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TOPIC HIGHLIGHT

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Impact of proteolytic enzymes in colorectal cancer development and progression

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Abstract

Tumor invasion and metastasis is a highly complicated, multi-step phenomenon. In the complex event of tumor progression, tumor cells interact with basement membrane and extracellular matrix components. Proteolytic enzymes (proteinases) are involved in the degradation of extracellular matrix, but also in cancer invasion and metastasis. The four categories of proteinases (cysteine-, serine-, aspartic-, and metalloproteinases) are named and classified according to the essential catalytic component in their active site. We and others have shown that proteolytic enzymes play a major role not only in colorectal cancer (CRC) invasion and metastasis, but also in malignant transformation of precancerous lesions into cancer. Tissue and serum-plasma antigen concentrations of proteinases might be of great value in identifying patients with poor prognosis in CRC. Our results, in concordance with others indicate the potential tumor marker impact of proteinases for the early diagnosis of CRC. In addition, proteinases may also serve as potential target molecules for therapeutic agents.

Key words: Proteinase; Cathepsin; Plasminogen activator; Matrix metalloproteinase; Colorectal cancer; Adenoma; Invasion; Metastasis; Biomarker; Prognosis

Core tip: Tumor invasion and metastasis is a highly complex phenomenon. Proteolytic enzymes (proteinases) are involved in the degradation of extracellular matrix, in colorectal cancer (CRC) invasion and metastasis, as well as in the malignant transformation of colorectal adenomas. Tissue and serum-plasma antigen concentrations of proteinases are strong prognostic factors in CRC and may have tumor marker impact for early diagnosis. Proteolytic enzymes may serve as potential target molecules for CRC therapy. Their use in combination with established chemotherapeutic strategies might have the potential to become a valuable oncological treatment modality.

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MECHANISMS OF TUMOR PROGRESSION

Tumor invasion and metastasis is a highly complicated, multi-step phenomenon. The multistep metastatic process requires the actions of several genes and involves the

Table 1 Categories and main properties of proteolytic enzymes

Property	Cysteine proteases	Serine proteases	Aspartic proteases	Metallo proteases
Active site	Cysteine	Serine	Aspartic acid	Zinc
Optimum pH	7-9	3-7	2-4	5-9
Location	Lysosomes	Intra-extracellular	Lysosomes	Intra-extracellular
Examples	Cathepsins	Elastase	Pepsinogen I - II	Collagenase
	B, L, C, H	Trypsin	Cathepsins D, E	Stromelysin
		PA: uPA, tPA	Gelatinase	Matrilysin
Inhibitors	Cystatin	Antitrypsin Antithrombin III PAI	Unknown	TIMP

PA: Plasminogen activators; uPA: Uroinase-type plasminogen activator; tPA: Tissue-type plasminogen activator; PAI: Plasminogen activator inhibitor; TIMP: Tissue inhibitor of metalloproteinases.

initial transforming event (*i.e.*, oncogene activation), proliferation of transformed cells and the ability of tumor cells to avoid destruction by immune-mechanisms. Furthermore, it comprises of nutrition supply to the tumor mass by the release of tumor angiogenesis factors, cancer cell local invasion and destruction of extracellular matrix (ECM) components, epithelial mesenchymal transition (EMT), shedding from primary tumor, intravasation, arrest, extravasation and colonization at a preferential site resulting in the formation of a secondary tumor (distant metastases)[1-9].

Chronic and persistent inflammation can predispose to carcinogenesis and contribute to cancer development. Cancer-associated inflammation includes infiltrating leucocytes, cytokines, chemokines, growth factors and matrix-degrading enzymes. Inflammatory conditions can initiate oncogenic transformation and epigenetic and genetic changes in malignant cells. In essence, two interrelated pathways connect inflammation and cancer: (1) genetic alterations (including chromosomal amplification, activation of oncogenes and inactivation of tumor-suppressor genes) leading to neoplastic transformation; and (2) presence of tumor-infiltrating leukocytes that are prime regulators of cancer-related inflammation. The integration of these two pathways activates transcription factors and finally creates a tumor-associated inflammatory milieu[10-19].

