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TRANSLATIONAL MEDICINE: BENCH TO BEDSIDE

Use of Macrophage Inhibitory Cytokine-1 as a Biomarker in Screening and Surveillance of Colorectal Neoplasia

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Colorectal cancer (CRC) remains the second most common cause of cancer death in the United States. The use of biomarkers may aid by identifying individuals at risk for CRC. One possible marker may be macrophage inhibitory cytokine-1 (MIC1), a member of the human transforming growth factor (TGF-B) superfamily, which is also known as the circulating inflammatory cytokine growth differentiation factor-15. The primary function of MIC1 is not well understood, but this cytokine may have a pleiotropic role in cancer, having antitumor effects in the early stages and facilitating tumor growth in the later stages of CRC.[1] For example, there is evidence that MIC1 can act as a mediator of apoptotic response to DNA damage.[2] Conversely, MIC1 may facilitate growth, invasion, and metastatic spread of cancer in the later stages of the disease. Elevated MIC1 levels have been shown to be associated with the incidence and survival of several types of tumors, including colorectal, prostate, ovarian, glioblastoma, and pancreato-biliary cancers.

In a prospective study, Mehta *et al*.,[3] examined the link between MIC1 and CRC mortality in a cohort consisting of 618 individuals enrolled in both the Nurses' Health Study and the Health Professionals Follow-up Study. MIC1 levels were measured from serum samples obtained at baseline, before any diagnosis of CRC. After controlling for other factors, including age, sex, stage at diagnosis, tumor grade, anatomic site, body mass index, and family history of CRC, the investigators observed that elevated MIC1 levels were associated with poor survival (CRC-specific death hazard ratio 2.40). Interestingly, there was no association between another known marker of inflammation, C-reactive protein, and CRC-specific mortality.

PTGS2 (COX-2) immunohistochemical staining was also performed on the 245 cases with available tissue. Whereas high levels of MIC1 were associated with CRC-specific mortality in individuals with PTGS2 (COX-2)-positive tumors, MIC1 was not associated with CRC death in those individuals with PTGS2-negative tumors. To further explore the link with inflammation, the authors examined the association of aspirin–nonsteroidal anti-inflammatory drugs (NSAIDs), MIC1 levels, and CRC death. Although aspirin use had a protective effect with regards to CRC-specific death, the current analysis showed no association between aspirin, MIC1 levels, and CRC mortality. Thus, high serum MIC1 levels can serve as prognostic markers by predicting CRC mortality, especially in tumors that develop through a proinflammatory pathway.

Are MIC1 levels useful in predicting neoplasia in individuals with colorectal adenomas, the precursors to CRC? In a study by Brown *et al*.,[4] the investigators examined MIC1 levels in serum taken from subjects who were enrolled in the Polyp Prevention Trial. They examined these levels and their association with the risk for baseline adenomas, as well as metachronous adenomas detected on surveillance colonoscopy performed within the trial. Higher MIC1 levels were observed in individuals who had adenomas at the time the samples were obtained, both at index and at follow-up colonoscopy. Thus, high levels of MIC1 were predictive of baseline and metachronous neoplasia. The authors also observed that MIC1 levels could discriminate between those individuals who had advanced neoplasia on follow-up colonoscopy and those without this finding.

One interesting finding was that a subset of NSAID users had an inverse relationship between MIC1 levels and presence of colorectal neoplasia. Specifically, high levels of MIC1 drawn at the time of the colonoscopy were associated with a lower risk of colorectal neoplasia detected at that exam. Conversely, low levels of MIC1 were associated with a higher risk for colorectal neoplasia in subjects who were regularly taking NSAIDs. Further, elevated MIC1 levels at baseline were also associated with a lower risk of metachronous adenomas detected on follow-up colonoscopy. Thus, these findings in individuals with adenomas support the findings of Mehta *et al*. that MIC1 has a role in colorectal neoplasia, which develops through a proinflammatory pathway. These findings also suggest that MIC1 levels could be used to determine which individuals might benefit from NSAID/aspirin (ASA) chemoprevention of colorectal adenomas. High levels of MIC1 in serum from those individuals who have been regularly taking NSAIDs/ASA and have no adenomas would favor continuing the chemoprevention. This strategy using MIC1 levels might mitigate risks for NSAID/ASA complications by reducing the number of adults receiving these medications for chemoprevention by reserving it for only those who would benefit.

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What are other possible applications of MIC1 serum levels? One possible use is a biomarker in subjects with adenomas. The current paradigm for surveillance of colorectal polyps relies on using baseline colonoscopy findings to stratify individuals into high- and low-risk groups. Those individuals with adenomas that contain villous elements, have high-grade dysplasia, and are larger than 1 cm or number 3 or more are considered to be at high risk for metachronous neoplasia.[5] Unfortunately, this strategy results in only a modest difference in risk for metachronous advanced lesions detected on follow-up exam for the high as compared with the low-risk group.[6] Therefore, the use of additional markers may add discriminatory power to the current paradigm with regard to identifying those high-risk individuals who may require more intense surveillance. Potentially, serum levels could be combined with data such as number, size, and histology of baseline adenomas, and other known risk factors to identify those individuals who may benefit from colorectal adenoma surveillance.

In addition to a potential role as a diagnostic marker for adenomas, MIC1 can also be used as a biomarker in the later stages of the disease. One possibility includes the monitoring of disease activity along with other markers such as CEA levels in individuals who have had CRC resection or are undergoing chemotherapy. In breast cancer, high levels of MIC1 have been associated with resistance to chemotherapy in women with breast cancer.[7] This proposed application for CRC would require data from studies designed to examine MIC1 serum levels in individuals undergoing treatment for CRC. Finally, one author has suggested that MIC1 levels might also serve as a potential target for cancer treatment.[1]

There are many advantages regarding the use of MIC1 assays, which include the observation that MIC1 levels within individuals are reproducible at different time points.[1] In addition, MIC1 is stable in serum, assays can be standardized, and MIC1 testing can be performed at a relatively cheap cost. Finally, collection of MIC1 would not require a specialized protocol, as no blood elements such as platelets produce this cytokine.[8]

There are also some concerns regarding the use of MIC1 clinically, including the storage of serum for subsequent MIC1 analysis. Some studies suggest that blood may need to be stored at −80° C. Other concerns include the performance characteristics for MIC1 as a prognostic and diagnostic marker for CRC, as well as adenomas. Larger trials using data from diverse populations will be needed to address these questions.

Disclaimer

The contents of this work do not represent the views of the Department of Veterans Affairs or the United States Government.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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