Original Article

Plasma levels of progranulin, a tumorigenic protein, are persistently elevated during the first month after minimally invasive colorectal cancer resection

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Background: Progranulin (PGRN), also identified as Precursor cell-derived growth factor (PCDGF), is a glycoprotein that is expressed and released ubiquitously. PGRN is plays a crucial role in regulating cell proliferation, differentiation, and pathological pathways. PGRN overexpression has been noted in many cancers and plays an important role in wound healing. Surgery's impact on PGRN levels is unknown. The aim of this study was to assess the levels of plasma PGRN before during the first month after minimally invasive colorectal resection (MICR) for colorectal cancer (CRC) resection.

Methods: CRC patients who were enrolled in a data/plasma bank approved by an Institutional Review Board and underwent MICR for whom adequate plasma samples were available were studied. Blood samples were obtained before surgery and at different time intervals after the operation and late samples were grouped into 7-day blocks and considered as single time points. PGRN levels (pg/mL) were determined in duplicate via ELISA and reported as median and 95% confidence interval (95% CI) values. The paired *t*-test was used for statistical analysis.

Results: Preoperative and 1 or more late postoperative plasma sample were available for 93 MICR CRC patients. The distribution of cancer stages in the final analysis was: stage I accounted for 37% of cases, stage II for 27%, stage III for 32%, and stage IV for 4%. The median preoperative PGRN level was 50.69 pg/mL, 95% CI: 47.71–56.30, n=93. When compared to preoperative levels, significantly elevated (P<0.001) median levels (pg/mL) were noted on postoperative day (POD) 1 (64.78, 95% CI: 60.86–68.83, n=92), POD 3 (69.15, 95% CI: 66.43–74.32, n=85), POD 7–13 (63.93, 95% CI: 59.62–68.35, n=68), and POD 14–20 (68.19, 95% CI: 60.12–73.37, n=26), POD 21–27 (67.38, 95% CI: 60.30–76.65, n=20) and on POD 28–41 (75.13, 95% CI: 54.02–83.16, n=22; P<0.01).

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Conclusions: Following surgery for CRC, plasma PGRN levels showed a significant increase compared to baseline levels, persisting for a duration of one month. This initial surge post-operation could potentially be attributed to the transient acute inflammatory response. The elevation observed in weeks 2 and 4 could potentially be attributed to the process of wound healing, as PGRN has been shown to enhance the accumulation of fibroblasts and facilitate angiogenesis within wounds. Additional investigation is warranted.

Keywords: Progranulin (PGRN); colorectal cancer (CRC); post-operative; plasma levels; minimally invasive resection

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Introduction

Progranulin (PGRN), also known as Precursor cell-derived growth factor (PCDGF), or granulin/epithelin precursor (GEP), is an 88-kDa, 576 amino acid glycoprotein autocrine growth factor that is secreted or stored throughout many tissue types (1). PGRN is involved in regulating not only tissue development, growth, and repair, but also mediates tumorigenesis, as high levels are expressed in human cancers (2). The PGRN gene itself, located on human chromosome 17, is expressed in many epithelial, hematopoietic, and some fibroblast cell lines. It is more constitutively expressed in rapidly dividing cells such as skin, gastrointestinal, immune, and male reproductive systems, and less so in less mitotic tissue such as muscle and connective tissue. PGRN is also increased in fibroblast and endothelial cells (ECs) after cutaneous wounds (3-5). The PGRN protein contains 7.5 domains, known as granulins, after secretion, PGRN may be lysed into effector granulins, each approximately 6-kDa in molecular weight (6). This lysis occurs generally as a response to inflammation, as serine proteases released by neutrophils and macrophages, and metalloproteinases break down PGRN into the individual pro-inflammatory granulins. These individual granulins can neutralize the anti-inflammatory properties of an intact PGRN. Binding proteins such as leukocyte protease inhibitor and apolipoprotein A1 can however protect PGRN from degeneration (7-9).