BASEMENT MEMBRANE, EXTRACELLULAR MATRIX AND CANCER CELLS

All normal or pre-invasive tumor epithelia are physically segregated from vascular structures within the stroma by the basement membrane (BM). The BM consists of laminins, type Ⅳ collagen and surrounding epithelial cells. The tumor stroma is comprised of ECM, non-malignant cells, and the signalling molecules they produce. During tumor invasion and metastasis, tumor cells are interacting with the BM and the ECM. The disruption of the BM and the ECM is an essential pre-requisite for cancer cell invasion and metastasis. Interaction of tumor cells with the BM and ECM comprises of three steps: attachment, matrix dissolution and migration. The first step is tumor cell attachment to the matrix. The attachment is mediated by tumor cell surface receptors, when tumor cells bind to BM surface. This process involves specific glycoproteins such as fibronectin, type Ⅳ collagen and laminin. In the second step tumor cells directly secrete degradative enzymes or induce the host to produce proteolytic enzymes to degrade ECM. The matrix lysis takes place in a highly localized region close to the tumor cell surface. During the third step (migration), cancer cells are propelled across the BM and stroma through the zone of matrix proteolysis. Invasion of ECM is accomplished by reverberation of these three steps[3,6,9,20-27].

Table 2 General roles of proteolytic enzymes in cancers

Degradation or disruption of basement membrane and extracellular matrix
Produce components which allow the *in situ* cancer cells to disseminate to distant organ
Formation of a complex microenvironment that promotes malignant transformation
Activation of growth factors, adhesion molecules
Suppression of tumor cell apoptosis
Destruction of chemokine gradients
Modulation of antitumor immune reactions
Dual and complex role in angiogenesis

GENERAL ROLES OF PROTEOLYTIC ENZYMES IN CANCERS

The four categories of proteinases (cysteine-, serine-, aspartic-, and metalloproteinases) are named and classified according to the essential catalytic component (usually an amino acid) in their active site[3,28]. Table 1 summarises the four categories and some general properties of each group. Proteolytic enzymes play a major role in the breakdown and reconstitution of ECM in a variety of physiological and pathological processes, such as protein turnover, tissue remodeling, wound repair, angiogenesis, destructive diseases, inflammatory disorders as well as tumor invasion and metastasis (Table 2). Tumor cells have been shown to produce and release several proteolytic enzymes, which are thought to be involved in tumor invasion and metastasis. Proteolytic enzymes are also frequently produced by surrounding stromal cells, including fibroblasts and inflammatory cells. It has been proposed that these proteolytic enzymes cause degradation or disruption of BM and ECM components allowing the *in situ* cancer cells to migrate into the adjacent stroma or to disseminate to distant organ. It is commonly accepted that progression from *in situ* to invasive or metastatic cancer is caused by proteolytic enzymes (proteinases) produced

by tumor cells that increase linearly in concentration with tumor progression[3,6,9,29-31].

The impact of proteolytic enzymes in tumor progression is much more complex than that derived from their direct degradative action on BM and ECM components. Now they are known to have functions that extend far outside matrix remodeling. Proteolytic processing of bioactive molecules by proteinases contributes to the formation of a complex microenvironment that promotes malignant transformation. Proteolytic enzymes can contribute to tumor growth either directly or indirectly via growth factors such as transforming growth factor-β (TGF-β), basic fibroblast growth factor (bFGF) or, insulin-like growth factor (IGF). Proteinases also act on other non-matrix substrates (*e.g.*, chemokines, adhesion molecules, apoptotic mediators, angiogenic factors) that yield the critical cellular responses that are essential for tumor growth and progression. Proteolytic enzymes are also associated with a variety of escape mechanisms that tumor cells develop to avoid immune response including chemokine cleavage and regulation of chemokine mobilization. Tumor cells produce chemokines, cytokines, and the extracellular matrix metalloprotease inducer (EMMPRIN), which in turn activates tumor-cell invasion. During angiogenesis, proteolytic enzymes can have both a pro-angiogenic impact, by releasing matrix-bound pro-angiogenic factors such as TGF-β, bFGF, triggering the angiogenic switch during carcinogenesis and facilitating vascular remodeling and neovascularization at distant sites during metastasis, and also may have anti-angiogenic role, by cleaving the ECM components into anti-angiogenic factors[32-36].

