Editorial

Micro-managers of disease: the long and short of miRNA regulation in colorectal cancer

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Comment on: Yi H, Geng L, Black A, *et al.* The miR-487b-3p/GRM3/TGFβ signaling axis is an important regulator of colon cancer tumorigenesis. Oncogene 2017;36:3477-89.

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The expression of non-coding RNAs is often altered in cancer cells. In particular, microRNAs (miRNAs) have progressively emerged as instrumental regulators of cancer progression, metastatic development, cancer stem cell properties and treatment response (1). In colorectal cancer, miRNAs have been shown to control the activity of major signaling pathways involved in tumor cell proliferation, apoptosis, or motility and invasion. In addition, identification of specific roles for individual miRNAs has allowed the characterization of previously unsuspected regulatory mechanisms in the pathogenesis of colorectal cancer.

Thus, in a recent study, Yi *et al.* (2) described the role of a miR-487b-3p/GRM3/TGF axis in the regulation of colorectal cancer cell tumorigenicity. Yi and collaborators found that expression of miR-487b-3p was decreased in colon adenocarcinoma samples and they identified *GRM3*, the gene encoding the Metabotropic Glutamate Receptor 3, as a key target of this miRNA. Upregulation of *GRM3* expression in colorectal tumours, due to the defective repression by miR-487b-3p, was found to antagonize the tumor suppressor function of TGF-β by reducing its role in the activation of protein kinase A and the inhibition of AKT. Accordingly, these authors found that experimental overexpression of miR-487b-3p mimicked the effects of GRM3 down-regulation and suppressed the tumorigenicity of colorectal cancer cells (2). Several aspects of this study relate to exciting avenues of research into the role of miRNAs in the regulation of colorectal cancer, the implications of a possible role for GRM3 in colorectal tumor progression and therapeutic response, and the context-dependent regulation of TGF-β function in colorectal cancer.

Role of miR-487-3p

Disruption of miR-487-3p has been reported previously in other cancer types. In accordance with the study by Yi *et al.*, miR-487-3b was reported to have tumour suppressor activities in prostate cancer (3), where it is detectable in patient's blood samples. In contrast, miR-487-3p expression increased after stimulation of human U251 glioma cells by Glial cell line-derived neurotrophic factor (GDNF), a potent promoter of glioma growth and invasion (4). In a physiological context, miR-487b-3p was found to be instrumental for the initiation of Wnt signaling in ligamentous tissue cells during the ossification process (5). Considering the strong oncogenic role of the Wnt pathway in colorectal cancer, a similar Wnt-promoting role for miR-487-3p in colorectal cancer would counteract its tumor suppressive effect on the GRM3/TGF regulatory loop, and the miR-487-3p down-regulation reported by Yi *et al.* (2) would work towards reducing Wnt activity. These apparent discrepancies re-emphasize the importance of examining how contextual differences modulate the activity of miRNAs in different tissues and different physiological or pathological situations. They also highlight the importance of large-scale miRNA and target gene expression profiling

studies to gain a holistic understanding of regulatory networks that underpin these contextual differences.

MiRNAs in colorectal cancer: biological understanding and translational applications

The discovery of a regulatory role for miR-487-3p in colorectal cancer cells complements an already significant body of literature concerning the complex role of miRNA networks in this disease. This epigenetic regulation of gene expression by miRNAs has far-reaching consequences, as reflected by its contribution to the molecular stratification of colorectal cancer subtypes (6). Large-scale studies of miRNA involvement as well as more targeted analyses of miRNA-target gene roles on phenotypic outcomes have driven our current understanding of miRNAs as regulators of the balance between proliferation and differentiation, of the invasion/metastasis cascade, and of cancer stem cell self-renewal in colorectal cancers. Importantly, different miRNAs have activating or inhibitory impacts on these biological processes, resulting in tumor-promoting or tumor-suppressing functions and highlighting the essential role of miRNAs to fine tune homeostatic processes in the intestine and other organs. Thus, miRNAs contribute as upstream regulators and/or downstream effectors of key pathways that regulate intestinal cell differentiation and cell cycle progression through their interplay with master regulator genes such as CDX1 (7), or BMI1 (8). In addition, several miRNAs such as miR-132, miR-138 and miR-335 have been shown to target genes encoding the Epithelial to Mesenchymal transition regulators TWIST2 and ZEB2, thereby exerting a negative pressure on cell invasion and motility. Down-regulation these miRNAs thus facilitates cell dissemination and has indeed been reported as a feature of metastatic progression in colorectal cancer (9). Importantly also, multiple recent studies have highlighted the instrumental role of miRNAs in the regulation of self-renewal (10-13), a defining property of cancer stem cells that underlies their ability to initiate primary and metastatic tumors and to sustain long-term tumor growth.

