

Review

Up-regulated Circular RNAs in Colorectal Cancer: New Entities for Therapy and Tools for Identification of Therapeutic Targets

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Abstract. *Patients with disseminated colorectal cancer have a dismal prognosis with a 5-year survival rate of only 13%. In order to identify new treatment modalities and new targets, we searched the literature for up-regulated circular RNAs in colorectal cancer which induce tumor growth in corresponding preclinical in vivo models. We identified nine circular RNAs that mediate resistance against chemotherapeutic agents, seven that up-regulate transmembrane receptors, five that induce secreted factors, nine that activate signaling components, five which up-regulate enzymes, six which activate actin-related proteins, six which induce transcription factors and two which up-regulate the MUSASHI family of RNA binding proteins. All of the circular RNAs discussed in this paper induce the corresponding targets by sponging microRNAs (miRs) and can be inhibited by RNAi or shRNA in vitro and in xenograft models. We have focused on circular RNAs with demonstrated activity in preclinical in vivo models because the latter is an important milestone in drug development. All circular RNAs with in vitro activity only data are not referenced in this review. The translational impact of inhibition of these circular RNAs and of the identified targets for treatment of colorectal cancer (CRC) are discussed.*

CRC is the third most common malignancy and the second cause of cancer-related death worldwide (1). In patients with early disease, the 5-year survival rate is in the range of 90% (2). However, in patients with advanced and metastatic disease the 5-year survival rate is only around 13% (2). Standard conventional treatment of CRC are surgery, chemotherapy, and radiotherapy (3). Chemotherapy is mainly based on 5-fluoro-uracil (5-FU), oxaliplatin (L-OHP), capecitabine and drug combinations. Several monoclonal antibodies (mAbs) have been approved for the treatment of CRC. One of them is Cetuximab which is directed against the epidermal growth factor receptor (EGFR). Two others are directed against endothelial targets, such as Bevacizumab that is directed against vascular endothelial growth factor (VEGF) and Ramucicurumab, which binds to vascular endothelial growth factor receptor 2 (VEGFR2). Three other mAbs target immune checkpoint proteins. Ipilumab is directed against cytotoxic T-lymphocyte associated protein 4 (CTLA4) as well as Nivolumab and Pembrolizumab which both target programmed cell death ligand 1 (PD-1L). However, the percentage of responding patients as well as the therapeutic benefit is limited (3, 4). Genetic instability such as chromosomal and microsatellite instability, mutations in adenomatous polyposis coli (APC), protein p53 (p53), Kirsten rat sarcoma virus (Ki-RAS), signal transduction protein SMAD4 and phosphatidylinositol 3-kinase, its catalytic subunit PIK3CA, as well as epigenetic modifications such as methylation, are characteristics of subsets of CRCs (5, 6). Four molecular subtypes based on gene expression have been identified: CMS1 (immune), CMS2 (canonical), CMS3 (metabolic) and CMS4 (mesenchymal); these may respond differentially to treatment (7, 8). Taken together, identification of new targets and treatment modalities is an issue of paramount importance. Therefore, we have searched the literature for up-regulated circular RNAs (circRNAs) and their corresponding targets for possible therapeutic intervention in CRC patients.

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Role of Circular RNAs in Cancer

CircRNAs are covalently closed RNAs which have a length between hundred to thousands of nucleotides and are generated by backsplicing (9). They are exceptionably stable and have potential as diagnostic and prognostic biomarkers as well as therapeutic targets in cancer patients (10, 11). In addition, they exhibit a regulatory function in tissue development, neurogenesis and myogenesis (12). As a rule, they do not encode proteins, but in a few cases an internal ribosome binding site mediates translation of peptides (13, 14). They act as efficient sponges for miRs (15), protein scaffolding, protein sponges or decoys and regulators of transcription, splicing and translation (16). circRNAs can function as tumor suppressors or oncogenes, affecting hallmarks of cancer such as proliferation, epithelial mesenchymal transition (EMT), apoptosis, angiogenesis, and metastasis (16). The role of circRNAs in CRC has been summarized in previous studies (17, 18). In order to define new modalities for therapeutic intervention and to identify new targets for treatment of patients with CRC we have searched the literature for circRNAs which are up-regulated in CRC tissues and mediate efficacy in preclinical *in vivo* models. We have excluded down-regulated circRNAs. The identified RNAs can be inhibited by siRNA or shRNA and the corresponding targets can be attenuated with mAbs, small molecules or other entities if they are druggable.

Up-regulated circRNAs Conferring Drug Resistance

Circular RNAs conferring resistance to 5-fluoro-uracil (5-FU) and oxaliplatin (L-OHP). Circ_0032833: Circ_0032833 (Figure 1) was up-regulated in folinic acid, 5-FU, oxaliplatin (FOLFOX)-resistant CRC and was associated with resistance against 5-FU and L-OHP (19). Knock-down of circ 0032833 sensitized FOLFOX resistant CRC cell lines to 5-FU and L-OHP. Circ 0032833 sponged miR-125-5p which led to up-regulation of the RNA binding protein Musashi-1 (MSI-1). Down-regulation of circ 0032833 sensitized HCT-116R CRC xenografts in nude mice against 5-FU and L-OHP. MSI-1 acts as an RNA binding protein and is involved in tumorigenesis, progression, and resistance (20, 21).

Circ 0007031: Circ 0007031 (Figure 1) knock-down repressed CRC cell proliferation, migration, invasion and enhanced 5-FU sensitivity (22). Knockdown of circ 007031 inhibited growth of 5-FU-resistant CRC xenografts in nude mice. Circ 007031 sponged miR-133b and led to up-regulation of ATP binding cassette subfamily C, member 5 multidrug resistance associated protein 5 (ABCC5) which acts as drug efflux transporter and functions as a mediator of chemotherapy response (23, 24).

circRNA protein kinase, DNA activated, catalytic subunit (circ-PRKDC): Circ-PRKDC (Figure 1) was up-regulated in

5-FU resistant CRC tissues and cell lines such as SW480/5-FU and SW620/5-FU (25). Knockdown of circ-PRKDC suppressed 5-FU resistance in CRC cells. Circ-PRKDC sponged miR-375 which led to expression of transcription factor FOXM1, an activator of the WNT/ β catenin pathway (26-28). The latter has been shown to induce 5-FU resistance (29). Knockdown of circ-PRKDC suppressed 5-FU resistance of SW480/5-FU CRC xenografts in nude mice (30).

Circ 0000338: Knockdown of circ 0000338 (Figure 1) reversed 5-FU resistance in SW480/5-FU and HCT116/5-FU CRC cells *in vitro* (31). Circ 0000338 was packaged into exosomes and could be internalized by 5-FU sensitive CRC cells. Inter-cellular transfer of circ 0000338 conferred 5-FU resistance in HCT116 and SW480 CRC cells *in vitro* (31). *Intra-tumoral* injection of circ 0000338 into SW480 CRC xenografts enhanced 5-FU resistance in nude mice (31). Circ 0000338 sponged miRs-217 and 485-3p (31). miR-217 can target astrocyte-elevated gene 1 (AEG-1, metadherin), mitogen-activated protein kinase (MAPK) and transcription factor ZEB1 (32-34). miR-485-3p was shown to target the spindle-assembly factor TPX2 (35).

Circ 0071589 confers resistance to cis-platin (CDDP). Circ 0071589 (Figure 1) was found to be overexpressed in CDDP-resistant CRC tissues and cell lines (36). Knockdown of circ 0071589 inhibited CDDP resistance, proliferation, migration, and invasion and promoted apoptosis in CDDP resistant CRC cell lines HCT116/CDDP and LoVo/CDDP *in vitro* (36). In nude mice, knockdown of circ 0071589 enhanced cytotoxicity of CDDP in HCT116/CDDP xenografts (36). From a mechanistic point of view, circ 0071589 sponged miR-526b-3p which led to the up-regulation of transcription factor Krueppel-like factor 12 (KLF12), which can act as an oncogene (36-38).

Exosomal circular sponge for miR-122 (ciRS-122) confers oxaliplatin resistance (L-OHP). ciRS-122 (Figure 1) is highly expressed in L-OHP resistant cells such as SW480/L-OHP (39). Exosomes from the L-OHP resistant CRC cell line SW480/L-OHP could transfer ciRS-122 to SW480 cells *in vitro* and *in vivo* and enhance expression of the M2 isoform of pyruvate kinase (PKM2) accelerating glycolysis and drug resistance (39). It was shown that drug resistance was induced by sponging of miR-122 by ciRS-122 and subsequent up-regulation of PKM2. Systematically injected exosomal si-ciRS-122 could sensitize the response to L-OHP of SW480/L-OHP xenografts in nude mice (39).

