PVT1: novel colorectal cancer biomarker

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Colorectal cancer is a very deadly disease with a current lack of a reliable biomarker for early detection, non-invasive diagnosis, treatment, prognostication, and monitoring of treatment. This entry provides information that indicates that PVT1 is a novel biomarker in colorectal cancer. Further research is required to establish how this knowledge can be used for clinical applications.

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Colorectal cancer (CRC) is a leading cause of death worldwide, despite progress made in detection and management through surgery, chemotherapy, radiotherapy, and immunotherapy. Novel therapeutic agents have improved survival in both the adjuvant and advanced disease settings, albeit with an increased risk of toxicity and cost. However, metastatic disease continues to have a poor long-term prognosis and significant challenges remain due to late stage diagnosis and treatment failure. Biomarkers are a key tool in early detection, prognostication, survival, and predicting treatment response. The past three decades have seen advances in genomics and molecular pathology of cancer biomarkers, allowing for greater individualization of therapy with a positive impact on survival outcomes. Clinically useful predictive biomarkers aid clinical decision making, such as the presence of KRAS gene mutations predicting benefit from epidermal growth factor receptor (EGFR) inhibiting antibodies. However, few biomarkers have been translated into clinical practice highlighting the need for further investigation. We review a range of protein, DNA and RNA-based biomarkers under investigation for diagnostic, predictive, and prognostic properties for CRC. In particular, long non-coding RNAs (lncRNA), have been investigated as biomarkers in a range of cancers including colorectal cancer. Specifically, we evaluate the potential role of lncRNA plasmacytoma variant translocation 1 (PVT1), an oncogene, as a diagnostic, prognostic, and therapeutic biomarker in colorectal cancer.

1. Introduction: Epidemiology, Burden of Disease and Challenges in Treatment & Chemoresistance

1.1. Epidemiology

Colorectal cancer (CRC) is the fourth most common cancer overall worldwide contributing to 9.7% of global cancer burden [1][2][3][4][5]. It affects 746,000 men (10% of all cancer cases) and 614,000 women (9.2% of all cancer cases) with most cases (55%) occurring in developed countries [3][6]. Furthermore, in the UK, 42,300 new colorectal cancer cases are diagnosed each year making it the fourth most common cancer overall, and third most common in males and females [5]. In addition, the incidence of colorectal cancer increased between 1991 and 2016 and is attributed to lifestyle, environmental changes, and aging populations [7][8]. Although bowel cancer incidence has

fallen in the UK in the past decade by 4%, the lifestyle risk factors remain. Moreover, the burden of CRC is expected to increase with 2.2 million new cases and 1.1 million deaths expected globally by 2030 [9]. In addition, significant challenges remain in managing disease burden. In England, five-year overall survival for CRC is 58.4% which is lower than the US reported 60–65% [10][11]. Moreover, US reported survival was static between 1996 and 2014 [10][11]. Further challenges remain due to the ageing demographic and advanced presentation of disease [12]. Older patients, above age 75 years, make up 44% of new colorectal cancer diagnoses and an estimated 20–25% of CRC is diagnosed at the metastatic stage with an additional 25% of patients developing metastasis during their illness [5][13]. As a result, CRC accounts for 8.5% of cancer related deaths worldwide with 16,300 deaths per year in the UK making it the second most frequent cause of cancer related deaths at 10%. Although survival is stage dependent with 92% survival for stage I, compared to 10% in stage IV, there has been an improvement in survival for the 60–69 year age group attributed to screening [5]. Thus, CRC remains a prevalent challenge in cancer management emphasizing the need for early diagnosis.

1.2. Screening Programs

Declining mortality due to improvements has been shown with early detection through screening and effective treatment [14][15][16][17]. The UK CRC screening program relying on fecal detected occult blood (FOBT) and colonoscopy has led to 16% decline in overall mortality rate without affecting incidence [18]. However, FOBT has reduced sensitivity for advanced adenomas and CRC which may improve with newly implemented immunochemical testing (FIT) [19][20]. This screening test is offered in the UK every 2 years between 60–74 years with a one-off test aged 55 years [5]. These tests are precursors for more invasive colonoscopy to identify pre-malignant or malignant lesions. Furthermore, studies randomized trials have shown a reduction in CRC incidence up to 23% and CRC-related mortality by 31% using flexible sigmoidoscopy as a primary screening tool [21]. However, this remains an invasive and resource intensive technique. There is no universally agreed screening protocol for early disease stages, and significant variation remains. In addition, up to 70% of cancers presenting with symptoms are at an advanced stage [22]. This emphasizes the value of screening programs with early detection of pre-malignant or early stage (I-II) CRC leading to improved CRC survival, quality of life and disease-free outcomes. Moreover, screening for biomarkers at all stages, including diagnostic, prognostic, and predictive, may provide opportunities for targeted intervention to improve outcomes whilst reducing the risk of treatment toxicity [10][22].