Discovery of a regulatory role for miRNAs on such key biological processes suggests that their quantification and manipulation may have important translational applications in the biomarker and therapeutic fields. Indeed, several miRNA signatures with clinical significance have recently been published that distinguish populations with better or worse prognosis among patients with stage II and III colorectal carcinomas (14,15), for which prognostic and predictive biomarkers are urgently needed. A role for individual miRNAs as predictive biomarkers of treatment response has also been suggested with, for example, high miR-214 expression potentially predicting increased radio-sensitivity (16). Manipulation of miRNA levels for therapeutic purposes is also an emerging and exciting field, although the potential for important side effects of this strategy should obviously not be underestimated. Among recent examples of this approach, miR-129 mimics have been developed to target chemo-resistant colon cancer stem cells (17), and modified miR-15a was shown to have the potential to improve treatment efficacy in advanced stage colorectal cancer through the inhibition of BCL2, BMI1, YAP1 and DCLK1 (18). Another interesting therapeutic avenue is based on the premise that inhibition of homeostasis maintenance processes such as autophagy by specific miRNAs may reduce the ability of tumor cells to sustain radio-therapeutic insult. Thus, downregulation of ATG12 by miR-214 (16) and of CARM1 by miR-195 (19) were recently shown to enhance the radio-sensitivity of colorectal cancer cells. These findings support those from previous studies in pancreatic cancer, where low miR-23b levels were shown to promote radio-resistance by minimizing the repression of ATG12 and thereby fostering autophagy (20).

The miR-487-3p target GRM3 in cancer

The study by Yi *et al.* identified *GRM3* as a key target of miR-487-3p. Interestingly, frequent activating mutations of GRM3 have been identified in melanoma, where they promote anchorage-independent growth and cell migration by activating cAMP and MEK/MAP kinase signaling, a pathway that is known to contribute to melanoma progression and drug resistance (21). *GRM3* mutations and/or copy number gains are also found in around 3–5% of samples in gastric, colon, and lung cancer (Catalogue of Somatic Mutations in Cancer, https://cancer.sanger.ac.uk/cosmic/gene/analysis?ln=GRM3). Additionally, GRM3 may contribute to the metastatic ability of breast cancer cells (22), and activation of GRM3 promotes the proliferation of glioma cells, where glutamate acts a potent growth factor (23). The work by Yi *et al.* (2) now provides the first demonstration of a potentially important role for GRM3 in regulating the progression of colorectal cancer, suggesting that GRM3 antagonists may have therapeutic value in this cancer. Interestingly, glutamate is an evolutionary conserved bioactive molecule, secreted

in significant quantities by the gut microbiota, and that can act to regulate neuro-endocrine processes in the gut (24). Considering the emerging body of work describing the influence of microbiota on intestinal proliferation, differentiation and stem cell function in mammals (25), it will be fascinating to determine whether the secretion of glutamate by gut microbiota provides an early pro-oncogenic context during colorectal tumor initiation and acts later on to sustain the long-term growth of primary colorectal tumors.

miR-487 as a transactivator of TGF-β signaling

In the context of CRC cells analysed by Yi *et al.* (2), GRM3 overexpression due to decreased miR-487-3p levels was found to antagonise the tumor-suppressing effect of TGF-β. Overexpression of miR-487-3p and experimental GRM3 knockdown had similar effects in reducing colon cancer cell tumorigenicity. Decreased GRM3 expression sensitized cells to TGF-β-induced apoptosis and TGF-β-mediated inhibition of anchorage-independent growth, without affecting the expression of SMAD isoforms or directly impacting on canonical TGF-β signalling. Instead, GRM3 and TGF-β signalling appear to converge on Protein Kinase A, balancing the regulation of CREB and AKT. This pathway provides an interesting example of miRNA-driven transactivation of TGF-β signalling, again highlighting the importance of miRNAs in fine tuning the levels of signalling pathway activation. It complements the role of several previously identified miRNA in the direct regulation of TGF-β signalling, usually via the targeting of SMAD molecules (26,27). Interestingly several of these miRNAs are themselves transcriptional targets of TGF-β. Enhanced understanding of feedback regulatory loops and transactivation mechanisms involving miRNAs is likely to shed new lights onto the complex biological roles of TGF-β signaling as a tumor-suppressing or tumor-promoting effector at various stages of colorectal cancer development (28). In this context, additional insight concerning the relative expression levels of miR-487-3p, GRM3 and TGF-β targets across various stages of colorectal cancer would help determine whether the regulatory loop identified by Yi *et al.* is an important driver of this complexity.

In conclusion, the study by Yi *et al.* (2) is a significant contributor to the ever-increasing body of work characterizing the role of miRNAs in the initiation and progression of colorectal cancer. A fascinating avenue for additional studies will be to further assess the degree of intra-tumor heterogeneity in the expression and activity of miRNAs within colorectal tumors. As suggested by a small number of emerging studies, heterogeneous expression of miRNA networks can be detected among cells from individual colorectal tumors (29,30). This heterogeneity may underpin the selective ability of small cell subpopulations only to develop plasticity and drug-resistant phenotypes when exposed to a therapeutic insult, thus enabling post-treatment recurrence, a major clinical issue in this disease. Thus, improving our understanding of miRNA heterogeneity in colorectal cancer may open exciting therapeutic avenues to undermine the resistance ability of these cells and thereby to improve patient survival.

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Footnote

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