Cancer and Metastasis Reviews (2018) 37:805–820
https://doi.org/10.1007/s10555-018-9771-8

NON-THEMATIC REVIEW

MACC1—the first decade of a key metastasis molecule from gene discovery to clinical translation

Harikrishnan Radhakrishnan[1] · Wolfgang Walther[1,2] · Fabian Zincke[1,2] · Dennis Kobelt[1,2] · Francesca Imbastari[1] · Müge Erdem[1] · Benedikt Kortüm[1] · Mathias Dahlmann[1,2] · Ulrike Stein[1,2]

Published online: 3 January 2019
© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract
Deciphering the paths to metastasis and identifying key molecules driving this process is one important issue for understanding and treatment of cancer. Such a key driver molecule is Metastasis Associated in Colon Cancer 1 (MACC1). A decade long research on this evolutionarily conserved molecule with features of a transcription factor as well as an adapter protein for versatile protein-protein interactions has shown that it has manifold properties driving tumors to their metastatic stage. MACC1 transcriptionally regulates genes involved in epithelial-mesenchymal transition (EMT), including those which are able to directly induce metastasis like c-MET, impacts tumor cell migration and invasion, and induces metastasis in solid cancers. MACC1 has proven as a valuable biomarker for prognosis of metastasis formation linked to patient survival and gives promise to also act as a predictive marker for individualized therapies in a broad variety of cancers. This review discusses the many features of MACC1 in the context of the hallmarks of cancer and the potential of this molecule as biomarker and novel therapeutic target for restriction and prevention of metastasis.

Key words MACC1 · metastasis · solid cancers · biomarker · prognosis and prediction · targeted therapy

1 Discovery of a novel gene as key player of metastasis

Cancer metastasis is directly linked to patient survival representing the most lethal attribute of cancer. It critically limits successful therapy in many tumor entities. For example, survival of colorectal cancer (CRC) patients is about 90% in early, non-metastasized stages, but below 10%, when distant metastases have formed [1–3]. When presenting the first time, about 25-30% of all CRC patients have distant metastasis. However, 40-50% of all newly diagnosed, non-metastasized CRC patients will develop distant metastasis after primary surgery. Thus, novel biomarkers, which are prognostic, predictive, and more importantly causal for cancer metastasis, are ultimately desired.

More than a decade ago, we started our ambitious endeavor to search for a new gene which is ideally – (a) prognostic for the disease course, allowing identification of patients at high risk for metastasis formation already in early stages before occult metastases are determined, (b) predictive for therapy response, (c) biologically causal for tumor initiation, progression and metastasis formation, and (d) representing a molecular target to restrict/prevent metastasis resulting in longer patient survival. By performing differential display RT-PCR using human colon cancer tissues, metastases and normal colon mucosa, we identified a novel, previously not described differentially expressed complementary DNA (cDNA) fragment and cloned the full length cDNA. We named this newly identified gene *Metastasis-Associated in Colon Cancer 1, MACC1* (GenBank gene ID 346389, European Molecular Biology Laboratory (EMBL) data bank accession code AJ313524) [4] (Fig. 1).

Remarkably, we found in this pioneer study, that those tumors with UICC stages I, II and III (due to TNM classification not

Harikrishnan Radhakrishnan and Wolfgang Walther contributed equally to this work.

✉ Ulrike Stein
ustein@mdc-berlin.de

[1] Experimental and Clinical Research Center, Charité—Universitätsmedizin Berlin and Max-Delbrück-Center for Molecular Medicine, Robert-Rössle-Straße 10, 13125 Berlin, Germany

[2] German Cancer Consortium (DKTK), German Cancer Research Center, Heidelberg, Germany

