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Basic Study

c-MET immunohistochemical expression in sporadic and inflammatory bowel disease associated lesions

Grant Halliday, Ross J Porter, Catherine J Black, Mark J Arends, Shahida Din

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Abstract

BACKGROUND

Post-colonoscopy colorectal cancer (CRC) rates for patients with inflammatory bowel disease (IBD) are unacceptably high. During colonoscopy, an intravenous fluorescent anti-c-MET probe may improve endoscopic detection of lesions. However, c-MET expression in IBD lesions is poorly defined, limiting translational studies.

AIM

To comprehensively define c-MET expression in sporadic and IBD-associated colorectal carcinogenesis.

METHODS

c-MET expression was immunohistochemically assessed in 319 formalin-fixed paraffin-embedded tissue specimens, colonoscopically or surgically retrieved between 1994-2017. Tissue included: 30 normal colorectal biopsies, 30 hyperplastic polyps (HP), 31 sessile serrated lesions (SSL), 55 tubular/tubulovillous adenomas with low (TA-LGD, $n = 32$) or high grade dysplasia (TA-HGD, $n = 23$), 26 sporadic (s)-CRCs, 16 quiescent IBD biopsies, 11 active/inflamed IBD biopsies, 18 IBD-associated dysplastic lesions (IBD-dys), and 102 IBD-CRCs. Expression was scored by two independent observers as: 0 = absent, 1 = weak, 2 = moderate or 3 = strong. Mann-Whitney U and Kruskal-Wallis tests were used to assess significant

ce.

RESULTS

Positive epithelial cytoplasmic and membranous c-MET expression was observed in all tissues, indicating there is ubiquitous expression in the colorectum. c-MET expression was weak in normal colonic epithelium compared with each of the sporadic colonic lesions, including TA-LGD ($P < 0.001$), TA-HGD ($P = 0.004$), HP ($P < 0.001$), SSL ($P < 0.001$), and s-CRC ($P < 0.001$). Specifically, in sporadic (non-IBD) lesions, expression was stronger in TA-LGD compared with normal mucosa ($P < 0.001$), and stronger in s-CRC compared with TA-HGD ($P = 0.004$). However, there was no significant difference between TA-LGD and TA-HGD ($P = 0.852$). Further, there was no difference in c-MET expression between HP and SSL ($P = 0.065$). In IBD, expression was weaker in quiescent colonic mucosa compared with inflamed colonic mucosa ($P < 0.001$). There was no difference between inflamed colonic mucosa and IBD-dys ($P = 0.512$) or IBD-CRC ($P = 0.296$). However, expression was stronger in IBD-dys ($P < 0.001$) and IBD-CRC ($P < 0.001$) compared with quiescent IBD colonic mucosa.

CONCLUSION

The characterisation of c-MET expression suggest that an intravenous probe may improve the endoscopic detection of lesions in both non-IBD patients and IBD patients with quiescent disease.

Key Words: Inflammatory bowel diseases; Colorectal cancer; Surveillance; Detection; c-MET; Immunohistochemistry

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Core Tip: During colonoscopy, an intravenous fluorescent anti-c-MET probe may improve endoscopic detection of dysplasia and cancer. However, c-MET expression in inflammatory bowel disease (IBD) lesions is poorly defined, limiting translational studies. We demonstrate that stronger immunohistochemical c-MET expression is associated with dysplasia and cancer in both sporadic and IBD-associated lesions. Therefore, c-MET expression could be exploited clinically to enhance endoscopic detection of pre-malignant lesions and cancer, particularly in IBD where post-colonoscopy colorectal cancer rates are unacceptably high.