1.3. Current Treatment Effectiveness

Treatment of CRC depends upon stage of disease according to the TNM classification, patient health, and curative versus palliative intent [12][23][24][25]. This comprises surgery, chemotherapy, and immunotherapy. Factors including stage, circumferential resection margin, lymphovascular invasion, perineural invasion, and genotyping are used to determine need for and type of adjuvant treatment [26][27]. Fluorouracil (5-FU), a fluoropyrimidine is used as part of the FOLFOX (Folinic acid + Oxaliplatin) or FOLFIRI (Folinic acid + Irinotecan) regimens leading to improved overall disease-free and progression-free survival in both advanced and metastatic disease [24][27][28][29]. However, 5-FU is associated with toxicity and reduced clinical response in patients with microsatellite instability (MSI) status as well

as dihydropyrimidine dehydrogenase (DPYD) deficiency [30][31][32][33][34]. In addition, 5-FU leads to a modest 2–4% improvement in five-year disease free survival in stage II CRC [35]. However, previous studies have shown between 20–25% recurrence in treated Stage II lymph node negative colon cancer within five years [36][37]. In addition, the anti-EGFR cetuximab and anti-vascular endothelial growth factor receptor (VEGFR) bevacizumab response rate is higher in Kirsten rat sarcoma viral oncogene (*KRAS)* wildtype compared to *KRAS* mutants leading to its application in clinical practice [38][39]. Moreover, in metastatic CRC, the anti-programmed cell death receptor-1 agents Nivolumab and Ipilimumab have shown benefit in MSI and mismatch repair deficient genotypes thereby gaining approval in patients progressing on first line chemotherapy [40]. Further experimental treatments such as Regofarenib, an anti-angiogenic compound, shows poor overall survival in *KRAS* mutants but improved progression free survival in association with phosphorylated proline-rich protein kinase B (AKT) in metastatic CRC [41][42]. Thus, although the revised TNM application may lead to a reduction in over or undertreatment of CRC, the risks versus benefits of treatment selection need to be informed by molecular characteristics of individual tumors to develop personalized treatment, overcome poor efficacy and chemoresistance.

2. Why Do We Need a Biomarker: The Role for Biomarkers in Early Detection of Colorectal Cancer

Biomarkers are molecular patterns that can be used as a tool for early cancer detection and individualized CRC treatment [30][43][44]. They can be divided into diagnostic, prognostic, or predictive categories. Thus, biomarkers provide utility at different stages of the disease to determine disease progression, recurrence, as well as providing a personalized indicator for therapeutic effectiveness.

Firstly, early diagnosis in asymptomatic patients remains a key target to achieve favorable survival outcomes through identification of early CRC as well as pre-malignant lesions including high risk polyps. The sensitivity for detecting CRC using current FIT testing (100ng/mL) is 73.8% versus 92.3% for a stool-based DNA assay screening *KRAS*, aberrant *NDRG4* and *BMP3* methylation [19]. Furthermore, FIT testing sensitivity for advanced precancerous lesions is 23.8% versus 42.4% with stool DNA testing [19]. Moreover, the rate of detection of polyps with high-grade dysplasia is 46.2% with FIT testing verses 69.2% with stool DNA testing, whereas the detection rate of serrated sessile polyps measuring > 1 cm is only 5.1% (FIT) versus 42.4% with stool DNA sampling [19]. These findings highlight the limits of current diagnostic screening and difficulty in establishing appropriate surrogate markers for early disease detection. Current non-invasive screening stools are not sensitive to detect pre-cancerous lesions and may miss significant early CRC. A low threshold must therefore be maintained for more invasive colonoscopy in these patients and further tools are required to support identifying early CRC.

Secondly, prognostic biomarkers can be used to predict disease progression including early recurrence and mortality [10][45]. KRAS is part of the *RAS* proto-oncogene family of GTPases which acts to turn off cell proliferation [45]. Mutations in *KRAS* are associated with increased risk recurrent metastatic CRC following curative resection as well as worse overall survival following hepatic metastasectomy in metastatic CRC [46][47]. Furthermore, the *BRAF* proto-oncogene works via the RAS-RAF-MEK-ERK pathway regulating cell transcription [48]. The *BRAF* V600E mutation is associated with reduced survival, including progression-free and up to 50% worse overall survival

compared to *BRAF* wildtype [49][50][51][52]. In the emerging field of radiogenomics, a combination of radiological and genetic features may give greater prognostic sensitivity than either of these modalities in isolation [53][54]. Finally, the carcinoembryonic antigen (CEA), a high molecular weight glycoprotein is used as a biomarker to predict early recurrence in post-operative patients despite low sensitivity and specificity [55][56]. Thus, using prognostic markers may alter thresholds for further investigation of recurrent disease and provide opportunities for early intervention. Moreover, they may alter thresholds at which patients are offered more aggressive treatment.