Circ 001680 confers irinotecan (IRT) resistance. Circ 001680 (Figure 1) was overexpressed in CRC tissues in comparison to matching normal tissues (40). It promoted proliferation and migration of SW480 and HCT116 CRC cells and induced stem cell spheres and IRT resistance (40). In nude mice, circ 001680

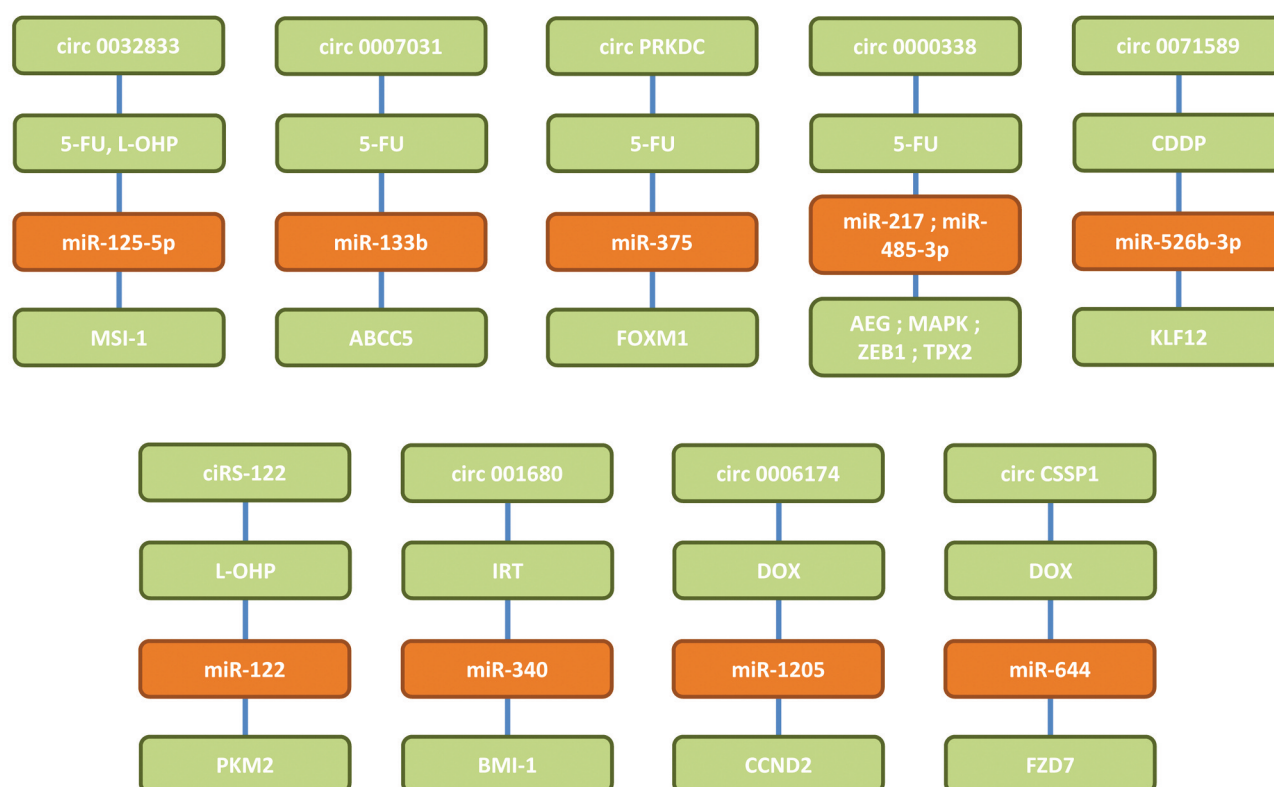


Figure 1. Circular RNAs conferring resistance to chemotherapeutic agents in colon-cancer related preclinical in vivo models. The first line shows the corresponding circ-RNA, the second line displays the chemotherapeutic agents against which resistance is induced, the third line shows the microRNA which is sponged by the circ RNA and the fourth line shows the corresponding target(s). 5-FU: 5-Fluoro-uracil; ABCC5: ATP binding cassette subfamily C member 5; AEG: astrocyte elevate gene 1; BMI-1: B lymphoma Mo-MLV insertion region 1 homolog; CCND2: cyclin D2; CDDP: cisplatin; circ CSPP1: centrosome/spindle pole associated protein 1; ciRS: circ sponge for miR-122; DOX: doxorubicin; circ PRKDC: protein kinase, DNA activated, catalytic subunit; FOXM1: transcription factor M1; FZD7: frizzled 7; IRT: irinotecan; KLF12: Krüppel-like factor 12; L-OHP: oxaliplatin; MAPK: mitogen-activated protein kinase; miR: micro RNA; MSI1: Musashi; PKM2: pyruvate kinase, isoform M2; TPX2: spindle-assembly factor TPX2; ZEB1: transcription factor ZEB1.

expressing CRC cells were resistant to intra-peritoneally delivered IRT and knockdown of circ 001680 decreased tumor volume. Circ 001680 sponged miR-340 resulting in up-regulation of B lymphoma Mo-MLV insertion region 1 homolog (BMI-1). The latter acted as a transcriptional repressor and is a member of the polycomb group of proteins which modify chromatin structure (41). BMI-1 mediates EMT, liver metastasis and drug resistance (42, 43).

Circ 0006174 confers doxorubicin (DOX) resistance. Circ 0006174 (Figure 1) was up-regulated in DOX-resistant CRC tissues and cell lines (44). Down-regulation of circ 0006174 inhibited DOX resistance, cell proliferation, invasion, and migration of CRC cells (44). Circ 0006174 could enhance DOX-resistance *via* exosomal intercellular transfer. Circ 0006174 sponged miR-1205 resulting in up-regulation of cyclin D2 (CCND2). The latter functions as an allosteric regulator of cyclin-dependent kinase 4,6 (CDK4, CDK6) to

regulate cell-cycle transition from the G1 to S phase (45). In nude mice, knockdown of circ 0006174 enhanced sensitivity to DOX. Exosomal circ 0006174 is a potential biomarker for diagnosis of chemoresistance in CRC.

Circ centrosome/spindle pole associated protein 1 (circ CSPP1) confers doxorubicin resistance. Circ CSPP1 (Figure 1) was found to be overexpressed in DOX-resistant CRC tissues and cell lines such as LoVo/DOX and HCT116/DOX (46). Knockdown of circ CSPP1 enhanced DOX sensitivity and suppressed cell proliferation, migration and invasion in these CRC cell lines (46). In nude mice, knockdown of circ CSPP1 repressed tumor growth of LoVo/DOX xenografts (46). Circ CSPP1 sponged miR-944 resulting in up-regulation of frizzled 7 (FZD7). The latter is a member of the frizzled (FZD) family which regulates canonical and non-canonical WNT pathways, is involved in metastasis and represents a promising target for drug discovery (47-49).

Circular RNAs Up-regulating Transmembrane Proteins and Secreted Factors

Circ 0000467 targets transmembrane tyrosine kinase (TYRO3). Circ 0000467 (Figure 2) was highly expressed in CRC tissues and cells (50). *In vitro*, silencing of circ 0000467 inhibited proliferation, migration, invasion, glycolysis, and accelerated apoptosis in CRC cells. Silencing of circ 0000467 hindered growth of CRC-related xenografts in nude mice (50). Circ 0000467 sponged miR-330-5p resulting in up-regulation of transmembrane tyrosine kinase TYRO3. The latter is a member of the TAM (TYRO3, AXL, MERTK) family of transmembrane receptor tyrosine kinases, is overexpressed in tumors and induces proliferation, migration, invasion, EMT and chemoresistance of tumor cells and activates phosphoinositide-3 kinase (PI3K)/ser-thr kinase AKT/mammalian target of rapamycin (mTOR), MAPK/ extracellular signal regulated kinase (ERK), src family kinase FYN and Janus kinase JAK/signal transducer and activator of transcription (STAT) signaling. Expression of circ 0000467 correlates with poor prognosis in CRC patients (51-53). TYRO3 also induces resistance against PD1/PD-1L therapy (54).