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INTRODUCTION

Patients with inflammatory bowel disease (IBD) have an increased risk of developing colorectal cancer (CRC), with poorer survival compared with the general population[1,2]. The British Society of Gastroenterology currently recommends high-definition surveillance ileocolonoscopy ± chromoendoscopy, with targeted biopsies starting 8-years after the onset of IBD symptoms[3]. Despite this, IBD post-colonoscopy CRC rates - defined as a diagnosis of cancer or high-grade dysplasia > 6 mo to 3 years following a colonoscopy that was negative for cancer - are unacceptably high, at 28%-45%[4,5]. One challenge in identifying dysplastic and malignant lesions in IBD is the morphological changes associated with flat lesions which are difficult to detect endoscopically. With an ageing population and rising global burden of IBD[6], there is an increasing requirement for endoscopic surveillance indicating an urgent clinical need to improve the endoscopic detection of IBD-associated dysplasia and cancer.

c-MET is a receptor tyrosine kinase (encoded by the *MET* gene on chromosome 7q21-31) overexpressed at a protein level in a variety of human primary tumours, including in the colorectum where it is associated with the sporadic adenoma-carcinoma pathway[7-11]. In 2015, Burggraaf and colleagues published a first-in-human study demonstrating that an intravenous injection of a fluorescently labelled peptide with a high affinity for c-MET was safe, well tolerated in humans, and could improve the detection of colonic polyps in a high-risk asymptomatic patient cohort[12]. Since then, translational data have emerged in support of this technology for sporadic CRC[13,14].

The original data from Burggraaf and colleagues stated that there were several lesions visible with fluorescence assisted colonoscopy that were not identified during first or second pass conventional

white light colonoscopy. These small lesions were mostly < 6 mm and non-polypoid[12]. Given this, we hypothesise that this technology may be especially useful for identifying IBD-associated lesions with similar flat morphology. However, the clinical utility of c-MET is unclear in the setting of chronic inflammation and injury to the colonic mucosa, as c-MET has been reported to be upregulated in tissue repair[15].

While the efficacy of an *in vivo* c-MET probe has never been investigated in the setting of human IBD, there are some murine data. The azoxymethane (AOM)/dextran sulphate sodium (DSS) mouse model is commonly used to simulate colitis-associated carcinogenesis in the laboratory[16]. Using this model, Tao and colleagues reported that there was an accumulation of fluorescence from their c-MET probe (Crizotinib and MPA, a water-soluble cyanine dye, covalently conjugate *via* PEG4) in colonic lesions, while there was minimal fluorescence in adjacent tissue[17]. While an acceptable surrogate model, AOM/DSS lesions are not identical to those seen in human disease. Further, Tao *et al*[17] resected colons for imaging *in vitro*, rather than assessment by *in situ* fluorescence colonoscopy. Nonetheless, these data are encouraging and warrant investigation in human IBD: there are a paucity of histopathological studies that define c-MET expression in human IBD and IBD-associated carcinogenesis.

To address this need, this study comprehensively defines the expression of c-MET in a large cohort of 319 paraffin-embedded tissue sections, representing the spectrum of both sporadic and IBD-associated colorectal carcinogenesis. Our results suggest that c-MET could be exploited clinically to enhance detection of potentially malignant lesions in IBD.

MATERIALS AND METHODS

Patient tissue selection

217 formalin fixed paraffin embedded (FFPE) human tissue specimens, colonoscopically or surgically retrieved between January 2000 to December 2017, were identified from the Edinburgh Pathology database. Tissue included: 30 normal colorectal biopsies, 30 hyperplastic polyps (HP), 31 sessile serrated lesions (SSL), 55 tubular/tubulovillous adenomas with low (TA-LGD, $n = 32$) or high (TA-HGD, $n = 23$) grade dysplasia, 26 sporadic colorectal adenocarcinomas (s-CRC), 16 quiescent IBD biopsies, 11 active/inflamed IBD biopsies, and 18 conventional IBD-associated dysplastic lesions (IBD-dys)-15 were considered low-grade and 3 were considered high-grade. A tissue microarray comprising 102 IBD-associated CRC (IBD-CRC) cores from 43 patient tumours, retrieved from surgical resection specimens between 1994 and 2011, was also used. For all tissue, the original haematoxylin and eosin (HE) diagnostic slide, case history and pathology report were reviewed by two expert gastrointestinal pathologists (MJA, CJB) to ensure consensual agreement and accurate tissue diagnosis. All selected cases were anonymised. Ethical approval was obtained from Lothian NRS Bioresource Research Tissue Bank (15/ES/0094; SR148, SR389, SR400 and SR588).

