cancer stage, malignancy and tumor mass, and is also associated with shorter survival times.[24,25] The relationship of IL-6 with colorectal cancer has also been demonstrated, in which the concentration of this cytokine increases with the stage of advancement, low cell differentiation as well as tumor infiltration and progression, correlating with the concentration of the carcinoembryonic antigen CEA.[26] and with the survival time of patients.[27] Recent studies have reported an increase in interleukin-6 (IL-6) and soluble interleukin-6 receptor (sIL-6R) levels in the sera of patients affected by colon cancer that correlate with the tumor size, suggesting a potential role for IL-6 in colon cancer progression.

NAP1L1

Qeiroz et al. and Aydin et al. utility of nucleosome assembly protein 1-like 1 (NAP1L1), in animal models and colon cancer patients. Adenomatous polyposis coli (*APC*) inactivating mutations are the earliest and most common genetic alterations in the colon cancer. Queiroz et al. of analyzed mouse models of *Apc* deletion and tried to discover new colon cancer biomarkers. Scientist decided to research Nap1L1 expression in Apc deficient mice. *NAP1L1* expression is increased in the mouse small intestine following *Apc* inactivation and its expression is also altered in human with colon cancer and correlated with overall survival in a patient.[28] Aydin et al. conducted research on 95 patients with colon cancer and 50 healthy people. Serum NAP1L1 levels were higher in colon cancer patients as compared with control. This makes a NAP1L1 promising biomarker in the diagnosis and prognosis of colorectal cancer.[29]

MUC1

The normal surface of the colon is lined with various types of mucins, secreted by specialized epithelial cells that protect the lining of the epithelium against pathogens. Some mucins, such as MUC1 and MUC13, act as oncogenes, whereas others: MUC2, MUC6 are suppressors.[30] The immunohistochemical analysis of colon cancer tissues from 45 patients revealed positive expression of MUC1 (in 55.6%) and totally negatively of nontumor tissue.[31] In another histopathological study of tissues removed from 381 patients with colon cancer, it was discovered that MUC1 is expressed in 64%.[32] Zhang et al. demonstrated that MUC1 has a pro-tumor role in immune-competent mice.[33]

Conclusion

That predictive and prognostic biomarkers for colon cancer has become a vast and modern field. Widely used carcinoembryonic antigen (CEA) is also observed in inflammatory bowel disease reducing its utility as a single marker for early cancer. Recent advances in molecular technologies have led to the discovery of multiple biomarkers that might facilitate early detection of colorectal lesions.

Declarations

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Author contributions

Conceptualization, A.C.C., D.B.A., A.K.K., D.A., M.K.O., W.L. and G.C.; Formal Analysis, A.C.C., D.B.A., A.K.K., D.A., M.K.O., W.L. and G.C.; Writing – Review & Editing, A.C.C., D.B.A., G.C., D.A., M.K.O., W.L. and A.K.K.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Dilly CK, Craven HJ, Molleston JP. Perspectives on Colon Cancer Screening-A Physician Panel Discussion for Preclinical Medical Students. *MedEdPORTAL*. 2020;16:11019.
2. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017;66:683-691.
3. Screening for Colorectal Cancer. Montminy EM, Jang A, Conner M, Karlitz JJ. *Med Clin North Am*. 2020;104(6):1023-1036.
4. Orlando FA, Tan D, Baltodano JD, Khoury T, Gibbs JF, Hassid VJ, Ahmed BH, Alrawi SJ. Aberrant crypt foci as precursors in colorectal cancer progression. *J Surg Oncol*. 2008; 98:207-213.
5. Chakrabarti S, Peterson CY, Sriram D, Mahipal A. Early stage colon cancer: Current treatment standards, evolving paradigms, and future directions. *World J Gastrointest Oncol*. 2020;12(8):808-832.
6. Keller ET , Wanagat J, Ershler WB. Molecular and cellular biology of interleukin-6 and its receptor. *Front Biosci*. 1996;1:d340-d357.
7. Schellerer VS, Croner RS, Weinländer K, Hohenberger W, Stürzl M, Naschberger E. Endothelial cells of human colorectal cancer and healthy colon reveal phenotypic differences in culture. *Lab Invest*. 2007;87(11):1159-1170.
8. Whiteway M., Szostak J.W. The ARD1 gene of yeast functions in the switch between the mitotic cell cycle and alternative developmental pathways. *Cell*. 1985;43:483-492.
9. Jiang B, Ren T, Dong B, et al. Peptide mimic isolated by autoantibody reveals human arrest defective 1 overexpression is associated with poor prognosis for colon cancer patients. *Am J Pathol*. 2010;177:1095-1103.