Circ 0067835 targets insulin- like growth factor receptor 1 (IGF-1R). Exosomal circ 0067835 (Figure 2) was up-regulated in the serum of CRC patients after radiotherapy (55). Its knock-down inhibited proliferation, cell-cycle progression and enhanced radiosensitivity *in vitro* in SW620 and HCT-116 CRC cells after exosomal transfer. In nude mice, its knockdown inhibited tumor growth and enhanced radiosensitivity in SW620 CRC cells. It targeted miR-296-5p resulting in up-regulation of IGF-1R (55). In preclinical CRC-related models, IGF-1R is a driver of tumor growth and metastasis and can be targeted with oligonucleotides, tyrosine kinase inhibitors and mAbs (56, 57). However, in clinical studies, with single agent-based therapy, consistently, lack of efficacy was noted in cancer patients (58-60). The challenge will be the identification of effective therapies based on biomarkers.

Circ-Denn domain containing 4C (circ DENND4C) up-regulates glucose transporter 1 (GLUT1). Circ DENND4C (Figure 2) was up-regulated in CRC tissues in comparison to corresponding matching tissues (61). Knockdown of circ DENND4C in SW480 and HCT-116 CRC cells inhibited cell proliferation, migration, and glycolysis *in vitro*. Silencing of circ DENND4C in SW480 CRC cells led to reduced tumor growth in immunodeficient mice. Circ DENND4C sponged miR-760 induced up-regulation of glucose transporter 1 (GLUT1). The latter is highly expressed in tumor cells and acts as a major glucose transporter and is involved in glycolysis of mammalian cells. Since glycolysis generates

less ATP than complete oxidative breakdown, cancer cells need more molecules of glucose than normal cells. GLUT1 is expressed in most normal tissues and represents a transmembrane receptor with 12 membrane spanning α -helices (62-63). GLUT1 is a potential target for anticancer therapy and can be inhibited with small molecules, mAbs, siRNA and shRNA (64-66).

Circ-ASXL1 transcriptional regulator1 (circ ASXL1) targets glutamate ionotropic receptor kainate type subunit 3 (GRIK3). Circ ASXL1 (Figure 2) was up-regulated in CRC tissues in comparison to non-transformed cell line NCM460 representing normal intestinal tissues (67). Knock-down of circ ASXL1 in SW480 and SW620 CRC cell lines repressed proliferation, invasion, induced G0/G1 phase arrest and induced apoptosis *in vitro* and inhibited tumor growth in immuno-deficient mice (67). Circ ASXL1 acted as a sponge for miR-1205 resulting in up-regulation of GRIK3 (67). The latter responds to neurotransmitter glutamate and is associated with diseases such as depersonalization disorders and schizophrenia (68). It has been shown that GRIK3 is involved in CRC proliferation and migration (69).

Circ runt related transcription factor (circ-RUNX1) targets solute carrier family 38, member 1 (SLC38A1). Circ RUNX1 (Figure 2) was up-regulated in CRC tissues and cells in comparison to normal colonic tissues and cells (70). Its knockdown restrained CRC colony formation, migration, invasion, glutaminolysis, induced apoptosis *in vitro* and blocked tumor growth in immuno-deficient mice (70). Circ RUNX1 sponged miR-485-5p leading to up-regulation of SLC38A1. The latter functions as a glutamine transporter and promotes proliferation and migration of human CRC cells (71). Targeting glutamine metabolism is part of ongoing efforts to treat CRC (72).

Circ HERC family of ubiquitin liases 4 (circ-HERC4) targets C-terminal binding protein 2 (CTBP2) and down-regulates E-cadherin. Expression of circ HERC4 (Figure 2) was correlated with poor prognosis in patients with CRC (73). Circ-HERC4 behaved as an oncogene and promoted proliferation, migration, and invasion of CRC cell lines HCT-116, DLD-1 and SW480 *in vitro*. Knockdown of circ HERC4 in HCT-116 CRC cells inhibited tumor growth in immuno-deficient mice (73). HERC4 sponged miR-556-5p and subsequent up-regulation of CTBP2 which suppressed expression of E-cadherin (73). Two major splice variants (CTBP1 and CTBP2) have been identified which are involved in EMT, inhibition of apoptosis and repression of tumor suppressors such as E-cadherin, p16 inhibitor p16Ink4a, p15 inhibitor p15Ink4b and phosphatase and tensin homolog (PTEN) (74, 75).

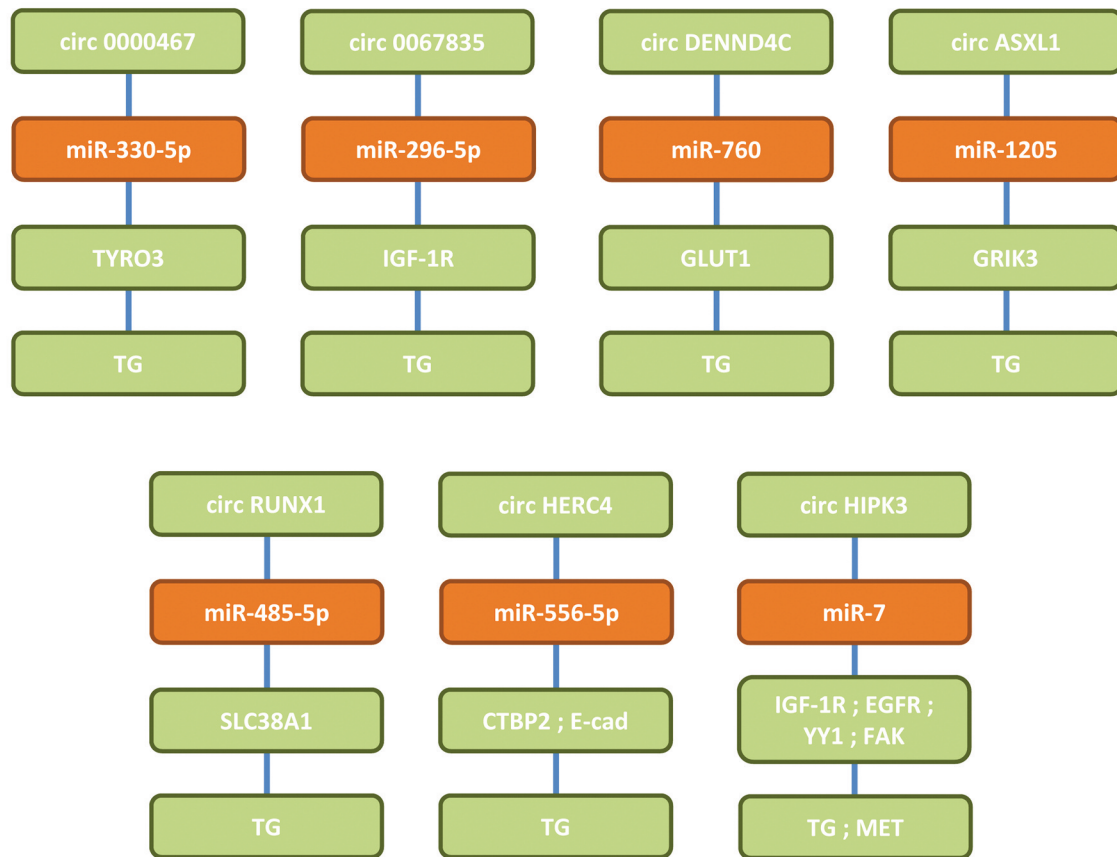


Figure 2. Circular RNAs up-regulating transmembrane receptors in colon-cancer related preclinical in vivo models. The first line shows the corresponding circ-RNA, the second line shows the miR which is sponged by the specific circ-RNA, the third line displays the specific transmembrane receptor up-regulated and the fourth line indicates the effect of inhibition of the specific circ-RNA on tumor growth and metastasis in nude mice. Circ ASXL1: Circ transcriptional regulator 1; circ DENND4C: domain containing 4C; circ HERC4: circ HERC family of ligases 4; circ HIPK3: circ homeodomain-interacting protein kinase 3; circ RUNX1: runt related transcription factor 1; CTBP2: C-terminal binding protein 2; E-cad: E-cadherin; EGFR: epidermal growth factor; FAK: focal adhesion kinase; GLUT1: glucose transporter 1; GRIK3: glutamate ionotropic receptor kainate type subunit 3; IGF-1R: insulin-like kinase receptor 3; MET: metastasis; miR: micro RNA; SLC38A1: solute carrier family 38 member 1; TG: tumor growth; YY1: transcription factor Ying-Yang1.