Immunohistochemistry

Immunohistochemistry (IHC) was performed using an optimised protocol. In summary, 3µm tissue sections were cut by microtomy from each selected FFPE block and floated onto positively charged glass slides. Tissue was oven-dried overnight. Sections were deparaffinised and underwent heat-mediated antigen retrieval in pH6 citrate buffer for 15 min (BOND Epitope Retrieval Solution 1, Leica Biosystems, United Kingdom). After 5 min of peroxidase blocking, tissue was stained for 15 min with recombinant monoclonal anti-MET (c-MET) antibody (ab51067, clone EP1454Y, Abcam, United Kingdom) at a 1:200 dilution, on Leica Bond-III and BONDMAX autostainers (Leica Biosystems, United Kingdom). Primary antibody detection used the BOND Polymer Refine Detection Kit (Leica Biosystems, United Kingdom).

Interpretation of IHC staining

Two expert gastrointestinal pathologists (MJA, CJB) independently assessed c-MET expression as: 0=no staining, 1+ = weak intensity staining, 2+ = moderate intensity staining, and 3+ = strong intensity staining. Epithelial cytoplasmic and epithelial membranous immunopositivity was ubiquitously equivalent in this study which meant one representative score was assigned to each biopsy. Discrepant scores were resolved by discussion and consensus reached. Use of a histoscore was not considered appropriate in small dysplastic lesions. Scoring methodology and staining intensity agreement came from comparison with internal control normal tissue adjacent to the lesions, and previously published staining intensities[7,9-12,14,18]. Negative control slides were used to allow observers to account for background staining (which was negligible due to IHC optimisation).

Statistical analysis

Statistical analysis was performed using IBM®SPSS® V25.0.0.1 and GraphPad Prism software. Associations between ordinal and categorical variables were assessed using exact two-tailed Mann-Whitney *U* and Kruskal-Wallis tests. Scores of 0, 1+, 2+ and 3+ were thus compared and statistical significance was determined at $P \leq 0.05$.

RESULTS

c-MET is ubiquitously expressed in the colorectum, with increased expression in colonic dysplastic and other lesions

Positive epithelial cytoplasmic and membranous c-MET expression was observed in all tissues, indicating there is ubiquitous expression in the colorectum. As anticipated, c-MET expression was weak in normal colonic epithelium compared with each of the sporadic colonic lesions, including TA-LGD ($P < 0.001$), TA-HGD ($P = 0.004$), HP ($P < 0.001$), SSL ($P < 0.001$), and s-CRC ($P < 0.001$) (Figure 1).

Increased c-MET expression is associated with sporadic colonic dysplasia and adenocarcinoma

c-MET expression was stronger in TA-LGD compared with normal colonic mucosa ($P < 0.001$), and stronger in s-CRC compared with TA-HGD ($P = 0.004$). There was no significant difference in c-MET expression between TA-LGD and TA-HGD ($P = 0.852$).

There is no significant difference in c-MET expression between hyperplastic polyps vs sessile serrated lesions

Given the association between c-MET expression and malignancy, we investigated whether there was a difference between hyperplastic polyps (with low malignant potential) and sessile serrated lesions (with higher malignant potential). There was no statistically significant difference in c-MET expression between these lesions ($P = 0.065$).

c-MET shows increased expression in IBD-dysplasia and IBD-cancer compared with quiescent, but not actively inflamed, IBD mucosa

Given the association between c-MET expression and sporadic colorectal carcinogenesis, we assessed whether this was also true for IBD-associated dysplasia and cancer, where detection of dysplasia and cancer is more challenging. c-MET expression was weak in quiescent IBD mucosa compared with active / inflamed IBD ($P < 0.001$). There was no difference in c-MET expression between inflamed IBD mucosa and IBD-dys ($P = 0.512$) or IBD-CRC ($P = 0.296$). However, c-MET expression was stronger in IBD-dys ($P < 0.001$) and IBD-CRC ($P < 0.001$) compared with quiescent IBD mucosa. There was no difference between IBD-dys and IBD-CRC ($P = 0.673$) (Figure 2).