PGRN acts primarily through the mitogen activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways, stimulating mitogenesis and progression through the cell cycle (10). It is expressed abundantly in multiple human cancers, and is known to contribute to tumorigenesis in breast, ovarian, hepatocellular, colon, and, likely, gastric cancer, with increased expression correlating with aggressive tumor features across multiple cell types (11,12). Notably, PGRN has been found to increase cellular proliferation, reduce apoptosis, and increase invasiveness—all aiding tumor growth (13). Yang *et al.* in 2015 demonstrated poorer prognoses in colorectal cancer (CRC) patients with PGRN overexpression, possibly through the regulation of vascular endothelial growth factor (VEGF) (14). PGRN is also secreted in response to tissue trauma, likely a growth factor playing a part in wound healing. He *et al.* demonstrated elevated levels in adult murine models after transcutaneous punctures, with increased PGRN mRNA expressed in wound infiltrates along with dermal fibroblasts and ECs (15).

Highlight box

Key findings

- Plasma progranulin levels were significantly elevated over baseline for one month after minimally invasive cancer resection for colorectal cancer.

What is known and what is new?

- Progranulin is released in reaction to tissue injury, recognized as a growth factor involved in the process of wound healing, and is expressed abundantly in multiple human cancers. The current study, which is the initial one to examine progranulin (PGRN) levels postoperatively, indicates that, despite not being related to colon cancer, plasma PGRN concentrations stay significantly increased compared to preoperative levels for approximately one month.

What is the implication, and what should change now?

- Progranulin and other angiogenic proteins that remain elevated for an extended period after surgery have the potential to enhance tumor growth through angiogenesis-related pathways. It is essential to conduct additional research to create perioperative anti-cancer therapies that are both efficient and do not impede the wound healing process.

Furthermore, application of PGRN to wound beds was found to stimulate inflammatory cells and wound healing processes (15). Similar factors are known increase after surgical trauma in cancer patients; Kumara *et al.* demonstrated that minimally invasive colorectal resection (MICR) is associated with plasma VEGF and angiopoietin-(Ang) 2 elevations changes for 4 weeks after surgery (16). Furthermore, when plasma from up to 20 days post-operatively was added to *in vitro* EC cultures, cell growth, invasion, and migration was stimulated (16,17). The plasma levels of 14 proangiogenic plasma proteins have been found to be persistently increased post-operatively in surgical patients, including: interleukin-8, osteopontin, and keratinocyte growth factor, among many others (16-30). Given these changes it is possible that post-operative plasma may promote the growth of residual tumor deposits after resection of the primary tumor. Whereas plasma PGRN levels have been shown to be elevated preoperatively in CRC patients, the impact of surgical resection, if any, on blood levels is unknown. The aim of this study was to assess the levels of plasma PGRN prior to and within the initial month following MICR for CRC. We present this article in accordance with the MDAR reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-114/rc).

Methods

Study population

This study was carried out with plasma and data from CRC patients who underwent elective MICR between 2009 and 2014 and had voluntarily enrolled in an Institutional Review Board (IRB) approved prospective perioperative tissue and data bank at Mount Sinai West Hospital (New York, NY, Institutional Review Board of the Mount Sinai School of Medicine, New York; IRB reference No.: GCO1: 16-2619). This tissue /data bank also contained specimens from MICR CRC patients (operations in 2007–2009) enrolled in a similar tissue/data bank at New York Presbyterian Hospital (Columbia University campus, Institutional Review Board of the Columbia university medical center, New York; IRB reference No.: AAAA4473). Preoperative and multiple postoperative blood samples were obtained from all consented patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The blood samples were centrifuged in a timely fashion and the plasma harvested, aliquoted and stored at −80 ℃ until further utilized. The purpose of the tissue/data banks, as per the IRB protocols, was the evaluation of the physiologic, immunologic, and oncologic impact of colorectal resection. Patients who received a novel drug or underwent other surgical procedures were excluded as were immunosuppressed patients and those who received perioperative blood transfusion(s). Only patients for whom blood samples had been obtained preoperative, on postoperative day (POD) 1 or 3 and at least one late post-operative day beyond POD 7 were included in the study group. The late post discharge specimens were collected during follow-up office visits and were spread out over a 3–4-week period. Since post discharge blood samples were not obtained on set PODs, the late samples were bundled into 7-day time blocks (POD 7–13, POD 14–20, POD 21–27, and POD 28–41) and were considered at single time points for the data analysis.