Cysteine and serine proteinases

It has been observed that cysteine proteinases [cathepsin B (CATB) and cathepsin L (CATL)], play a crucial role in the destruction of various elements of the cell-surrounding ECM. The serine proteinase urokinase-type plasminogen inhibitor (uPA) is also involved in many protein degrading processes. uPA seems to promote invasion through a plasmin mediated degradation of ECM proteins. Active uPA catalyzes the conversion from plasminogen to plasmin, which is a potent activator of several metalloproteinase proenzymes, such as prostromelysin, procollagenase, and progelatinase B. Beyond its direct proteolytic capacity, CATB has also been shown to activate the prourokinase-type plasminogen activator (pro-uPA). The tissue-type plasminogen activator (TPA) is a key enzyme in the fibrinolytic cascade. Plasminogen activators (PA) are controlled by plasminogen activator inhibitors, which are members of the serine proteinase inhibitors (serpin) family. The PA inhibitor type-1 (PAI-1) under normal physiologic conditions inhibits both uPA and TPA. The exact role of PAI-1 in tumor biology is complex: PAI-1 may represent a specific protein of transformed malignant tissue; may protect cancer tissue against the proteolytic degradation triggered by the tumor on surrounding normal tissue; and finally, PAI-1 has a role in angiogenesis playing a part in tumor spread[37-45].

Cathepsins and components of the plasminogen activator and inhibitor system have been demonstrated in various malignant tissues, *e.g.*, breast cancer[46-48], lung cancer[49,50], head and neck cancer[51], ovarian cancer[52] or gastric cancer[53-56] and might therefore be useful as a diagnostic tool.

With respect to the gastrointestinal (GI) tract, we have previously shown that cysteine and serine proteinases are widely distributed in GI tissues, being implicated in processes of GI tissue remodelling, angiogenesis, wound healing, inflammation, may have a role not only in the process of esophageal or gastric cancer invasion, but also in the progression of GI precancerous lesions into cancer[57-61]. Several studies, along with our own, have also pointed to the prognostic value of cysteine and serine proteinases for survival, for instance, in gastric cancer[56,58,59,62,63], pancreatic cancer[64], or hepatocellular carcinoma[65].

Matrix metalloproteinases

Matrix metalloproteinases (MMPs) family consists of 26 members of homologous zinc-dependent endopeptidases. The expression of MMPs is induced by a variety of external stimuli such as cytokines and growth factors, including interleukins, interferons, vascular endothelial growth factor, fibroblast growth factor (FGF), tumor necrosis factor-alpha (TNF-α) or TNF-β, and EMMPRIN. MMPs play an important role in the degradation of ECM components, are crucial for tumor growth, invasion and metastasis. MMPs are synthesized as inactive zymogens, which are then activated by either other MMPs or by serine proteinases. Based on substrate specificities and sequence homology, MMPs can be classified as gelatinases, collagenases, stromelysins and matrilysins. MMPs are responsible for cleaving all of the major ECM proteins[66-74].

We and others have shown that MMPs, particularly type Ⅳ collagenase MMP-9 (gelatinase B), are essential in the process of tumor invasion and metastasis, as well as in the remodeling and inflammatory processes in IBD[75-82].

MMPs have also been considered as potential diagnostic and prognostic biomarkers in many types and stages of GI cancer[83-85].

Tissue inhibitors of matrix metalloproteinases

MMPs activity is specifically inhibited by natural inhibitors, called tissue inhibitors of metalloproteinases (TIMPs). Currently, four different TIMPs have been characterized in humans (TIMP-1, -2, -3 and -4). The balanced interaction of MMPs with TIMPs regulates ECM homeostasis. The imbalance between MMPs and TIMPs is an essential step in the development of malignancies. TIMPs might display a dual influence on tumor progression: either beneficial by inhibiting MMPs and impairing angiogenesis or harmful by facilitating cancer cell generation, tumor growth and metastasis. The sensitive balance between MMPs and TIMPs is essential for many physi-

Table 3 Clinical significance of proteolytic enzymes in colorectal cancer

Role in colorectal tumor biology, in the process of tumor invasion and metastasis
Role in malignant transformation of colorectal precancerous conditions and lesions
Potential diagnostic tool
New and independent prognostic factors
Potential tumor marker impact for early diagnosis
Potential target molecules for therapeutic agents

ological processes in the gut[6,86-91].

We have recently demonstrated that not only MMPs but also TIMPs may contribute to the inflammatory and remodeling processes in IBD and serum TIMP-1 might be useful as additional biomarker in the assessment of IBD activity[82].