Circular homeodomain-interacting protein kinase 3 (circ-HIPK3) targets IGF-1R, epidermal growth factor receptor (EGFR), transcription factor ying-yang1 (YY1) and focal adhesion kinase (FAK). Circ HIPK3 (Figure 2) was up-regulated in patients with CRC and predicted poor prognosis (76). Silencing of circ HIPK3 in HCT-116 and HT29 CRC cells inhibited proliferation, migration, invasion, and induced apoptosis *in vitro*. Circ HIPK3 sponged miR-7 resulting in up-regulation of IGF-1R, EGFR, YY1 and FAK (76). In immuno-compromised mice, a miR-7 agomir reduced tumor volume and weight and inhibited liver metastasis in the tail vein injection model. IGF-1R and EGFR play oncogenic roles in CRC (77-79). YY1 acts as a transcriptional repressor protein and inducer of cancer metastasis (79). FAK functions both as a non-

receptor tyrosine kinase and as an adaptor protein regulating adhesion, signaling and cell migration. It also promotes cell survival in response to stress (80, 81).

Circular RNAs Which Up-regulate Secreted Factors

Circ 0030998 targets vascular endothelial growth factor-A (VEGF-A). Circ 0030998 (Figure 3) was up-regulated in CRC tissues and associated with poor prognosis in CRC patients (82). It promoted proliferation of HCT-116 and SW480 CRC cells and tube-like structure formation in HUVECs (82). Knockdown of circ 0030998 reduced tumor growth of SW480 cells in immuno-deficient mice. Circ 0030998 sponged miR-567 resulting in up-regulation of VEGF-A. The latter is the primary factor for tumor vascular

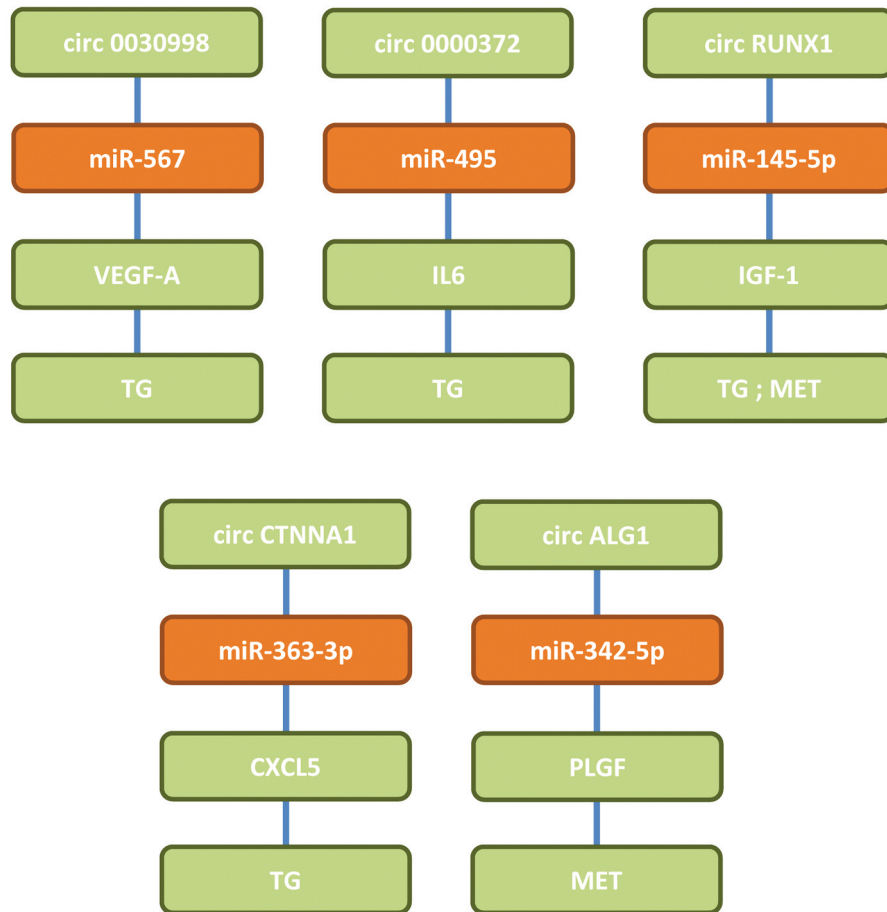


Figure 3. Circular RNAs up-regulating secreted factors in colon-cancer related preclinical in vivo models. The first line shows the corresponding circ-RNA, the second line displays the miR which is sponged by the specific circ-RNA, the third line indicates the specific secreted factor up-regulated and the fourth line outlines the effect of inhibition of the specific circ-RNA on tumor growth and metastasis in nude mice. Circ ALG1: Circ chitobiosyldiphosphorodolchilol β -mannosyltransferase; circ CTNNA1: circ catenin α 1; circ RUNX1: circ runt-related transcription factor 1; CXCL5: C-X-C motif ligand 5; IGF-1: insulin-growth factor 1; IL6: interleukin 6; MET: metastasis; miR: microRNA; PLGF: placental growth factor; TG: tumor growth; VEGF A: vascular endothelial growth factor A.

function, promoting EMT and metastasis (83). For CRC, Bevacizumab, a mAb directed against VEGF-A (84) and Ramucirumab, a mAb directed against VEGFR2 (85), are approved therapeutic agents.

Circ 0000372 targets interleukin 6 (IL6). Circ 0000372 (Figure 3) was up-regulated in CRC tissues and correlated with poor prognosis (86). Its silencing suppressed proliferation, migration, and invasion of CRC cells *in vitro* and growth of CRC-related xenografts in nude mice (86). It sponged miR-495 resulting in up-regulation of IL6 and JAK2/STAT3 signaling (86). The IL6 pathway is activated in many types of tumors resulting in proliferation, survival, invasion, and metastasis (87, 88). Presently the food and drug administration agency (FDA) has approved inhibitors

of the IL6/JAK/STAT3 pathway targeting IL6, interleukin 6 receptor (IL6R) or JAKs for the treatment of inflammatory conditions and myeloproliferative neoplasms (89). IL6 signaling is activated in CRC and it remains to be seen whether its inhibition can be converted into clinical benefit in patients with CRC (90).

Circ runt-related transcription factor 1 (RUNX1) targets insulin-growth factor 1 (IGF-1). Circ RUNX1 (Figure 3) was up-regulated in CRC patients and correlated with cancer progression (91). *In vitro*, circ RUNX1 promoted proliferation, migration, invasion, and inhibited apoptosis in HCT-116 and SW480 CRC cells. In HCT-116 cells, circ RUNX1 enhanced tumor growth in nude mice and liver metastasis after intrasplenic injection (91). It sponged miR-145-5p resulting in

up-regulation of IGF-1, a circulating neuroendocrine hormone which promotes CRC tumorigenesis and metastasis (92, 93). In CRC, IGF-1 signaling is involved in glucose metabolism and circulating IGF-1 correlates with risk of CRC (94, 95).

Circ catenin $\alpha 1$ (circ CTNNA1) targets chemokine C-X-C motif ligand 5 (CXCL5). Circ CTNNA1 (Figure 3) was up-regulated in CRC tissues and cell lines (96). In SW480 and SW620 CRC cells, silencing of circ CTNNA1 suppressed proliferation, metastasis, induced G0/S cell-cycle arrest and enhanced apoptosis *in vitro*. In immunodeficient mice, sh-circ CTNNA1 treated CRC cells inhibited tumor growth after subcutaneous implantation (96). Circ CTNNA1 sponged miR-363-3p resulting in up-regulation of C-X-C motif chemokine (CXCL5). It has been independently shown that CXCL5 mediates proliferation, migration and invasion of CRC cells and might be a serum prognostic factor in CRC patients (96). It was shown that CXCL5 can activate tumor angiogenesis by the AKT/nuclear factor κ B (NF κ B) pathway (97). CXCL5 also can activate transcription factor SNAIL and AKT/GSK3 β / β catenin pathways through interaction with C-X-C motif-chemokine receptor 2 (CXCR2) (98, 99).

Circ chitobiosyldiphosphodolichol β -mannosyltransferase (circ ALG1) targets placental growth factor (PLGF). Circ ALG1 (Figure 3) was highly expressed in CRC tissues and enhanced migration and invasion in HT-29, HCT-116 and SW480 CRC cells *in vitro* (100). Interference with circ ALG1 decreased liver and lung metastasis in HCT-116 and SW480 CRC cells in nude mice after tail vein injection. Circ ALG1 sponged miR-342-5p which could be enhanced by m6A modification of circ ALG1 and led to up-regulation of PLGF (100). The latter is a member of the VEGF family that binds to VEGFR1, but not to VEGFR2, and might be involved in pathological angiogenesis (101-103). However, PLGF is a highly controversial target, because it has also been reported that inhibition of PLGF with mAbs does not inhibit angiogenesis during primary tumor growth and combination of anti-VEGF-1 mAbs with anti-PLGF mAbs did not result in improved anti-angiogenic activity (104). The mechanistic details of the possible role of PLGF with respect to pro-tumoral activity as described above have to be worked out in more detail due to the multifaceted role of PLGF in cancer (105). In CRC, PLGF expression correlates with disease progression and patient survival and may be used as a prognostic indicator (106).