DISCUSSION

This immunohistochemistry study of 319 human tissue specimens provides a comprehensive overview of c-MET expression in both sporadic and IBD-associated colorectal carcinogenesis (Supplementary Table 1). We demonstrate c-MET expression in the colorectum, with an increase in expression in sporadic dysplasia and s-CRC. In IBD-associated lesions we report increased c-MET expression in IBD-dysplasia and IBD-CRC compared with quiescent, but not actively inflamed IBD mucosa.

Previous histopathological studies report overexpression of c-MET in sporadic CRC, associated with tumour invasion, metastasis, local recurrence, and poor overall survival[7-10]. Less data exist for pre-cancerous lesions. However, studies suggest that c-MET expression is increased across the adenoma-dysplasia-carcinoma sequence[11]. These data are in keeping with our comprehensive assessment of sporadic lesions; there is an increase in c-MET expression from normal colonic mucosa to dysplasia to colorectal adenocarcinoma.

Gayyed and colleagues reported increased c-MET expression in colonic polyps with HGD compared with LGD[11]. Our study reported no statistically significant difference between these LGD and HGD groups, using a rigorous approach to achieve full diagnostic agreement from two expert gastrointestinal pathologists, based upon review of the HE slide, and all available clinico-pathological data. The proposed use for c-MET is not necessarily to discriminate LGD from HGD; instead, it is as an *in vivo* probe to improve endoscopic detection of colonic lesions. Both lesions had stronger c-MET expression compared with normal mucosa suggesting that either lesion would be positively identified at colonoscopy allowing targeted biopsy for histopathological assessment.

Identification of SSL from HP is useful as the former have higher malignant potential which is not fully appreciated during endoscopic assessment[19]. Joshi and colleagues report increased c-MET expression in SSL compared with HP, using immunofluorescence on FFPE SSL ($n = 17$) and HP ($n = 10$) tissue. This was also observed by Wu *et al*[13]. In our study, there was no statistically significant difference between SSL ($n = 31$) and HP ($n = 30$) ($P = 0.065$). One reason could be that we used IHC whereas previous studies used immunofluorescence. There has been inconsistent reporting of SSLs; due to previous high inter-observer variability, lack of robust diagnostic criteria and prior misclassification of hyperplastic polyps[19-21]. As previously discussed, our study ensured accurate polyp sub-classification (through consensual agreement by two expert gastrointestinal pathologists) and it is reassuring both lesions had increased expression compared with normal mucosa, as this infers both lesions would