IMPACT OF PROTEOLYTIC ENZYMES IN COLORECTAL CANCER

colorectal cancer (CRC) is the third most common malignant neoplasm worldwide. CRC is the second most common newly diagnosed cancer and the second most common cause of cancer death in the European Union (EU). Despite the advances in screening, diagnosis, and treatment, the overall long-term outcome of curatively resected patients has not significantly changed in the last decades, the five-year survival rate being approximately 60%. More than a half of CRCs are still diagnosed only when the disease involves regional or distant organs, and these patients are candidates for systemic chemotherapy. The prognosis of CRC is determined primarily by TNM staging and pathomorphological parameters. Furthermore, therapeutic strategies for chemotherapy are based on traditional prognostic systems. For risk stratification, it would be useful for clinicians to have new and more efficient preoperative tumor markers and prognostic indicators available, for instance to better identify patients who need adjuvant or neoadjuvant treatment[92-97].

We review hereinafter the prognostic value and potential tumor marker impact of a number of proteolytic enzymes. We also discuss proteinases as potential target molecules for therapeutic agents Table 3 summarises the clinical significance of proteolytic enzymes in CRC.

Tissue expression of cysteine and serine proteinases in CRC

Cathepsins or components of the plasminogen activator and inhibitor system have been demonstrated in colorectal cancer tissue and might therefore be useful as diagnostic tools[98-100]. Some of the studies also showed that cathepsins or some of PAs also have a prognostic significance for patients with CRC[98-106]. In a former study we have demonstrated the simultaneous up-regulation of both cysteine and serine proteinases in CRC confirming their role in colorectal tumor biology and particularly in the process of tumor invasion and metastasis. We have also shown that CATL, uPA and PAI-1 have a major prognostic impact in patients with CRC[107].

Serum and plasma concentrations of cysteine and serine proteinases in CRC

Given the lack in the literature of a comparison of the behavior of cysteine proteinase CATB and serine proteinase uPA in the same experimental setting in different GI tumors, in a previous study we have surveyed the possible clinical impact of serum CATB and plasma UPA antigen in CRC, gastric cancer, hepatocellular carcinoma, pancreatic cancer, and colorectal adenomas[61]. We have demonstrated that preoperative serum CATB and plasma uPA antigen concentrations were significantly higher in GI tract cancers overall than those found in control non-cancer patients, thus confirming the relevance of cysteine and serine protease-dependent mechanisms in GI cancers. We have also further confirmed that serum CATB and uPA plasma levels were elevated in patients with CRC[108-111]. In addition, we have shown that serum CATB and plasma uPA did show a significant increase in advanced CRC stage. We have also demonstrated for the first time that antigen levels of CATB and uPA were significantly higher in blood samples of patients with colorectal adenomas as compared to controls. Furthermore, we have found significantly higher CATB and uPA antigen levels in patients with tubulovillous adenomas with high-grade dysplasia (HGD) compared to those with tubular adenomas with low-grade dysplasia (LGD). Thus taken together, the data from blood samples with previous results obtained in colorectal tissues confirm that a concomitant activation of serine (CATB) and uPA may be involved in the progression from premalignant colorectal adenomas into CRC[112,113].

Some other studies have also suggested the potential impact of cysteine or serine proteases as tumor markers in CRC[108-111]. Given the lack in the literature for a comparison of the tumor marker utility and possible prognostic relevance of cathepsins (CATB, CATL) and the uPA/PAI-1 system in the same experimental setting, we have surveyed the behavior of CATB, CATL, uPA, PAI-1 in CRC and compared it with the commonly used gastrointestinal tumor markers CEA and CA 19-9, and then evaluated any correlation between these parameters and the clinico-pathological staging of CRC[114]. In this study, we have demonstrated the potential tumor marker utility and prognostic relevance of cysteine and serine proteinases for patients with CRC. We have also shown the concomitant activation of these systems in CRC. At the time of clinical presentation, proteinases were more sensitive indicators of diagnosis than the most commonly used markers CEA and CA 19-9. When proteinases, CEA and CA 19-9 were used as single markers, we found that their sensitivity was more indicative of CRC than CEA or CA 19-9. The simultaneous determination of several markers led to a higher sensitivity in our group of CRC patients: PAI-1 combined with CATB or

uPA was superior compared to the combinations of all other markers. In addition, the sensitivity of CEA or CA 19-9 in combination with a proteinase antigen level was more indicative for CRC than CEA or CA 19-9 alone. In this study increased serum or plasma proteinase concentrations significantly correlated with advanced tumor stage. In a univariate survival analysis high serum CATB, CATL and plasma PAI-1 antigen levels identified patients with shorter survival and those who were at higher risk of death. In addition, PAI-1 and CATB were proved as independent predictor variables in a multivariate statistical analysis. We also confirmed that cysteine and serine proteinases were significantly higher in blood samples of patients with colorectal adenomas compared to controls, suggesting that these proteinases may be involved in the malignant transformation of colorectal adenomas[114].