Circular RNAs Up-regulating Signaling Components

Circ 3823 up-regulates transcription factor 7 (TCF7). Circ 3823 (Figure 4) was highly expressed in CRC tissues compared to matching normal tissues (107). In HCT-116 and

SW 480 CRC cells circ 3823 promoted proliferation and invasion, inhibited apoptosis and supernatants of these cells transfected with circ 3823 induced tube formation of HUVECs. In nude mice, HCT-116 cells transfected with circ 3823 exhibited increased tumor growth after subcutaneous implantation and promoted metastasis to the lungs after tail vein injection (107). Circ 3823 sponged miR-30c-5p and subsequently up-regulated TCF-7. The latter mediates proliferation, angiogenesis, and metastasis by up-regulation of CCND1 and transcription factor MYC (108-110) and has therapeutic potential in CRC (111). The deregulation of WNT/ β catenin signaling in CRC is well documented (112). *Circ Arf GAP with FG repeats 1 (circ AGFG1) up-regulates transcription factor YY1 and β -catenin (CTNNB1).* Circ AGFG1 (Figure 4) was up-regulated in CRC patients and was higher in patients with liver metastases compared to patients without liver metastasis (113). Its silencing suppressed migration, invasion and stemness in SW480 and HCT-116 CRC cells *in vitro*. In nude mice, circ AGFG1 promoted tumor growth and liver metastasis after subcutaneous implantation of these cell lines (113). It sponged miRs-4262 and -185-5p resulting in up-regulation of YY1 and CTNNB1. YY1 promotes CRC cell proliferation (114) and migration and invasion of CRC through the WNT/ β catenin signaling pathway (115). CTNNB1 is the downstream effector component of WNT signaling in CRC (116) and has potential as a biomarker to stratify patients with CRC (117).

Circ ras association domain-containing protein 2 (circ RASSF2) up-regulates frizzled 4 (FZD4). Circ RASSF2 (Figure 4) was up-regulated in CRC patients and high expression correlated with poor prognosis (118). Its knockdown inhibited proliferation, invasion, migration, and enhanced apoptosis in CRC cells *in vitro*, whereas overexpression had the opposite effects. Its knockdown also restrained tumor growth of CRC xenografts in nude mice after subcutaneous implantation. Circ RASSF2 sponged miR-195-5p leading to overexpression of FZD4. FZD receptors are seven transmembrane GPCRs which mediate WNT signaling with a cysteine-rich domain which is involved WNT binding (119). They are potential targets for cancer therapy (120).

Circ 0000392 targets phosphatidyl 3 kinase regulatory subunit γ (PIK3R3). Circ 0000392 (Figure 4) was up-regulated in CRC and associated with tumor progression (121). Knock-down in SW620 and RKO CRC cells inhibited proliferation and invasion *in vitro*. Knock-down of circ 0000392 in SW620 xenografts decreased tumor growth after subcutaneous implantation into nude mice. Circ 0000392 acted as a sponge for miR-193a-5p resulting in up-regulation of PIK3R3 (121). The latter induces EMT and promotes metastasis in CRC (122). PI3K is an important target in

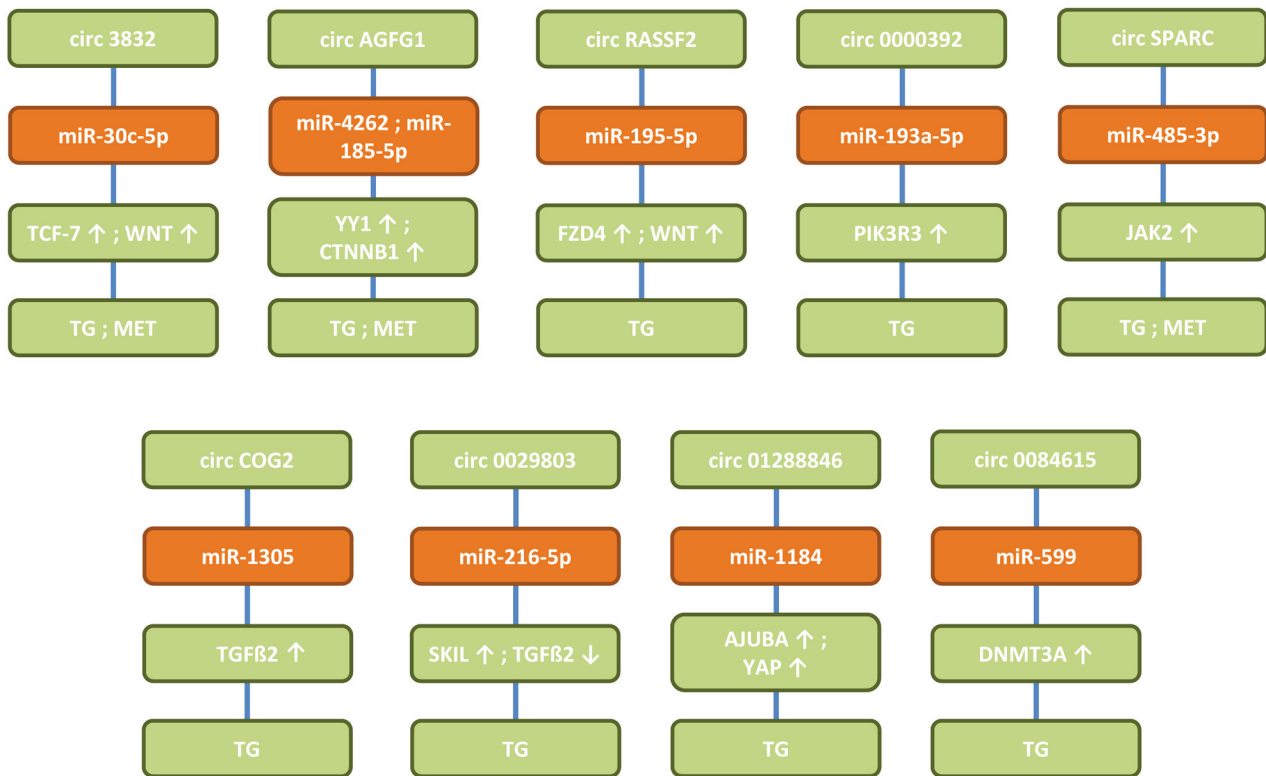


Figure 4. Circular RNAs up-regulating signaling components in colon cancer preclinical in vivo models. The first line shows the corresponding circ-RNA, the second line displays the miR which is sponged by the specific circ-RNA, the third line indicates the specific signaling component up-regulated and the fourth line outlines the effect of inhibition of the specific circ-RNA on tumor growth and metastasis in nude mice. AJUBA: LIM protein AJUBA; circ AGFG1: circ Arf GAP with FC repeats 1; circ COG2: circ component of oligomeric complex 2; circ RASSF2: circ ras-associated domain-containing protein 2; circ SPARC: circ secreted protein acidic and rich in cysteine; CTNNB1: β catenin; DNMT3A: DNA methyltransferase 3A; FZD4: frizzled 4; JAK2: Janus kinase 2; MET: metastasis; PIK3R3: phosphatidylyl 3 kinase regulatory subunit γ 3; SKIL: Ski oncogene like; TCF-7: transcription factor 7; TG: tumor growth; TGF: transforming growth factor; TGF β 2: transforming growth factor β 2; YAP: yes-associated protein; YY1: transcription factor ying-yang1; WNT: wingless-related integration site.

cancer and several clinical studies are ongoing (123-125). *Circ secreted protein acidic and rich in cysteine (circ SPARC)* targets JAK2/STAT3 signaling. Circ SPARC (Figure 4) was overexpressed in the CRC tissues and plasma of patients (126). It promoted proliferation and invasion in HCT116 and DLD1 CRC cells. In immunodeficient mice, circ SPARC improved tumor growth of HCT116 xenografts after subcutaneous implantation and lung metastasis after tail vein injection. Circ SPARC targets miR-485-3p resulting in activation of JAK2. In addition, it facilitated translocation of STAT3 into the nucleus by recruiting RNA binding protein fused in sarcoma (FUS) (127, 128). JAK/STAT pathway inhibitors have been identified and are presently evaluated in clinical trials in cancer patients (129).