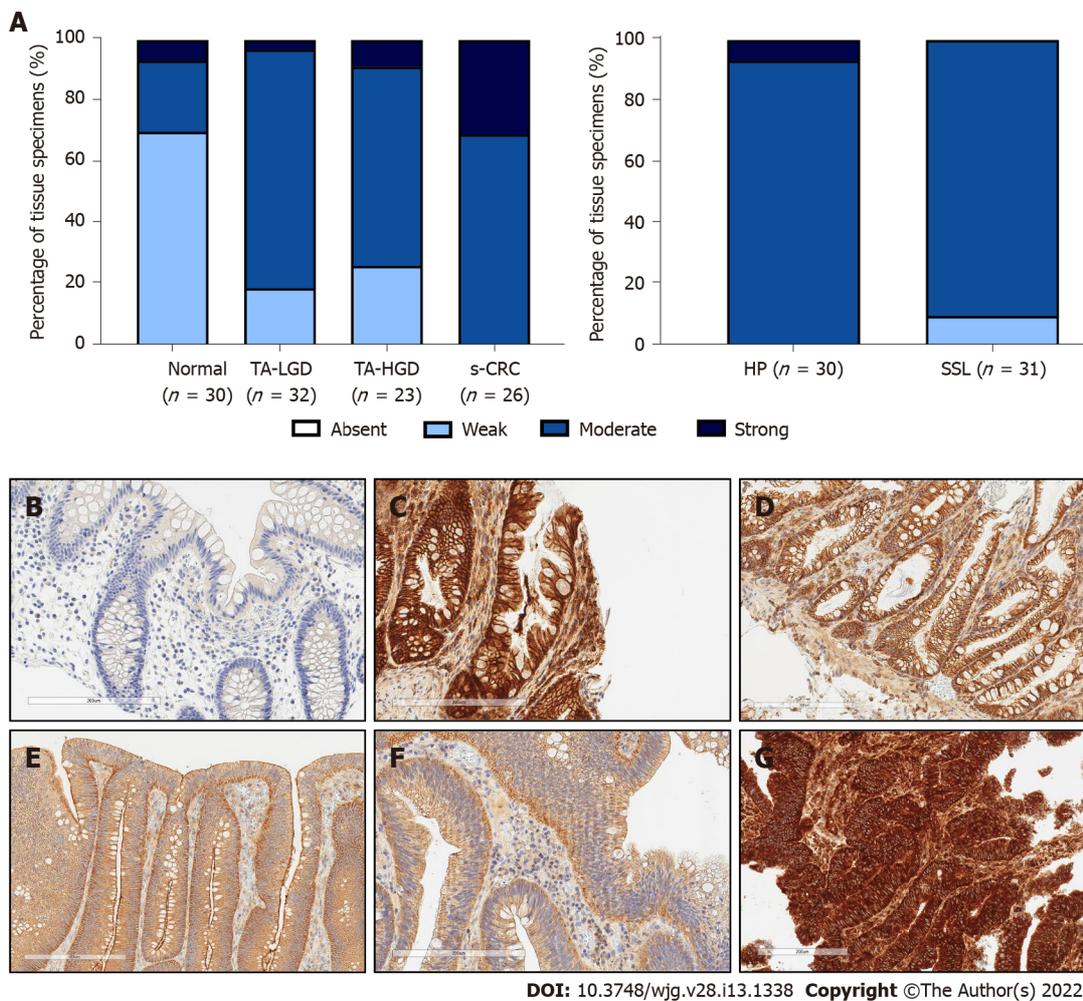


Figure 1 Expression intensity of c-MET in sporadic colonic lesions. A: Semi-quantitative assessment of c-MET expression intensity throughout sporadic colorectal carcinogenesis; B: Representative photomicrograph of normal colonic mucosa; C: Representative photomicrograph of hyperplastic polyp; D: Representative photomicrograph of sessile serrated lesion; E: Representative photomicrograph of tubular/tubulovillous adenoma with low grade dysplasia; F: Representative photomicrograph of tubular/tubulovillous adenoma with high grade dysplasia; G: Representative photomicrograph of sporadic colorectal adenocarcinoma. Tissue provided by Lothian NRS Bioresource. Brightfield photomicrographs taken at X20 magnification. TA-LGD: Tubular/tubulovillous adenoma with low grade dysplasia; TA-HGD: Tubular/tubulovillous adenoma with high grade dysplasia; s-CRC: Sporadic colorectal adenocarcinoma; HP: Hyperplastic polyp; SSL: Sessile serrated lesion.

be positively identified for histopathological assessment and SSL would thus not be missed.

Our study found no difference in c-MET expression between inflamed IBD mucosa, IBD-dys and IBD-CRC. This is in agreement with the IHC study from Harpaz *et al*[18]. A key challenge is detecting dysplasia in the context of inflammation-both endoscopically and histopathologically. While this is a major priority, it is based upon the assumption that the post-colonoscopy CRC rate in IBD is related to active inflammation which reduces the ability to detect dysplasia. Therefore, we need to improve detection across the board. While an inability to distinguish between inflamed IBD mucosa, IBD-dys and IBD-CRC could thus be perceived as a barrier to clinical translation, our study reports lower expression of c-MET in quiescent IBD mucosa. Therefore, careful selection of patients could help identify a cohort which would benefit from the use of such an adjunct in detecting subtle lesions during surveillance colonoscopy. Objective biomarkers such as faecal calprotectin \pm serum C-reactive protein levels could indicate whether a patient is more likely to have quiescent disease. Indeed, The British Society of Gastroenterology recommend surveillance colonoscopy in patients during quiescent phases of disease where possible[3]. Careful protocol optimisation will minimise any background fluorescence, due to microscopic histological inflammation, which may be present in endoscopically normal and/or quiescent mucosa in patients with IBD.