10. Kim SM, Ha E, Kim J, Cho C, Shin SJ, Seo JH. NAA10 as a New Prognostic Marker for Cancer Progression. *Int J Mol Sci*. 2020;21(21):8010.
11. Fu F, Yang X, Zheng M, Zhao Q, Zhang K, Li Z, Zhang H, Zhang S. Role of Transmembrane 4 L Six Family 1 in the Development and Progression of Cancer. *Front Mol Biosci*. 2020;7:202.
12. Otsuka M., Kato M., Yoshikawa T., Chen H., Brown E. J., Masuho Y., et al. Differential expression of the L-plastin gene in human colorectal cancer progression and metastasis. *Biochem. Biophys. Res. Commun.* 2001;289:876-881.
13. Park YR, Lee ST, Kim SL, et al. MicroRNA-9 suppresses cell migration and invasion through downregulation of TM4SF1 in colorectal cancer. *Int J Oncol.* 2016;48:2135-2143.
14. Garrett SC, Varney KV, Weber DJ, Bresnick AR. S100A4, a mediator of metastasis *J Biol Chem*. 2006;281(2):677-680.
15. Sherbet GV, Lakshmi MS. S100A4 (MTS1) calcium binding protein in cancer growth, invasion and metastasis *Anticancer Res*. 1998;18(4A):2415-2421.
16. Yasui Y, Tanaka T. Protein expression analysis of inflammation-related colon carcinogenesis. *J Carcinog* . 2009;8:10.
17. Zeng ML, Zhu XJ, Liu J, Shi PC, Kang YL, Lin Z, Cao YP. An Integrated Bioinformatic Analysis of the S100 Gene Family for the Prognosis of Colorectal Cancer. *Biomed Res Int*. 2020;2020:4746929.
18. Guo Y, Gabola M, Lattanzio R, et al. Cyclin A2 maintains colon homeostasis and is a prognostic factor in colorectal cancer. *J Clin Invest*. 2021;131(4):e131517.
19. Li J, Zhou L, Liu Y, Yang L, Jiang D, Li K, Xie S, Wang X, Wang S. Comprehensive Analysis of Cyclin Family Gene Expression in Colon Cancer. *Front Oncol*. 2021;11:674394.
20. Coussens LM , Werb Z Inflammation and cancer. *Nature*. 2002;420(6917):860-867.
21. Balkwill F, Coussens LM. Cancer: an inflammatory link *Nature*. 2003;431(7007):405-406.
22. Bartsch R, Woehrer S, Raderer M, Hejna M. Serum interleukin-6 levels in patients with gastric MALT lymphoma compared to gastric and pancreatic cancer. *Anticancer Res*. 2006;26(4B):3187-90.
23. Zhang GJ , Adachi I. Serum interleukin-6 levels correlate to tumor progression and prognosis in metastatic breast carcinoma Serum interleukin-6 levels in patients with gastric MALT lymphoma compared to gastric and pancreatic cancer *Anticancer Res*. 1999;19(2B):1427-1432.
24. Łukaszewicz M, Mroczko B, Szmitowski M. Znaczenie kliniczne interleukiny 6 (IL-6) jako czynnika rokowniczego w chorobie nowotworowej. *Pol Arch Med Wewn* 2007;117:247-251.
25. Wu CW, Wang SR, Chao MF, Wu TC, Lui WY, P'eng FK, Chi CW. Serum interleukin-6 levels reflect disease status of gastric cancer. *Am J Gastroenterol*. 1996;91(7):1417-1422.
26. Belluco C , Nitti D, Frantz M, Toppan P, Basso D, Plebani M, Lise M, Jessup JM. Interleukin-6 blood level is associated with circulating carcinoembryonic antigen and prognosis in patients with colorectal cancer. *Ann Surg Oncol*. 2000;7(2):133-138.
27. Esfandi F, Ghobadloo SM, Basati G. Interleukin-6 level in patients with colorectal cancer. *Cancer Lett* . 2006;244(1):76-78.
28. Queiroz CJS, Song F, Reed KR, et al. NAP1L1: A Novel Human Colorectal Cancer Biomarker Derived From Animal Models of Apc Inactivation. *Front Oncol*. 2020;10:1565.
29. Aydin MA, Gul G, Kiziltan R, Algul S, Kemik O. Nucleosome assembly protein 1-like 1 (NAP1L1) in colon cancer patients: a potential biomarker with diagnostic and prognostic utility. *Eur Rev Med Pharmacol Sci*. 2020;24(20):10512-10517.
30. Almasmoum H. The Roles of Transmembrane Mucins Located on Chromosome 7q22.1 in Colorectal Cancer.*Cancer Manag Res*. 2021;13:3271-3280.
31. Betge J, Schneider NI, Harbaum L, Pollheimer MJ, Lindtner RA, Kornprat P, et al. . Muc1, MUC2, MUC5AC, and MUC6 in Colorectal Cancer: Expression Profiles and Clinical Significance. *Virchows Arch Int J Pathol*. 2016;469(3):255-265.
32. Manhas J, Bhattacharya A, Argawal S, Gupta B. Characterization of Cancer Stem Cells From Different Grades of Human Colorectal Cancer. *Tumor Biol.* 2016;37(10):14069–14081.
33. Zhang Y, Dong X, Bai L, Shang X, Zeng Y. MUC1-induced immunosuppression in colon cancer can be reversed by blocking the PD1/PDL1 signaling pathway. *Oncol Lett*. 2020;20(6):317.