Additionally, predictive biomarkers are used to individually tailor treatments according to molecular subtype. *KRAS* mutations are associated poor response to anti-EGFR receptor therapy including cetuximab and panitummumab [57][58]. There was a 16% increase in overall response rate in *KRAS* wildtype patients with FOLFIRI and cetuximab compared to 4% decrease in *KRAS* mutants. Since *KRAS* mutantions are present in up to 40% of patients, a significant portion of patients can be spared expensive anti-EGFR treatment. Furthermore, irinotecan, a topoisomerase inhibitor used as part of FOLFIRI regimen, is metabolized by diphosphate-glucuronosyltransferase 1A (UGT1A). Homozygosity for *UGT1A1*28* allele is associated with dose dependent increase in toxicity compared to *UGT1A1*1* genotype [59]. Moreover, dihydropyrimidine dehydrogenase (DPD) is responsible for metabolizing more than 80% of 5-FU [56]. *DYPD*2A* and *DPYD*13* variants lead to increased toxicity with evidence that reducing 5-FU dose by 25–50% can lead to a reduction in toxicity [60]. These interventions may thus lead to improved treatment response and reduced toxicity arising from ineffectual interventions. They can also help in making dose adjustments to gain maximum benefit from a selected regimen. The need to develop further biomarkers is amplified by the fact that only *KRAS*, *NRAS*, *BRAF* and MSI status is recommended by national guidelines in evaluating treatment response and predicting outcomes in CRC [61]. However, several potential categories of biomarkers remain under investigation.

3. The Role of PVT1 in the Diagnosis, Treatment and Prognosis of Colorectal Cancer

Plasmacytoma variant translocation 1 (*PVT1*) is a lncRNA located on human chromosome 8q24.21 adjacent to the oncogene *C-MYC* and undergoing p53 dependent transcription [62]. It consists of 1957 base pairs encoding between nine and 12 exons that are variably spliced along with introns giving rise to six miRNAs: miR-1204, miR-1205, miR-1206, miR-1207-3p, and miR-1207-5p [63]. Moreover, at least 14 alternately spliced transcripts have been identified at tissue-detectable levels with 11 transcripts present in normal gastrointestinal mucosa as well as adenocarcinoma . The *PVT1* gene is differentially expressed among populations [64]. Furthermore, quantification of *PVT1* expression pattern reveals variations between tissue types with maximal expression in ovaries, lymph nodes and bone marrow and moderate levels of expression in the colon [65]. Of note, the PVT1-217 transcript is the most abundant in the gastrointestinal tract mucosa. Furthermore, *PVT1* expression is elevated in multiple cancer types including lung [66], prostate [67], cervical [68], and colon [69]. Possible functional roles for *PVT1* are mediated by miRNAs, and competing endogenous RNA (ceRNA), involving regulation of gene activity through *C-MYC* activation [70]. There is evidence of *PVT1* acting as a tumour-suppressor DNA boundary element through competition with the

C-*MYC* promoter for shared enhancers within the gene locus [71]. Moreover, *PVT1* activity may affect cell growth, replication and proliferation which may drive both carcinogenesis and chemoresistance [72].

Several studies have shown a potential oncogenic role for *PVT1* [73] with implications for tumor initiation, progression, spread and survival. Takahashi et al. examined cell lines from 164 CRC patients, showing an increase in *PVT1* expression in tumor cells which correlated with poor overall survival. Moreover, knockdown of *PVT1* with siRNA promoted apoptosis and reduced the invasive capability of cells [74]. High expression of specific splice variants like *PVT1* -214 is associated with poor overall survival and acquisition of stem-cell like properties including invasion and cell migration [75]. Furthermore, downstream targets of *PVT1* such as miR-26b could provide both a mechanism as well as more specific biomarker readouts of *PVT1* activity in CRC [65]. Poor overall survival with elevated *PVT1* expression as well as increased cell proliferation, invasion and metastasis has been shown in further studies [76]. In addition, high relative levels of *PVT1* in extracellular vesicles from CRC cell lines SW480 and SW620 with higher levels in the more aggressive SW620 line [77]. This was associated with co-amplification of *C-MYC* and C-MYC dependent genes *FUBP1*, *EZH2*, and *NPM1*. Moreover, this effect was reversed with inhibitory siRNA resulting in an increase in apoptosis and reduction in cell proliferation. Finally, quantification of *PVT1* expression from tumors and adjacent normal tissue in 210 CRC patients showed a 51.4% increase correlating with tumor differentiation, invasion, higher stage, and lymph node spread [78]. High *PVT1* expression in these patients was associated with reduced overall and disease-free survival. Interestingly, not all CRC cell lines show invasive behavior attributable to *PVT1*. The HCT116 CRC cell line did not show greater invasiveness compared to control lines [79]. Overall, the correlation of high *PVT1* expression and reduced overall survival in CRC as well as other types of cancer has been encapsulated in a meta-analysis of 39 studies [80]. Another promising area is the identification of *PVT1* polymorphisms which predict outcomes in CRC. The rs1252200336 polymorphism showed a 2.71 times higher risk of CRC in the ID vs II genotypes with lower survival in the Han Chinese population [81]. Thus, *PVT1* has the potential to be a prognostic biomarker in CRC that correlates with disease severity and aggressive phenotypes. Much of the work however has been done in cell-based assays which will need to be replicated in clinical settings. Table 1 summarises the current literature explaining the oncogenic role of *PVT1* through its actions on miRNAs in promoting CRC.