Circ component of oligomeric Golgi complex (circ COG2) targets transforming growth factor β 2 (TGF β 2). Circ COG2 (Figure 4) was up-regulated in CRC tissues and associated with

poor prognosis (130). It mediated proliferation, migration, and invasion in HCT8 and SW480 CRC cells *in vitro*. Circ COG2 sponged miR-1305 and up-regulated TGF β 2. Circ COG2 promoted EMT by the miR-1305/TGF β 2/SMAD3 pathway (130). Circ COG2 containing exosomes injected into HCT8 CRC cells gave rise to increased tumor growth in immunodeficient mice. TGF β /SMAD signaling can promote EMT and metastasis as shown in numerous examples (131, 132). However, it should be kept in mind that TGF β exerts pro- as well as antitumoral properties, depending on tumor-type stage of progression and molecular context (133).

Circ 0029803 targets Ski-oncogene like (SKIL). Increased expression of circ 0029803 (Figure 4) was associated with progression of CRC (134). Knockdown of circ 29803 in HCT116 and SW480 CRC cells inhibited colony formation, migration, invasion, EMT and glycolysis and induced apoptosis *in vitro* (134). Circ 0029803 sponged miR-216b-

5p resulting in up-regulation of SKIL. Down-regulation of circ 0029803 in SW480 CRC cells decreased *in vivo* growth in immuno-deficient mice. SKIL encodes a transcriptional co-repressor which antagonizes TGF β signaling. SKIL can act as an oncogene as well as a tumor suppressor (135-137).

Circ 01288846 up-regulates AJUBA and inhibits Hippo/YAP signaling. Circ 01288846 (Figure 4) was up-regulated in CRC tissues and mediated proliferation and migration in HCT116 and SW480 CRC cells (138) *in vitro*. Knockdown of circ 01288846 in SW480 cells resulted in reduced tumor growth in nude mice (138). Circ 01288846 sponged miR-1184 mediating up-regulation of AJUBA which inhibits HIPPO/YAP signaling. AJUBA is a 55 amino acid protein of the LIM protein family which transmits signals between cytoplasm and nucleus and exerts pro- and anti-tumoral functions (139, 140). AJUBA is up-regulated in CRC and promotes metastasis (141, 142).

Circ 0084615 targets DNA methyltransferase 3A (DNMT3A). Circ 0084615 (Figure 4) was up-regulated in CRC and correlated with advanced clinical stage and poor survival rate (143). Depletion of circ 0084615 impeded CRC cell proliferation, migration, and invasion *in vitro*. circ 0084615 mediated lung metastasis of CRC cells in immuno-deficient mice. It sponged miR-599 and up-regulated DNMT3A (143). The latter acts as an epigenetic modifier through methylation of CpG islands and promotes proliferation and metastasis of CRC (144). In mice, deletion of DNMT3A results in inhibition of intestinal tumor formation (144, 145). DNMTs are often deregulated in cancer and their inhibitors might be the basis for new directions of therapy (146).

Circ RNAs Up-regulating Enzymes

Circ 5615 up-regulates tankyrase (TNKS). Expression of circ 5615 (Figure 5) correlated with poor clinical outcome in patients with CRC (147). In HCT116 and SW480 CRC cells, circ 5615 mediated progression from G1/S to G2/M, proliferation, and invasion *in vitro*. It promoted growth of HCT116 xenografts after subcutaneous implantation into nude mice (147). Circ 5615 sponged miR-149-5p leading to up-regulation of TNKS and activation of the WNT/ β catenin pathway. TNKSes are multifunctional poly-ADP polymerases with protumoral functions involved in WNT signaling, telomere maintenance, regulation of mitosis and vesicle trafficking (148, 149). TNKS inhibitors have been identified and are presently evaluated as antitumoral agents (150, 151).

Circ formin 2 (circ FMN2) up-regulates human telomerase reverse transcriptase (hTERT). Circ FMN2 (Figure 5) was associated with advanced tumor stage and distant metastasis (152). Knock-down of circ FMN2 in HCT116 and HT29 CRC cells inhibited growth *in vitro*. Knock-down of circ FMN2 in

HCT116 cells resulted in decreased tumor growth in immuno-compromised mice after subcutaneous implantation. Circ FMN2 sponged miR-1182 leading to up-regulation of hTERT. Circ FMN2 was found in exosomes secreted into the serum of CRC patients (152). hTERT functions as a ribonucleoprotein that adds TTAGGG tandem repeats to telomere ends and is involved in replication, proliferation, and metastasis. Several small molecule telomerase inhibitors or hTERT-based immunotherapeutic agents are evaluated in clinical trials in cancer patients, but none has yet received approval (153-155).

Circ 101555 up-regulates cyclin-dependent kinase 6 (CDK6) and replication protein A3 (RPA3). Circ 101555 (Figure 5) was up-regulated in CRC cancer and correlated with poor prognosis (156). *In vitro* and *in vivo*, silencing of circ 101555 suppressed proliferation and induced apoptosis of CRC cells. It sponged miR-597-5p inducing up-regulation of CDK6 and RPA3 (156, 157).

Circ 000984 up-regulates CDK6. Circ 000984 (Figure 5) was up-regulated in CRC tissues compared to matched normal tissues and correlated with Tumor, Nodes and Metastasis (TNM) stage (158). In SW480 and SW620 CRC cells, silencing of circ 000984 inhibited proliferation, G0/G1 progression, migration, and invasion *in vitro*. Knockdown of circ 000984 attenuated growth of SW480 xenografts in immuno-compromised mice. Circ 000984 sponged miR-106b leading to up-regulation of CDK6. Enhanced CDK6 activity and constitutive activity of cyclin D/CDK4,6 has been found in several types of cancer (159, 160). Several CDK4/CDK6 inhibitors have been approved for hormone-dependent breast cancer. In CRC, comprehensive expression studies of CDK6 should be performed (161, 162).

Circ tumor protein 53 (circTP53) up-regulates cyclin-dependent kinase-like 3 (CDKL3). Circ TP53 (Figure 5) was up-regulated in CRC tissues (163). It promoted proliferation, invasion, migration and reduced the apoptotic rate of CRC cells *in vitro*. Knockdown of circ TP53 could inhibit tumor growth of CRC xenografts after subcutaneous implantation into nude mice (163). Circ TP53 sponged miR-876-3p resulting in up-regulation of CDKL3. The latter was found to be increased in anaplastic large cell lymphoma (164).

Circ 0007142 up-regulates glycerophosphodiesterase domain containing 5 (GDPD5). Circ 0007142 (Figure 5) was overexpressed in CRC and its knockdown facilitated apoptosis and ferroptosis in CRC cells *in vitro* and *in vivo* (165). It sponged miR-874-5p and subsequently up-regulated GDPD5. The latter mediates cleavage of glycosylphosphatidylinositol (GPI)-anchor of target proteins and is involved tumor cell migration, neurite formation and drives spinal motor neuro differentiation (166-168).



Figure 5. Circular RNAs up-regulating enzymes in colon-cancer preclinical in vivo models. The first line shows the corresponding circ-RNA, the second line displays the miR which is sponged by the specific circ RNA, the third line outlines the specific enzyme up-regulated and the fourth line indicates the effect of inhibition of the specific circ-RNA on tumor growth in nude mice. CDK6: Cyclin-dependent kinase 6; CDKL6: cyclin-dependent kinase-like 3; circ FMN2: circ formin 2; circ TP53: circ tumor protein 53; GDPD5: glycerophosphodiesterase domain containing 5; hTERT: telomerase reverse transcriptase; miR: micro RNA; TG: tumor growth; TNKS: tankyrase.

Circular RNAs Up-regulating Actin-related Components

Circ tubulin γ complex associated protein 3 (circTUBGCP3) up-regulates RHO-associated coiled coil containing protein kinase 1 (ROCK1). Circ TUBGCP3 (Figure 6) was up-regulated in CRC tissues and cell lines (169). Interference with circ TUBGCP3 inhibited colony formation, migration, invasion, cell-cycle progression, glycolysis and promoted apoptosis in CRC cell lines *in vitro* and *in vivo* after subcutaneous implantation into nude mice (169). Circ TUBGCP3 sponged miR-375 leading to up-regulation of ROCK1. The latter is a serine threonine kinase which acts as an effector of GTPase RHOA and promotes generation of contractile force and regulates the actomyosin cytoskeleton, cell-cell, and cell-matrix interactions (170). It has been

shown that up-regulated STAT3 and RHOA signaling in CRC cells promotes invasion and migration (171). Due to the involvement of ROCK1 in motility, metastasis, and angiogenesis, ROCK1 is a potential target for CRC therapy (172, 173).