Blood sampling and processing

Preoperative blood samples were obtained from all patients who were enrolled in the tissue/data banks. Samples were also obtained preoperatively, on POD 1 or 3, and at least 1 late time point (after POD 7). Blood samples were collected in heparin-containing tubes (Cat No.: 367878 Becton Dickinson, New Jersey, USA) and were processed within 5–6 hours. The plasma was isolated by centrifugation (450 ×g at 10 ℃) and stored in 500 µL aliquots at −80 ℃ until further analysis.

Plasma PGRN determination

PGRN levels in plasma were assayed in duplicate using commercially available enzyme linked immunosorbent assay (ELISA) (Cat No.: DPGRN0, R&D Systems, Minneapolis, USA) according to the manufacturer's instructions. PGRN concentrations were calculated via standard curve and expressed as median and 95% confidence interval (CI) values (picograms per milliliter, pg/mL).

Statistical analysis

The PGRN data were analyzed using the Wilcoxon's paired *t*-test. Significance was set at $P<0.05$. Continuous random variables such as age, surgical time, length of stay, surgical incision size of group was presented as mean and standard deviation whereas frequencies and percentages were determined for categorical variables. Blood samples

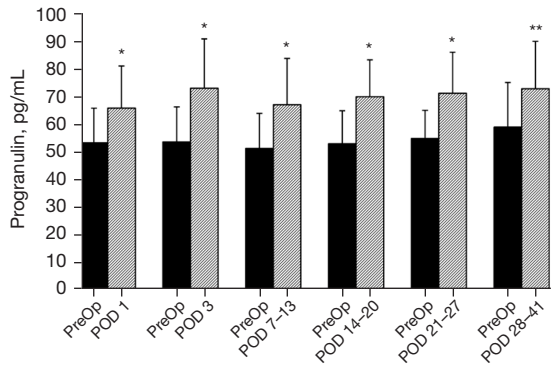

Figure 1 ELISA determined PreOp and postoperative plasma PGRN levels of colorectal cancer patients. Plasma PGRN levels are depicted as median and 95% CI values. *, PreOp *vs.* POD 1 (n=92, P<0.001); *, PreOp *vs.* POD 3 (n=85, P<0.001); *, PreOp *vs.* POD 7–13 (n=68, P<0.001); *, PreOp *vs.* POD 14–20 (n=26, P<0.001); *, PreOp *vs.* POD 21–27 (n=20, P<0.001); **, PreOp *vs.* POD 28–41 time point (n=22, P<0.01). PreOp, preoperative; POD, postoperative day; ELISA, enzyme linked immunosorbent assay; PGRN, progranulin; CI, confidence interval.

collected at postoperative time points were collected during postoperative follow-up visits and as such the late specimens were spread out over a 3–4-week period. The samples obtained at a later stage were organized into 7-day segments (POD 7–13, POD 14–20, POD 21–27, and POD 28–34) and were regarded as distinct time points for the purpose of statistical data analysis. Since preoperative and corresponding postoperative PGRN values were not normally distributed at later time points, the comparison of PGRN values for the preoperative *vs.* postoperative time points was performed with the use of non-parametric test (Wilcoxon signed rank paired) and outcome data were reported as median and 95% CI values. Preoperative *vs.* postoperative comparison data are depicted in a bar graph showing PGRN levels as median and 75% quartile range. The graph exhibits (*Figure 1*) the difference of preoperative *vs.* postoperative PGRN level at each time points. The comparison of PGRN levels between subgroups of patients who underwent laparoscopic assisted procedure *vs.* hand assisted procedures, advancing cancer stage groups and male *vs.* female groups were carried out using nonparametric Mann and Whitney test, because comparisons were done between different groups and numbers(n) of each group were small. Correlation between postoperative plasma PGRN levels and age and length of surgery was evaluated by the Spearman's rank correlation coefficient (rs). A P value of P<0.05 was considered as statistically significant. All data analysis was performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL, USA).