Tissue MMPs and TIMPs in CRC

The behavior of MMPs and TIMPs in CRC has recently been extensively reviewed by our own group[115]. Several studies have shown that the expression of several MMPs and TIMPs are enhanced in CRC. In an immunohistochemical study we have demonstrated that tissue expression of one particular MMP, MMP-9 was significantly higher in moderately (G2) and poorly (G3) differentiated tumors than in well differentiated (G1) cancers, as well as in advanced Dukes stages compared with Dukes stage A[116]. Some recent studies have confirmed that tissue MMP-9 can be considered as an independent prognostic marker in CRC[117-120]. In addition, it has been demonstrated that not only MMP-9, but also tissue expressions of other MMPs and TIMPs have strong prognostic impact in CRC[121-126].

MMPs and TIMPs also play a role in malignant transformation from colorectal adenomas to CRC. Our group in concordance with others has shown that tissue expression of MMP-9, MMP-2, TIMP-1 and TIMP-2 were significantly higher in advanced versus non-advanced adenomas, suggesting that MMPs and TIMPs might be markers for early colorectal carcinogenesis. The ability of MMPs and TIMPs to distinguish adenomas with HGD from adenomas without HGD may be of clinical value in predicting additional cancer risk for an individual patient[116,127-130].

Serum and plasma MMPs and TIMPs in CRC

The diagnostic, prognostic and tumor marker impact of serum-plasma MMPs and TIMPs in CRC has been extensively studied. We have demonstrated that serum antigen concentrations of MMP-2, MMP-7, MMP-9 as well as TIMP-1 and TIMP-2 were significantly higher in patients with CRC than in healthy controls. All examined parameters were significantly higher in patients with CRC than in patients with adenomas. Higher antigen concentrations of MMPs and TIMPs significantly correlated with preoperative tumor stage. The data from blood samples confirmed previous results of tissue expressions concluding that MMPs and their inhibitors TIMP-1 and TIMP-2 play an important role not only in CRC invasion and metastasis, but they are also activated in premalignant colorectal adenomas[82].

Several recent studies confirmed that high preoperative serum or plasma MMP-2, MMP-9 and mainly TIMP-1 antigen levels are strong predictive factors for poor prognosis in patients with CRC[131-137].

The potential tumor marker role of MMPs and TIMPs has also been extensively studied. It has been demonstrated that MMP-9 and TIMP-1 have significant potential as biomarkers in CRC. Diagnostic sensitivity of MMP-9 and TIMP-1 was consistently higher as compared with the conventional biomarkers (CEA or CA 19-9)[131,138-140].

It has also been proposed that TIMPs can predict individual response to chemotherapy and could be considered as an additional tool for monitoring chemotherapy in CRC[141-144].

One of the greatest challenges in CRC management is to predict the outcome of each patient so that we can determine who will really benefit from intensified adjuvant therapy. The classical TNM staging system relied heavily on the exact extent of cancer at the time of diagnosis and is greatly predictive in stage I and stage Ⅳ tumors. However, it is less informative for patients including stage Ⅱ and stage Ⅲ CRC. After curative surgery, stage Ⅲ CRC patients experience 50% chance of developing recurrence. It is well documented that the overall survival rate of stage Ⅲ CRC could clearly benefit from adjuvant chemotherapy. In contrast, the role of adjuvant chemotherapy for stage Ⅱ CRC is still controversial, despite the 20% recurrence in this group. We and others have suggested that proteolytic enzymes could constitute useful independent markers in addition to the TNM staging system for the intermediate groups including stage Ⅱ and stage Ⅲ CRC. Proteolytic enzymes may help to identify patients who are more likely to have disease relapse and high risk of death, thus those who are potential candidates to receive aggressive adjuvant chemotherapy[107,119,145-147].

On the other hand, taken into consideration that proteolytic enzymes may have a crucial role not only in the invasive process of CRC, but also in the progression of precancerous conditions and lesions into cancer, quantification of proteinases might be useful to identify patients at higher risk for progression to cancer, who could be subjected to a more strict follow-up protocol.