There are several practical questions that now need to be answered to determine the clinical viability of introducing a c-MET probe into IBD surveillance programs: (1) Is a c-MET probe safe and well tolerated in IBD patients; (2) Does inflammation confound endoscopic assessment of colonic lesions using a fluorescent c-MET probe; (3) Can a c-MET probe be optimised to differentiate between background quiescent/non-inflamed colonic mucosa and IBD-associated lesions, as assessed by fluorescence colonoscopy; (4) Can pre-screening patients using symptom questionnaires, faecal calpro-

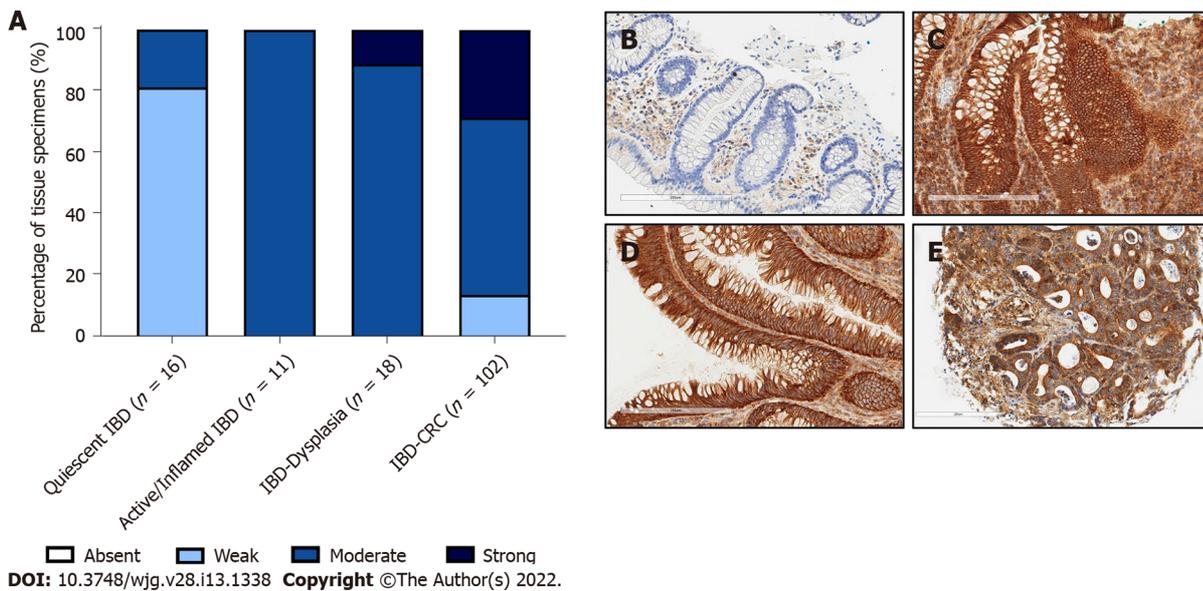


Figure 2 Expression intensity of c-MET in inflammatory bowel disease-associated lesions. A: Semi-quantitative assessment of c-MET expression intensity throughout inflammatory bowel disease (IBD)-associated colorectal carcinogenesis; B: Representative photomicrograph of quiescent IBD mucosa; C: Representative photomicrograph of active/inflamed IBD mucosa; D: Representative photomicrograph of IBD-associated dysplastic lesions; E: Representative photomicrograph of IBD-associated colorectal cancer. Tissue provided by Lothian NRS Bioresource. Brightfield photomicrographs taken at X20 magnification. IBD: Inflammatory bowel disease; CRC: Colorectal cancer.

tecin \pm serum C-reactive protein accurately identify quiescent disease, resulting in low false-positive fluorescence; and (5) Does a c-MET probe offer benefit compared with standard care or other advanced endoscopy techniques for the detection of IBD lesions: for example, can the probe detect endoscopically 'invisible' or flat dysplasia (*i.e.* dysplasia seen only histopathologically on a random biopsy of macroscopically normal mucosa)?

