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Matrix metalloproteinases in colorectal cancer: Is it worth talking about?

Rebecca A. Wagenaar-Miller, Lee Gorden, and Lynn M. Matrisian*
Department of Cancer Biology, Vanderbilt University, 771 Preston Research Building, 23rd and Pierce Avenue, Nashville TN 37232

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Summary

Matrix metalloproteinases (MMPs), a family of extracellular matrix degrading enzymes, are expressed in various stages of colorectal cancer (CRC) and correlate with survival and prognosis. There is considerable evidence in preclinical models that MMP inhibitors (MMPIs) are effective at multiple stages of CRC tumor progression, including reducing the number of intestinal adenomas, inhibiting the growth and establishment of primary CRC tumors, and reducing metastasis to the lung and liver. However, clinical trials with MMPIs in other tumor types have been largely unsuccessful, raising the question as to whether MMPs represent therapeutic targets in CRC. This review focuses on the expression, role, and contribution of MMP family members to various stages of CRC tumor progression. The conclusion is that there is considerable evidence to suggest that MMP inhibition may be an effective strategy if applied at either end of the tumor progression spectrum; the prevention of adenomas, or the treatment of micrometastatic disease.

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Colon cancer risk factors and targets for treatment

The incidence of colorectal cancer (CRC) has dramatically risen over the past 50 years such that it is now the third largest cause of cancer related deaths in both men and women in the United States. A number of risk factors have been identified that influence susceptibility to colorectal cancer, including a family history, the presence of adenomatous polyps, inflammatory bowel disease (ulcerative colitis or Crohn's disease), and a number of environmental factors of which diet is the most significant.

CRC differs from many other cancers in that diagnosis of the disease can be made earlier by screening techniques including colonoscopy. The progression of CRC is well established and begins with hyperproliferation of the colonic mucosa and adenoma formation and then adenocarcinomas that vary in metastatic potential. The progression from normal intestinal epithelium to an invasive carcinoma is estimated to take 7–12 years. With the advent of early screening measures developed over the last few decades, CRC has become a preventable disease by treating patients with adenomatous polyps. Of the patients who die from CRC, however, most will succumb with metastatic disease. Nearly 50% of patients diagnosed with CRC develop metastasis within five years. Most commonly these tumors metastasize to the liver and lungs but may be discovered in many other sites.

Patients with a hereditary form of colon cancer, familial adenomatous polyposis (FAP), make an ideal cohort for a prevention study. Prevention trials are possible in patients with an increased risk for developing CRC such as patients with a history of adenomatous polyps because it has been shown

* Corresponding author.
E-mail: lynn.matrisian@vanderbilt.edu

that there is a 29–35% recurrence rate in patients that have had previous polyps removed [1]. There are two forms of hereditary colon cancer, FAP and hereditary non-polyposis colon cancer (HNPCC). The genes involved in these two forms of colon cancer have been identified and are adenomatous polyposis coli (APC) and mismatch repair genes (MMR), respectively. In addition to identification of the genetic pathways altered in familial colorectal cancer, much progress has been made in elucidating the genetic alterations that occur in various stages of sporadic colon cancer. Progression from normal epithelium to carcinoma involves a number of different genetic alterations. Sporadic colon cancers involve mutations in the same genes implicated in the familial forms, *APC* and MMR genes [2–8]. In addition, mutations and loss of heterozygosity have been detected in oncogenes such as K-ras [9] and β-catenin, and tumor suppressor genes including p53 [10], MCC (mutated in colorectal cancer) [11], DCC (deleted in colon cancer) [12], DPC4 (deleted in pancreatic cancer), and nm23 [13]. The products of these genes, and their ensuing pathways, all represent potential targets for the treatment and prevention of CRC.

In addition to genetic alteration, many genes are upregulated in colon cancer. These genes can be downstream of oncogenes and tumor suppressors mutated in cancer of the colon or are induced in response to the tumor cells. One class of genes often upregulated in multiple forms of cancer, including colon cancer, is the matrix metalloproteinase (MMP) family. MMPs are not traditional oncogenes in the sense that they are not activated by gene mutations but rather their expression is increased either as a direct effect of the activation of an oncogenic pathway, or an indirect response to the tumor cells. The products of such genes also represent potential targets for the treatment and prevention of further progression of CRC.

Chemoprevention therapy is aimed at reducing the risk of developing clinical cancer through inhibition or reversal of carcinogenesis with the use of pharmacologic agents. A number of possible standards or endpoints are used to measure the effectiveness of chemoprevention of colon cancer including regression of adenoma, suppression of adenoma formation or the prevention of new adenomas. Additionally, the development of biomarkers such as cellular proliferation or apoptosis within the colon could be used to assess the response. The ability to identify precancerous lesions, the accessibility of tissue, and the extensive knowledge of the molecular events that lead to CRC development and progression make CRC an ideal disease for the development of chemopreventitive strategies.

Another stage at which significant intervention can be made is in the prevention of metastatic spread of CRC. Nearly 50% of patients diagnosed with CRC develop metastasis within five years. Treatments designed to intervene in the formation of metastasis through blocking tumor spread, angiogenesis, or growth of the metastasis would have a dramatic impact on survival of patients with CRC. Thus basic scientific discoveries into the molecular mechanisms underlying CRC metastasis can be translated to therapeutic advances to impact the lives of cancer patients.

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MMPs

The MMP family consists of over 20 human members that are historically divided into groups based on extracellular matrix substrate specificity and homology to other MMPs. Their common names reflect this practice (Figure 1, see Sternlicht and Werb [14] and Chambers and Matrisian [15] for review). A sequential numbering system is also used and will be used in this review as new family members are discovered with little information available concerning substrate specificity. The first members of the MMP family were originally described by Gross and Lapiere as the enzymes involved in the dissolution of the tadpole tail with enzymatic activity against triple helical collagen [16]. Since then a number of MMPs have been identified and shown to degrade ECM components important in a variety of normal and pathological conditions.

MMPs are classified based upon shared structural motifs. The signal or pre-peptide domain is usually rich in hydrophobic amino acids and targets the enzymes to the endoplasmic reticulum for possible excretion from the cell. The propeptide contains a highly conserved PR<u>C</u>GVPD sequence that contains the cysteine residue that interacts with the zinc atom in the catalytic site to