Results

The study group consists of 93 CRC (colon 73%, rectal 27%) MICR patients [mean age 66.3±13.2 years; male, 50 (54%); female, 43 (46.0%)]. The breakdown of operations performed was: right hemicolectomy, 37.0%, sigmoid resection, 24.0%, low anterior resection or anterior resection, 17%, and other 22% (*Table 1*). Laparoscopic-assisted operations were done in 68% [mean incision length (IL) 7.1±4.2 cm] and hand-assisted laparoscopic resection in 32.0% (mean incision size, 11.0±4.22 cm). The mean surgical time was 309.1±120.9 minutes. The mean hospital length of stay (LOS) was 6.7±4.1 days. Complications noted included: ileus (6 patients), urinary retention [6], urinary tract infection [4], atelectasis [3], pleural effusion [2], other [3]. There were no deaths. The final cancer stage breakdown was as; stage I (n=34,) stage II (n=25), stage III (n=30) and stage IV (n=4).

When compared to median preoperative PGRN levels (50.69 pg/mL, 95% CI: 47.71–56.30, n=93), significantly elevated (P<0.001) levels (pg/mL) were noted on POD 1 (64.78, 95% CI: 60.86–68.83, n=92), POD 3 (69.15, 95% CI: 66.43–74.32, n=85), POD 7–13 (63.93, 95% CI:59.62–68.35, n=68), and POD 14–20 (68.19, 95% CI: 60.12–73.37, n=26), POD 21–27 (67.38, 95% CI: 60.30–76.65, n=20) and on POD 28–41 (75.13, 95% CI: 54.02–83.16, n=22; P<0.01) (*Figure 1*). There was no significant correlation noted between postoperative PGRN levels and age or length of surgery. Also, no significance differences in PGRN levels were found between male *vs.* female patients at any perioperative time points or between the different cancer stage groups. The percent increase of the mean PGRN level from the mean preoperative baseline at each time point was as follows, POD 1, 23.5%; at POD 3, 36.01%; POD 7–13, 30.8%; POD 14–20, 32.2%; POD 21–27, 29.8%; and at POD 28–41, 23.6%.

The effect of surgical incision size (i.e., extent of largest abdominal wall trauma) on postoperative PGRN levels were assessed as the hand-assisted laparoscopic subgroup's mean incision size (n=30, mean IL) was higher than the mean incision size of laparoscopic assisted patient group (n=63, mean IL 7.1±4.2 cm). There was no significance difference found between the mean postoperative PGRN levels of the laparoscopic-assisted (mean IL 7.1±4.2 cm) and hand

Table 1 Clinical and demographic data of the study population

Demographic data	Values
Age (years)	66.3±13.2
Sex	
Male	50 (54.0)
Female	43 (46.0)
Incision size (cm)	
Total study patient population	8.4±4.5
Laparoscopic procedure group	7.1±4.2
Hand-assisted procedure group	11.0±4.22
Operative time (min)	309.1±120.9
Length of stay (days)	6.7±4.1
Type of resection	
Right	34 (37.0)
Sigmoid/Recto-sigmoid (17/5)	22 (24.0)
LAR/AR (12/4)	16 (17.0)
Transverse	8 (9.0)
Total/subtotal (2/5)	7 (7.0)
Left	4 (4.0)
APR	2 (2.0)
Surgical method	
LAP	63 (68.0)
HAL	30 (32.0)

Data are presented as mean ± SD or n (%). LAR, low anterior resection; AR, anterior resection; APR, abdominoperineal resection; LAP, laparoscopic procedure-assisted; HAL, hand-assisted/hybrid laparoscopic; SD, standard deviation.

assisted groups (mean IL, 11.0±4.2 cm) at any postoperative time point.

Discussion

This study revealed that plasma levels of PGRN are notably elevated after MICR in CRC patients when compared to preoperative levels and that these elevations persist for over 1 month after surgery. The study patients, thankfully, did not have any major complications and there were no perioperative deaths. The mean IL was 8.4±4.5 cm and mean LOS 6.7±4.1 days. The postoperative changes were not found to be related to the specific MIS method used, the location of the cancer (rectal *vs.* colon), cancer stage, or age or sex of the patient. The percent change from the mean baseline PGRN level at the 6 postoperative time points ranged from 23% to 36% ($P<0.05$ at all-time points).