PVT1 expression can be used as a readout of therapeutic drug response as well as drug resistance. In a comparison of cisplatin sensitive versus resistant CRC patients, overexpression of *PVT1* was associated with cisplatin resistance [82][83]. This was mediated by upregulation of multi-drug resistance protein 1 (MRP1) and inhibition of the intrinsic apoptotic pathway with decrease in *BCL-2* expression. These changes could be reversed by siRNA targeting *PVT1*. Furthermore, the HCT116 CRC cell line resistant to 5-FU displays high levels of *PVT1* expression and upregulation of MRP1 . siRNA against *PVT1* led to reduced cell survival and increased apoptosis as well as reduced MRP1 expression . Similar findings have been demonstrated within in vitro models showing 5-FU resistance with high PVT1 expression in gastric cancer [84][85] and glioma . Therefore, *PVT1* expression can be used as a biomarker to rationalize treatment selection in CRC patients by predicting drug resistance. Moreover, *PVT1* may itself be a target for therapeutic intervention .

Finally, *PVT1* has the potential to be a diagnostic biomarker although few studies have investigated this potential. Gharib et al. investigated *PVT1* expression as a biomarker of lymph node metastasis but noted a higher AUC when combined as part of panel of biomarkers including *PVT1*, *HOTTIP* and *UCA1* expression [86]. Currently, no studies have investigated the potential for *PVT1* expression as a biomarker for earlier stages of CRC. This in part is limited by lack of data on temporal variation with disease progress particularly within in vivo models.

Table 1. Summary of evidence for the role of PVT1 and miRNAs in promoting colorectal cancer.

miRNA	Role of PVT1	Proposed pathogenesis pathway	Reference
miRNA-146a	Decreases levels of miRNA-146a. rs13281615 G > A polymorphism on PVT1 and rs2910164 C > G polymorphism on miR-146a leads to favourable prognosis in CRC	PVT1/miRNA146a/COX2	[87]
miRNA-128	PVT1-214 upregulates Lin28 by competing for miRNA 128. let-7 is downregulated	PVT1-214/Lin28/let-7 axis	[74]
miRNA-216a-5p	PVT1 downregulates miRNA-216a-5p and reverses tumour suppressive effect in CRC	PVT1/miRNA-216a-5p/YBX1 axis	[88]
miRNA-455	PVT1 negatively regulates miRNA-455 and upregulates RUNX	RUNX2/PVT1/miRNA-455 regulatory axis	[89]
miRNA-214-3p	PVT1 downregulates miRNA-214-3p promoting CRC progression	PVT1/miRNA-214-3p/Insulin Receptor Substrate 1/ PI3K/Akt	[90]
miRNA-455-5p	rs1252200336 polymorphism in PVT1 with ID/DD genotype leads to worse survival in CRC affecting Han Chinese population	PVT1 suppresses miRNA-455-5p and miR-455-3p	[80]

miRNA-30d-5p	PVT1 suppresses miRNA-30d-5p whilst upregulating RUNX2	PVT1/miRNA-30d-5p/RUNX2 axis	[84]
miRNA-26b	PVT1 inhibits miRNA-26b in promoting proliferation and metastases in CRC	PVT1/miRNA-26b	[69]
miRNA-145	PVT1 downregulation via sponging of miRNA-145 promotes CRC metastases	PVT1/miRNA-145 pathway	[85]
miRNA-16-5p	PVT1 binds to miR-16-5p to promote cell proliferation, migration and invasion through VEGFA/VEGFR1/AKT pathway in CRC	PVT1-miR-16-5p/VEGFA/VEGFR1/AKT axis	[86]

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