Circ NOP2/SUN domain family member 2 (circ NSUN2) up-regulates RHO-associated coiled coil containing protein kinase 2 (ROCK2). Circ NSUN2 (Figure 6) was highly expressed in CRC tissues compared to adjacent tissues (174). It promoted proliferation, migration, and inhibited apoptosis in HCT116 and T84 CRC cells *in vitro* and attenuated tumor growth *in vivo* in nude mice. Circ NSUN2 sponged miR-181-5p resulting in up-regulation of ROCK2 (174), which is a downstream effector of RHOA GTPase. The latter affects CRC proliferation, apoptosis, invasion, and metastasis by



Figure 6. Circular RNAs up-regulating actin-related components in colon-cancer related preclinical in vivo models. The first line shows the corresponding circ-RNA, the second line displays the miR which is sponged by the specific circ RNA, the third line outlines the up-regulated actin-related protein, and the fourth line indicates the effect of inhibition of the specific circ RNA on tumor growth in nude mice. circ CSSP1: Circ-centrosome and spindle pole-associated protein 1; circ FARSA: circ phenylalanine-t-RNA ligase α subunit; circ NSUN 2: circ NOP2/SUN domain family member 2; circ TUBGCP3: circ tubulin γ complex associated protein 3; DIAPH1: diaphanous homolog 1; LASP1: LIM- and SH3 domain protein 1; miR: microRNA; MYO6: myosin 6; ROCK1,2: RHO-associated coiled coil protein kinase 1,2; TG: tumor growth.

stabilization of β -catenin (175) and therefore is a potential target for CRC therapy.

Circ-centrosome and spindle pole-associated protein 1 (circ CSPP1) up-regulates LIM and SH3-domain protein 1 (LASP1). Circ CSSP1 (Figure 6) was overexpressed in CRC and corresponding cell lines (176). Its knockdown attenuated proliferation, migration, invasion, and enhanced apoptosis in HCT-116 and SW480 CRC cells *in vitro*. Circ CSSP1 sponged miR-431 leading to up-regulation of LASP1 (176). Knockdown of circ CSSP1 in SW480 cells attenuated tumor growth in nude mice after subcutaneous implantation. LASP1 interacts with the cytoskeleton at sites of dynamic F-actin assembly and several other binding partners, and its overexpression is associated with tumor aggressiveness. It is

ubiquitously expressed in normal tissues, albeit at different levels (177).

Circ phenylalanine-t-RNA ligase α subunit (circ-FARSA) up-regulates LIM and SH3-domain protein 1 (LASP1). Circ-FARSA (Figure 6) was up-regulated in CRC and was associated with poor survival (178). Its knockdown inhibited proliferation, migration, and invasion of CRC cells. It sponged miR-330-5p which led to up-regulation of LASP1. The latter can interact with Wiskott-Aldrich syndrome protein to stimulate actin polymerization, migration, and invasion (179). LASP1 can activate signaling pathways such as PI3K/AKT and TGF- β /SMAD (180, 181). Activation of proliferation and survival pathways seems to be an important feature of LASP1 in oncology (182, 183). Inhibition of circ

FARSA inhibits growth of CRC cells *in vivo* in nude mice after subcutaneous implantation.

Circ 0044556 up-regulates diaphanous homolog 1 (DIAPH1). Circ 0044556 (Figure 6) was up-regulated in CRC and its silencing inhibited proliferation, cell-cycle progression, migration, invasion and EMT of CRC cells (184). It sponged miR-665 and up-regulated DIAPH1. In nude mice, circ 0044556 promoted growth of CRC xenografts after subcutaneous implantation. DIAPH1 is part of the formin family, a group of proteins involved in actin polymerization and acting as RHO-GTPase effector proteins (185). DIAPH1 is a potential target for cancer therapy (186).

Circ 0011385 up-regulates myosin 6 (MYO6). Circ 0011385 (Figure 6) was up-regulated in CRC tissues and cells (187). In HCT-116 and SW480 CRC cells its knockdown inhibited proliferation, migration and invasion and promoted apoptosis *in vitro*. circ 0011385 sponged miR-330-3p and up-regulated MYO6. Tumor growth of SW480 xenografts in nude mice was inhibited by down-regulation of circ 0011385. MYO6 represents a motor protein that moves cargo toward the minus ends of actin filaments, and its down-regulation reduces cell growth and migration and increases apoptosis in CRC cells (188-190).

Circular RNAs Up-regulating Transcription Factors and RNA-binding Protein Musashi Homolog 1

Circ 0000467 and circ 0007334 target Krüppel-like factor 12 (KLF12). Circ 0000467 (Figure 7) was up-regulated in CRC tissues and cell lines (191). Knockdown of circ 0000467 in LOVO and HCT-116 CRC cells inhibited proliferation, invasion and migration and tube formation of human umbilical vein endothelial cells (HUVECs) and promoted apoptosis (191). Down-regulation of circ 0000467 in HCT-116 cells impeded tumor growth in nude mice after subcutaneous implantation. Circ 0000467 sponged miR-4755-5p and subsequently up-regulated KLF12 (191).

Circ 0007334 (Figure 7) was increased in CRC tissues and in CRC-derived exosomes (192). Knockdown of 0007334 impaired viability, colony formation, migration, invasion, angiogenesis, and tumor growth of CRC cells *in vivo* in immuno-deficient mice (193). Circ 0007334 sponged miR-577 resulting in up-regulation of KLF12 (193). The latter is part of the Krüppel-like factor family comprising 17 members with involvement in cell differentiation, proliferation, and apoptosis. They can mediate either tumor-suppressive or oncogenic properties (192, 194). It has been shown that KLF12 promotes CRC growth through transcription factor growth response protein 1 (37). The role of KLF12 in CRC deserves further investigation.

Circ RNAs Up-regulating Forkhead-box Family Transcription Factors (FOXOs)

Circ α E-catenin (circCTNNA1) and circ ring finger 121 (circ RNF 121) up-regulate forkhead transcription factor M1 (FOXM1). Circ CTNNA1 (Figure 7) was up-regulated in CRC patients and correlated with poor survival (195). Circ CTNNA1 promoted proliferation, migration and invasion of SW 480 and SW 620 CRC cells *in vitro* and enhanced tumor growth of corresponding xenografts after subcutaneous implantation into nude mice. Circ CTNNA1 sponged miR-149-5p and up-regulated FOXM1.

Circ ring finger protein 121 (circ RNF121) up-regulates FOXM1. Circ-RNF121 (Figure 7) was up-regulated in CRC tissues with poor prognosis (196). Silencing of circ-RNF121 inhibited proliferation, migration, invasion and glycolysis and induced apoptosis in HCT-116 and SW480 CRC cells *in vitro*. In nude mice, knock-down of circ-RNF 121 repressed tumor growth (196). Circ-RNF121 sponged miR-1224-5p and up-regulated FOXM1. Circ-RNF 121 was secreted into exosomes in CRC cell lines HCT-116 and SW480.

Forkhead transcription factors comprise at least 14 subgroups sharing a DNA binding forkhead domain of at least 100 aa (197). Their function can be modulated by post-translational modifications such as phosphorylation, acetylation and ubiquitinylation (197). They have a dual function as tumor suppressors and as oncogenes (197). FOXM1 acts a regulator of the cell-cycle by up-regulation of cyclin B1 and D1 and down-regulation of p21 and p27 (197). In CRC, FOXM1 is overexpressed (198, 199), induces EMT (200), promotes growth *via* activation of β -catenin signaling (201) while its expression correlates with invasion and poor prognosis (202).

Circ ubiquitin-associated protein 2 (circ UBAP2) up-regulates forkhead transcription factor O1 (FOXO1). Circ UBAP2 (Figure 7) was up-regulated in CRC tissues and cell lines and induced autophagy *in vitro* and *in vivo* (203). Down-regulation of circ UBAP2 in CRC cell lines impeded proliferation, migration, and invasion. Circ UBAP2 sponged miR-582 with subsequent up-regulation of FOXO1. Class O FOX factors have been implicated in promoting anti-oxidant defenses by up-regulation of superoxide dismutase 2, periredoxins 3 and 5 in mitochondria and catalase in peroxisomes (204). Anti-neoplastic roles for FOXO1 have been described in digestive malignancies (205). The described functional discrepancies remain to be resolved.