PROTEOLYTIC ENZYMES AS POTENTIAL TARGET FOR CANCER THERAPY

The accumulated evidence strongly supports the concept of the use of cysteine proteinases (cathepsins) and serine proteinases (uPA-PAI system) as targets for cancer therapy. It has been suggested that cathepsin inhibition represents a potential therapeutic strategy for the treatment of cancer. Cathepsins inhibition seems to reduce invasion and metastasis, but there is concern that selective cathep-

sin inhibition induces compensatory activity by other cathepsins. The combination of cathepsin inhibition with conventional chemotherapy seems to be more effective and has yielded more consistent clinical results. Future research should be focused on the exact mechanisms and clinical effects of this combination treatment[148-151].

The multifunctionality of the uPA-uPAR-PAI-1 system in cancer spotlighted serine proteinases to become potential targets for anticancer treatment. In addition, uPA system is also increasingly being recognized as a candidate target for gene therapy in cancer[152-159]. Several strategies, including the use of ribozymes, DNAzyme, antisense oligodeoxynucleotides, uPA inhibitors, soluble uPAR, catalytically inactive uPA fragments, the interactions of uPAR with integrins and transmembrane receptors, synthetic peptides and synthetic hybrids are under study, as they all interfere with the activity of uPA or uPAR in tumor cells. Many clinical studies are ongoing and some uPA-related compounds have reached Phase Ⅱ clinical trials.

Several therapeutic MMP inhibitors (MMPIs) have also been developed to target MMPs. Various natural compounds have been identified as inhibiting MMPs. In addition, several generations of synthetic MMPIs were tested in phase Ⅲ clinical trials in humans, including peptidomimetics, non-peptidomimetic inhibitors or tetracycline derivates, targeting MMPs in the extracellular space. Other strategies of MMP inhibition involve small interfering and antisense RNA technology[160-165]. In contrast to their promising effect in preclinical models, most of these agents unfortunately failed in clinical trials, thus they are yet not available for routine use. The use of broad-spectrum MMPIs may lead to undesired clinical consequences as a result of the wide range of MMPs that are inhibited. In addition, toxic side effects, such as musculoskeletal syndrome, have limited drug efficiency.

The ADAMs is also a family of potential new targets for cancer therapy. ADAMs (a disintegrin and metalloproteinase) are members of a zinc-dependent family of matrix metalloproteinases. Preclinical findings suggest that selective ADAM inhibitors might be novel anticancer agents. ADAMs inhibitors may be particularly useful in treating cancers that depend on HER or TNF-α-mediated signalling[166-169].

One of the major challenges for the future is the development of monoclonal antibodies or inhibitors that are specific for certain MMPs, showing no cross-reaction with other MMPs with improved pharmacokinetic properties and selectivity. In addition, their use in combination with established chemotherapeutic strategies might have the potential to become valuable oncological treatment modalities[161,170-176].

CONCLUSION

Proteolytic enzymes play a sophisticated role in cancer development and progression due to their abilities to degrade various substrates. However, the role of proteolytic enzymes in tumor progression is much more complex than that derived from their direct degradative action on BM and ECM components. Proteinases may have a crucial role not only in the invasive process of CRC, but also in the progression of precancerous conditions and lesions to CRC. Proteolytic enzymes could constitute effective independent prognostic markers additive to TNM staging system in CRC. Their determination might be useful to identify patients at higher risk for progression to cancer, who could be subjected to a more strict endoscopic follow-up protocol.

It has recently been demonstrated in experimental settings that a newly developed near-infrared bioactivable probe (MMPSense) that reports the activity of a broad array of MMP isoforms detects both polypoid and non-polypoid early colorectal adenomas with a high specificity[177]. Future studies will focus on the use of such fluorescent probes combined with colonoscopy to identify neoplastic lesions based on their molecular "fingerprint" (*i.e.*, proteinase enzymatic activity) rather than solely on their morphologic properties. The ability to detect non-polypoid lesions using this fluorescent probe alone or in combination with other molecular probes may offer new future perspectives for colorectal screening. In addition, it might also serve as a potential strategy for the pharmacodynamic monitoring of targeted therapy. The pharmacological targeting of CRC by the development of a new generation of effective and selective proteinase inhibitors is another emerging area of research.

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