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Short communication

Novel laboratory biomarkers in colorectal cancer management

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Introduction

Approximately one million patients worldwide are being diagnosed with colorectal cancer (CRC) each year and about 500.000 death cases due to the disease. In the early stages, the disease is asymptomatic and therefore, most patients are being diagnosed at later stage with low survival rates despite the treatment. The possibility for early diagnosis of CRC prompts identification of novel biomarkers with sufficient specificity and sensitivity to be employed for diagnosis and monitoring (Lech et al., 2016). Several laboratory markers have been traditionally used to detect CRC including: carcinoembryonic antigen (CEA), carbohydrate antigen (CA 19-9), C-reactive protein (CRP), tissue polypeptide specific antigen (TPS) and tumor-associated glycoprotein-72 (TAG-72) but none of them has demonstrated efficient sensitivity and specificity so they are primarily employed in monitoring of the disease and the therapeutic effectiveness. Therefore, the aim of our study was to conduct review of the recent published literature of this field and summarize the current and potential status of laboratory analysis in the management of the disease.

Novel biomarkers in CRC management

Recent studies suggest the potential use of hematopoietic growth factors (HGFs) and enzymes for detection and prognosis of CRC. These include stem cell factor (SCF), macrophage-colony stimulating factor (M-CSF), granulocyte-macrophage-colony stimulating factor (GM-CSF), interleukin-3 (IL-3), interleukin-6 (IL-6) and alcohol dehydrogenase (ADH) (Jelski and Mroczko, 2020).

HGFs are involved in the regulation of growth and spread of cancer. HGFs can influence the proliferation of hematopoietic progenitor cells as well as nonhematopoietic cells. Studies have shown that CRC cells express cell surface receptor for HGF and these receptors enable tumor cell proliferation. HGFs can have an effect on cancer tissue in two ways: in an autocrine manner or on supporting tissue and blood vessels to obtain favorable conditions for the development of cancer. Additionally, HGFs may trigger the production of cytokines in normal tumor-associated macrophages (TAM) and endothelial cells and lead to malignant growth. Statistically, most CRC cases have a lethal outcome due to metastatic dissemination, which shows the importance of the potential use of HGFs (Jelski and Mroczko, 2020).

Several studies show increased production of CSFs by tumor cells and increased concentrations of both M-CSF and G-CSF has been reported in CRC patients; the former is considered to be more specific for CRC diagnosis. Furthermore, higher concentrations of M-CSF have been reported in patients with lymph node or distant metastases; thus, they can be used as potential biomarkers for diagnosis and prognosis of CRC (Jelski and Mroczko, 2020).

Insulin-like growth factor binding protein 2 (IGFBP-2) regulates the interaction between insulin-like growth factor ligand and insulin-like growth factor 1 (IGF-1) receptors. There is little available information on the physiological role of IGFBP-2, but several studies suggest an association of elevated serum IGFBP-2 levels with CRC. A study by the Liou's research group showed that elevated concentrations could differentiate healthy controls from patients with CRC or colon polyps. Due to its insufficient specificity and sensitivity, it cannot be used alone for early detection of CRC and colon polyps, but the combination of IGFBP-2 with other biomarkers such as CEA could increase the sensitivity. (Jelski and Mroczko, 2020; Oh and Joo, 2020).

TNF-α, as a potent mediator in the inflammatory process, plays an important role in cell growth, differentiation and apoptosis, which may affect

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carcinogenesis. Several mechanisms of its involvement have been proposed including oncogene activation, DNA damage and tumor metastases. Due to the association of inflammation and cancer, TNF-α may play an important role in the process of carcinogenesis. In addition to its action as a pro-inflammatory cytokine, TNF-α can also lead to tumor development and therefore it can be considered a potential biomarker (Min et al., 2014; Obeed et al., 2014).

IL-6 is a pleiotropic proinflammatory cytokine that promotes apoptosis of neoplastic cells by stimulating macrophages. On the other hand, its secretion by cancer cells can stimulate neoangiogenesis (Jelski and Mroczko, 2020; Min et al., 2014). Elevated CRP concentrations in CRC patients are the result of stimulated production of acute phase proteins by IL-6; therefore CRP and IL-6 concentrations can be used in multimarker panels for CRC diagnosis. CRP and IL-6 concentrations are dramatically increased in patients with lymph node and distant metastases which justifies their potential use as biomarkers for prognosis of CRC (Łukaszewicz-Zając and Mroczko, 2021).

Alcohol dehydrogenase (ADH) is one of the enzymes considered as potential markers of CRC. Increased activity of the isoenzyme ADH I has been detected in colon cancer cells compared to normal cells, while the activity of aldehyde dehydrogenase (ALDH) remains unchanged. This gives higher potential of cancer cells for ethanol oxidation and the simultaneously reduced elimination of acetaldehyde may result in intensified carcinogenesis. Most studies have demonstrated that an increased activity of class I ADH isoenzyme in cancer is correlated with total enzyme levels. Higher levels of the isoenzyme are detectable in the serum of patients and are even higher in CRC patients with more advanced stages (Jelski and Mroczko, 2020).

Circulating cancer cells (CTCs) may be involved in dissemination and metastatic deposits of CRC and hence their analysis may be useful in monitoring the treatment, and prognostic and predictive drug sensitivity testing. It is anticipated that the precise deciphering of the cancer cell phenotype will enable personalized approach in the treatment strategy (Jelski and Mroczko, 2020).

Findings from several studies highlight the potential of three main classes of molecular biomarkers in CRC screening including DNA, microRNA (miRNA) and long noncoding RNA (lncRNA) (Nikolouzakis et al., 2018) and also identify that the circulating free DNA is secreted at a higher rate by tumor cells compared to normal cells which was later confirmed by Oh (Oh and Joo, 2020). miRNA regulates the gene expression through binding to mRNA. Its oncogenic action is the main reason for miRNA to be associated with CRC. lncRNAs affect tumor cells through chromatin interactions. Their availability in blood, plasma, serum and urine samples makes them good potential biomarkers (Nikolouzakis et al., 2018; Oh and Joo, 2020). LncRNAs are involved in several oncogenic signaling pathways and as such can be used to distinguish CRC patients from healthy individuals.

Conclusion

Early diagnosis and timely treatment are crucial for the clinical outcome of CRC and can be facilitated with the use of highly specific biomarkers. The benefits of HGFs, CTCs and other potential biomarker molecular classes, warrant future research should be directed towards their implementation in CRC diagnosis, prognosis of clinical outcome and treatment monitoring.

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