Circ amyloid precursor-like protein 2 (circ APLP2) targets forkhead transcription factor K1 (FOXK1). Circ APLP2 (Figure 7) was increased in CRC tissues and cell lines (206). Knockdown of circ APLP2 inhibited proliferation, glycolysis and facilitated apoptosis in LOVO and SW480 CRC cells *in*

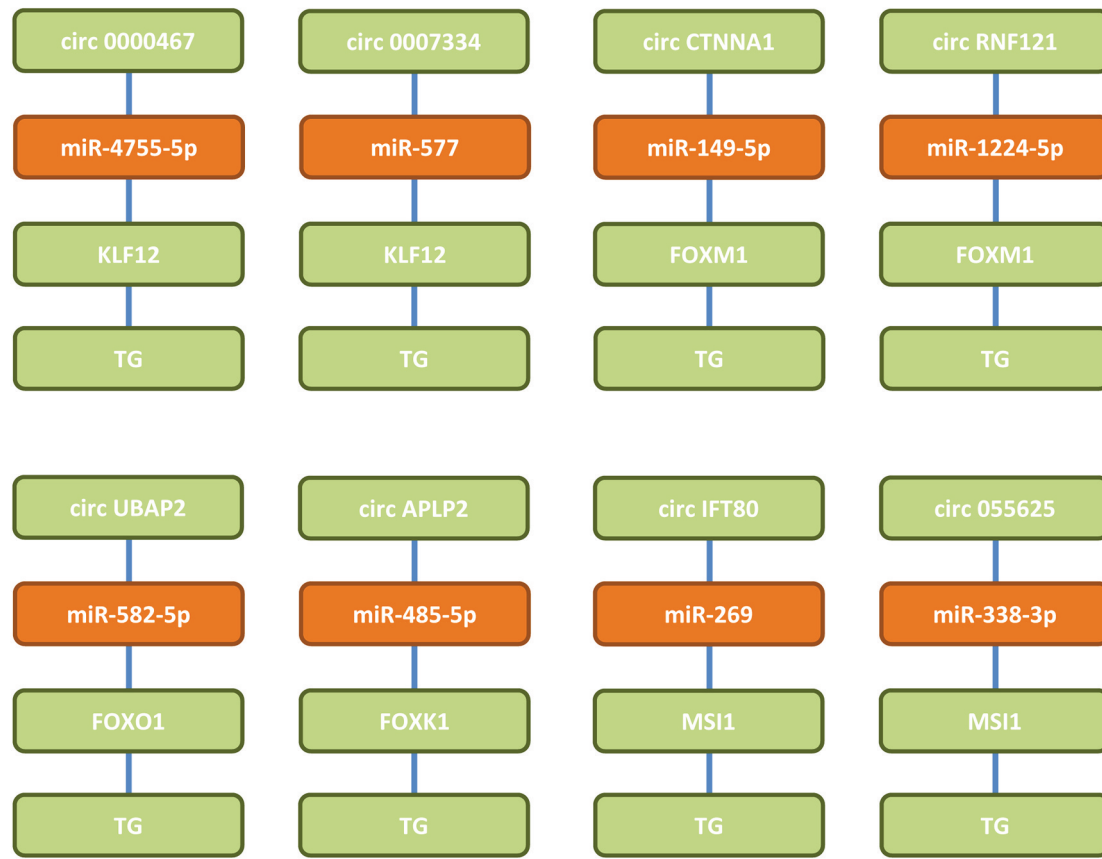


Figure 7. Circular RNAs up-regulating transcription factors and RNA binding protein Musashi in colon-cancer related preclinical *in vivo* models. The first line shows the corresponding circ-RNA, the second line displays the miR which is sponged by the specific circ-RNA, the third line indicates the up-regulated transcription factor or Musashi and the fourth line displays the effect of inhibition of the specific circ-RNA on tumor growth in nude mice. circ APLP2: Circ amyloid precursor like protein 2; circ CTNNA1: circ α E; circ IFT80: circ intra-flagellar transport; circ RNF 121: circ ring finger protein 121; circ UBAP2: circ ubiquitin-associated protein 2; FOXM1: forkhead transcription factor M1; FOXK1: forkhead transcription factor K1; FOXO1: forkhead transcription factor O1; KLF12: Krueppel-like factor 12; MSI1: Musashi homolog 1; TG: tumor growth.

in vitro. In nude mice, tumor growth of SW480 cells with knockdown of circ APLP2 was inhibited (206). Circ APLP2 sponged miR-485-5p resulting in up-regulation of FOXK1. The latter has been shown to promote proliferation, migration, invasion, and metastasis of CRC cells (207-210).

Circ intraflagellar transport 80 (circ IFT80) up-regulates Musashi homolog 1 (MSI1). Circ IFT80 (Figure 7) was up-regulated in exosomes from CRC patients and CRC cells (211). Exosomes promoted the growth of SW480 and SW620 CRC cells *in vitro*. circ IFT80 sponged miR-269, resulting in subsequent up-regulation of MSI1. Knockdown of circ IFT80 inhibited growth of SW480 CRC cells after subcutaneous implantation into immunodeficient mice. As previously described, MSI1 represents an RNA binding protein which regulates translation and splicing, exhibits oncogenic properties and acts as a regulator of stem cell

renewal (212, 213). MSI1 is overexpressed in CRC, is a predictor of survival in CRC patients and might be a therapeutic target for the treatment of CRC (214, 215).

Circ 0055625 up-regulates MSI1. Circ 0055625 (Figure 7) was found to be highly expressed in CRC tissues and correlated with poor survival (216). Knockdown of circ 0055625 repressed proliferation, migration, invasion and promoted apoptosis and radiosensitivity in SW480 and SW620 CRC cells *in vitro* and tumor growth of SW480 cells *in vivo* in nude mice. It sponged miR-338-3p resulting in up-regulation of MSI1 (216).

Conclusion

We have identified up-regulated circ RNAs which drive tumor growth in preclinical CRC-related *in vivo* models. They

sponge specific miRs which leads to the up-regulation of targets involved in tumor growth and metastasis. Their inhibition with siRNA or shRNA mediates inhibition of tumor growth. In addition, the corresponding targets can be inhibited by small molecules or antibody-related moieties in the context of target validation. However, the field of inhibition of circ RNAs is still associated with technical hurdles which are not discussed in detail in this review. The outstanding issues are delivery and immunogenicity (217-221).

Nine circ RNAs and their corresponding targets have been identified which mediate resistance against chemotherapeutic drugs such as 5-FU, L-OHP, CDDP, IRT and DOX (Figure 1). Since resistance against chemotherapeutic agents is a steadily occurring theme during treatment of CRC, the identified targets and corresponding circ RNAs deserve further validation. 7 circ RNAs target transmembrane receptors (Figure 2), whereas 4 of them up-regulated secreted factors (Figure 3). VEGF-A has emerged as a clinically validated target in CRC. Noteworthy, two circ RNAs target IGF-1R (Figure 2) and one of them up-regulates one of its ligands, IGF-1 (Figure 3). Since no clinical benefit has been observed with corresponding inhibitors in cancer patients, combination therapy and identification of biomarkers indicative of response should be explored. GLUT1, IL6, TYRO3 and CXCL5 as targets and their corresponding circ RNAs are recommended for further validation in CRC (Figure 2 and Figure 3). As shown in Figure 4, 9 circ RNAs up-regulating signaling components have been identified. The data support inhibition of WNT, PI3K and JAK2/STAT3 signaling as well as interference with DNMT mediated methylation for further preclinical validation. Figure 5 shows the identification of six circ RNAs promoting tumor growth with enzymatic functions. Further investigation of TNKS, CDK6 and corresponding circ RNAs in CRC is recommended. Six of the identified circ RNAs are involved in up-regulating components of the actin cytoskeleton (Figure 6). Inhibition of RHOA GTPase effector functions such as ROCK1,2 and DIAPH1 and their corresponding circ RNAs as targets for therapeutic intervention should be explored in more detail. Six circ RNAs up-regulate transcription factors such as KLF12, FOXM1, FOXO1 and FOXK1 and two circ RNAs up-regulate MSI1 (Figure 7). Inhibition of transcription factors with the proteolysis-targeting chimera (PROTAC) technology is under clinical investigation (222-225). It remains to be explored whether RNA binding protein MSI1 will emerge as a druggable and validated target for the treatment of CRC. Also, it is presently unclear whether the identified circ RNA and their corresponding targets are associated with one or more of the defined molecular subtypes of CRC.

Conflicts of Interest

AN is and UHW was an employee of Roche.

Authors' Contributions

AN and UHW equally contributed to all aspects of the paper.

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