CONCLUSION

In this comprehensive study, we have robustly defined the expression of c-MET in both sporadic and IBD-associated colorectal carcinogenesis. These data provide a platform for clinical studies to investigate the efficacy of an *in vivo* c-MET probe to enhance the endoscopic detection of colonic lesions during IBD surveillance colonoscopy. Such an application would be especially important for identifying IBD-associated dysplasia, to reduce the high post-colonoscopy CRC rate within a pre-selected cohort of patients with quiescent disease.

ARTICLE HIGHLIGHTS

Research background

Patients with inflammatory bowel disease (IBD) are more likely to develop colorectal cancer (CRC) compared with the general population, and surveillance colonoscopy is therefore performed at defined intervals to identify pre-malignant lesions. Despite this, IBD post-colonoscopy CRC rates remain unacceptably high. One key challenge is endoscopically identifying the more subtle and flat lesions associated with dysplasia and cancer in IBD.

Research motivation

There is an urgent need to improve endoscopic detection of pre-malignant lesions, especially in patients with IBD. Recent studies have suggested that an intravenously administered fluorescent probe against c-MET protein may improve the detection of sporadic colorectal lesions-specifically small non-polypoid lesions of similar morphology to IBD-associated (pre-) malignant lesions. However, most data come from murine studies or sporadic disease, and there are lack of immunohistochemical data defining c-MET expression in IBD-associated colonic lesions. This is limiting translational studies.

Research objectives

This study was designed to systematically assess the immunohistochemical expression of c-MET in both sporadic and inflammatory bowel disease-associated colonic lesions.

Research methods

c-MET expression intensity was semi-quantitatively assessed after immunohistochemically staining formalin-fixed paraffin-embedded tissue specimens with an anti-c-MET antibody. Tissue had been colonoscopically or surgically retrieved from patients with and without IBD between 1994-2017, and included normal colonic mucosa, hyperplastic polyps, sessile serrated lesions, tubular/tubulovillous adenomas with low or high grade dysplasia, sporadic-CRC, quiescent IBD mucosa, inflamed IBD mucosa, IBD-associated dysplastic lesions, and IBD-associated CRC.

Research results

There was ubiquitous expression of c-MET in normal colonic mucosa, as well as in sporadic and IBD lesions. c-MET expression intensity was similar between low *vs* high grade dysplasia, and between hyperplastic polyps *vs* sessile serrated lesions. However, c-MET expression was stronger in sporadic dysplasia and cancer compared with normal colonic mucosa. Similarly, c-MET expression was stronger in IBD-associated dysplastic and malignant lesions compared with quiescent IBD mucosa. There was no difference in c-MET expression between inflamed IBD mucosa and IBD-associated dysplasia or malignant lesions.

Research conclusions

c-MET expression intensity is stronger in dysplastic and malignant lesions compared with normal colonic epithelium and quiescent IBD mucosa. These data provide a platform to allow future studies to investigate whether an intravenous anti-c-MET probe could help endoscopically identify dysplasia and malignancy, particularly within surveillance colonoscopy programmes for IBD patients where post-colonoscopy CRC rates are unacceptably high.

Research perspectives

Further study is needed to determine whether histopathological expression correlates with mucosal expression at endoscopy in the context of IBD. The ability of such a probe to improve the endoscopic detection of colorectal lesions and reduce the post-colonoscopy CRC rate should then be assessed, in patients with quiescent IBD.

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FOOTNOTES

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