The long duration increase in plasma PGRN levels observed in this study population is similar to that observed in similar CRC patient populations for more than 12 other plasma proteins (16-30); PGRN joins this growing list. It should be noted that the vast majority of blood protein changes associated with major surgery are short lived with a duration lasting from hours to a few days [interleukin (IL)-2, C-reactive protein (CRP), IL-6, tumor necrosis factor (TNF), fibroblast growth factor (FGF), etc.]. Anesthesia, surgical trauma and the acute inflammatory response that has been well documented to occur post-surgery likely account for these short term changes. The etiology of the much rarer persistent increases that last weeks following MICR are harder to explain. There is evidence that for a number of these proteins [VEGF, PLGF, angiopoetin-2 (ANG2), MCP-1, CHI3L1, OPN, MMP2 and MMP3] the healing surgical wounds may be the source of the additional protein (31).

An investigation analyzing wound fluid and plasma samples from MICR CRC patients at various postoperative time points found that the protein levels in the wound were 3 to 10 times higher than in the plasma, which were significantly higher than preoperative levels (31). Although wound fluid PGRN levels were not assessed in this study, it is possible that the elevated PGRN levels late postoperative are related, at least in part, to wound healing. There is murine evidence suggesting that tissue trauma may stimulate PGRN release. He *et al.* in 2003 noted PGRN mRNA in infiltrate from transcutaneous wounds created by punch biopsy. PGRN mRNA was also found to be upregulated in dermal fibroblasts and ECs from the wounds. In addition, application of PGRN to cutaneous wounds brought about the migration of various inflammatory and angiogenic cells as well as fibroblasts to the wound bed; these cells, when activated, create conditions conducive to wound healing (15). These findings raise the possibility that tissue trauma in humans may stimulate PGRN release.

What is the significance, if any, of the long duration plasma PGRN increases? There is murine evidence that PGRN may indirectly promote mitogenesis. PGRN via the p44/42 MAPK, PI3K, and Shc pathways mimics, in some respects, IGF-1 signaling and may enhance IGF-1 signaling (32). IGF-1 via IGF-IR promotes mitogenesis and protects cells from apoptosis, induces differentiation, and initiate transformation. Overexpression of PGRN in

mice that do not express IGF-1R genes is associated with mitogenic effects similar to those induced via IGF/IGF-1R signaling (33). PGRN's properties as a growth factor able to bypass the need for an activated IGF-IR may have clinical implications related to tumorigenicity.

Notably, PGRN has been shown to actively confer malignancy when artificially overexpressed in normally less malignant adenocarcinoma cell lines in murine models (10). PGRN has also been found to increase cellular proliferation, reduce apoptosis, and increase invasiveness-all aiding tumor growth primarily through the ERK and PI3K pathways. Importantly, PGRN is expressed abundantly in multiple human cancers. In early-stage breast cancer patients, overexpression of PGRN correlates with lower disease-free and survival rates. Also, the mitogenic activity of estrogen has been shown to be mediated by PGRN through stimulation of cyclin D1 expression (34). Cyclin D1 overexpression has been linked to multiple cancers including lung, esophagus, and bladder cancer (35). As regards ovarian cancer, a pilot study evaluating PGRN as a biomarker in advanced cases found PGRN was independently associated with progression-free and overall survival (36). Liu *et al.* demonstrated decreased invasion and proliferation of ovarian cancer cell lines after inhibition of PGRN (1). Cheung *et al.* have also demonstrated in their research that aggressive characteristics of hepatocellular carcinoma (HCC), such as large tumors, venous infiltration, and early recurrence, are linked to the expression of PGRN. In *in vivo* HCC study, anti-PGRN monoclonal antibody A23 has been shown to inhibit HCC cell lines in a dose-dependent fashion, suggesting that targeting PGRN may in fact inhibit or decrease HCC tumor propagation (37).

In SW480 human colon cancer cell cultures increased migration and invasion was demonstrated when PGRN was overexpressed; likewise, decreased tumor cell migration and invasion was noted when PGRN was knocked out in SW620 cell line cultures (38). Koo *et al.* in a study of 109 CRC patients found that the subgroup with high PGRN-expressing tumors had a trend toward significantly elevated CEA and CA-19-9 levels. Patients with high PGRN tumors also had significantly lower 3-year recurrence-free survival (66.8%) compared to low PGRN patients (92.4%) after tumor resection (39). It is also possible that the increased PGRN plasma levels might impact tumor angiogenesis early after surgery.

VEGF is a known angiogenic and endothelial factor that plays a critical role in tumor spread and blood vessel formation; VEGF fosters EC adhesion, survival, migration, and invasion (40). PGRN has been found to stimulate VEGF expression in breast, mesothelioma, and CRC tumor cells, *in vitro* (41,42). PGRN overexpression has also been shown to promote Ki67 and VEGF-A expression as well as the rate of growth in CRC cell lines (14). PGRN's potential proangiogenic effects are similar to most of the proteins, mentioned above, whose levels are increased for 2–5 weeks after surgery. As noted earlier, at least in *in vitro* EC cultures, the impact of postoperative plasma from the first 2 weeks after MICR for CRC, is proangiogenic with increased EC growth, migration, and invasion (16).

Given PGRN's proangiogenic effects, although unproven, the postoperative elevations may contribute to the proangiogenic properties of postoperative plasma. Are there clinical ramifications of the persistently elevated PGRN levels? Or, collectively, of the similar long duration elevations noted for the other proteins mentioned above? It is possible, although unproven at this time, that the proangiogenic postoperative plasma might promote tumor angiogenesis in residual tumor deposits left behind in the early postoperative period. Although there is no conclusive evidence, a case can be made that increased PGRN in the plasma might be a stimulus for increased tumor growth post MICR (via mechanisms not related soley or at all to angiogenesis—by other tumor growth related effects).

The relatively small size of the current study is a weakness as is the fact that the 'n' of the late postoperative time points is limited. The fact that wound fluid was not also collected and analyzed makes it impossible to assess this possible source of the added protein. The study also cannot address the clinical relevancy of the noted changes. Also, ideally, the levels of the other proteins known to be increased along the same timeline (3–5 weeks postoperative) would be simultaneously measured perioperative. Further perioperative plasma PGRN study may be warranted, with a larger sample size and the inclusion of additional postoperative time points throughout the initial months following surgery to more accurately define the expression pattern of PGRN. Assessing PGRN levels in patient with benign pathology who undergo colorectal resection would likely demonstrate similar findings since it is not believed that the indication for surgery.

Conclusions

Our study demonstrated significantly elevated plasma PGRN levels *vs.* preoperative baseline levels for 1 month after MICR for CRC. The early increase after surgery may

be due to the short lived acute inflammatory response, however the persisting elevations noted during weeks 2 through 4 may be related to the wound healing process as PGRN stimulates fibroblast accumulation, promotes angiogenesis in wounds, and because wound levels are increased following tissue trauma in murine studies. Although unproven, after surgery, PGRN, in addition to the other proangiogenic proteins whose levels are elevated persistently postoperative, may stimulate angiogenesis in residual tumor deposits after surgery. It may also stimulate tumor growth via other mechanisms. Additional investigation is warranted to further elucidate the patterns of PGRN increase as well as the clinically relevancy of these changes.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-114/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-114/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-114/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-114/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The present study was carried out by using material collected from patients who consented preoperatively to participate in the Mount Sinai West Colorectal service's IRB-approved tissue and data banking protocol (No.: GCO1: 16-2619-Institutional Review Board of the Mount Sinai School of Medicine, New York); and in a similar tissue/data bank at New York Presbyterian Hospital (Columbia University campus, Institutional Review Board of the Columbia university medical center, New York; IRB reference No.: AAAA4473). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all participating colorectal cancer patients who were enrolled in an IRB approved data/plasma bank and all patients assented to analysis, to present and to publish the paper.

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