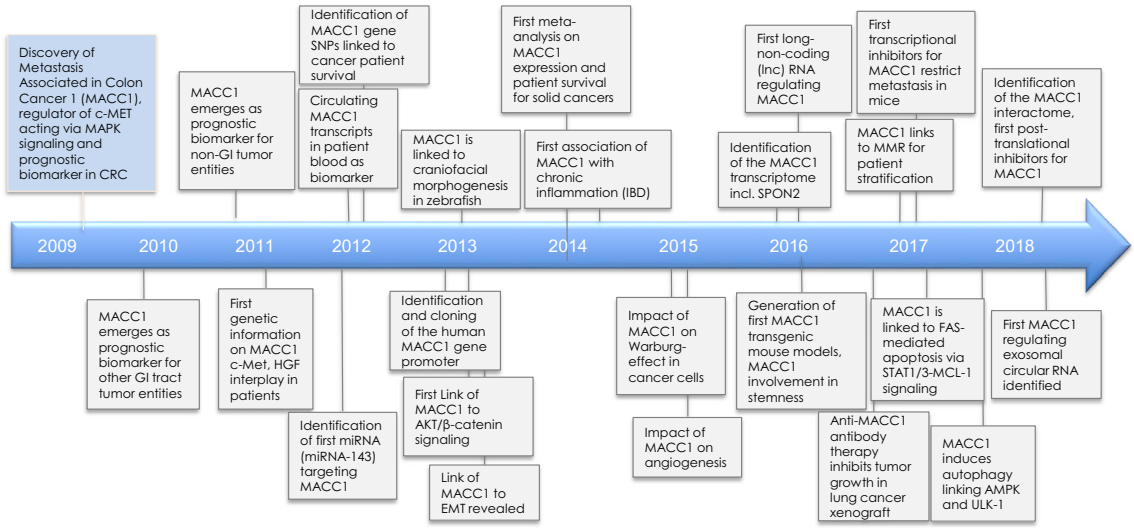

Fig. 1 Chronicle of MACC1 gene discovery. Time line of key findings regarding MACC1, its importance as biomarker and biological functions

distantly metastasized at the time point of surgery) showed a significantly higher MACC1 expression at the time of diagnosis, if they then developed metachronously (after surgery of the primary tumor) distant metastases, compared to non-metastasizing tumors with lower MACC1 expression of these disease stages. Consistently, the 5-year survival rate for patients with high MACC1 mRNA expression in their primary tumors was only 15%, whereas patients with low MACC1 expression showed a survival rate of 80%. These data provided first hints to have a strong biomarker and key molecule for metastasis in hand.

2 Clinical impact of MACC1 as prognostic and predictive biomarker

MACC1 has been established by many groups as key player and biomarker for tumor progression and metastasis in more than 20 solid cancer types, including CRC, bladder, breast, cervical, esophageal, gall bladder, gastric, head/neck, hepatocellular/biliary, lung, nasopharyngeal, ovarian, pancreatic, renal, kidney and tongue squamous cell cancer, as well as glioblastomas and osteosarcomas [4–11]. Following our initial discovery of MACC1, more than 180 successional papers (PubMed) from groups worldwide were published until today, including meta-analyses on the clinical impact of MACC1 for solid cancers [12], tumors of the digestive system [13], hepatocellular cancer (HCC) [14], and CRC [15] (Fig. 2). They strongly confirm the prognostic value of MACC1 for tumor progression and metastasis for a broad panel of solid cancer entities, associated with poor patient survival. High MACC1 expression in primary tumors predisposes the development of metachronous metastasis, allowing the early prognosis for metastasis and patient stratification. Furthermore, high circulating MACC1 transcripts or protein levels in liquid biopsies (non-invasive), such as patient's blood, predict tumor progression and metastasis formation. They were found to be linked to shorter survival of CRC, pancreatic, gastric, lung and breast cancer patients [16–21]. High expression of MACC1 was also demonstrated to predict post-operative recurrence of lung cancer [22], cancer recurrence after resection of CRC liver metastases [23], and HCC after liver transplantation [24].

Importantly, high MACC1 expression was predictive for treatment response towards conventional chemotherapeutics, such as cisplatin for tongue squamous cell cancer [25], glioblastoma multiforme (GBM) [26], ovarian cancer [27, 28], gastric cancer [29], and lung cancer [30], oxaliplatin for gastric cancer [31], and 5-fluorouracil (5-FU) for CRC [32, 33] and gastric cancer [29]. High MACC1 expression levels also predicted treatment response to gemcitabine in pancreatic cancer [17] and temozolomide/Endothelial-Monocyte-Activating Polypeptide–II (EMAP-II) in GBM [34], as well as poor outcomes after neo-adjuvant chemo-radiotherapy for rectal cancer [35] and after cryoablation therapy for advanced HCC [36].

Taken together, MACC1 is proven by many groups for multiple cancer entities as clinically useful prognostic and predictive biomarker.

3 Unique structural features and regulation of MACC1

The gene *MACC1* has an overall length of about 82.7 kbp and is located on the complementary strand of the p-arm of human chromosome 7 (7p21.1) between position 20,134,655 and 20,217,390 (GRCh38.p12). MACC1 contains seven exons and six introns, with its last intron harboring *MACC1-AS1* on the opposite strand (Fig. 3), giving rise to a long non-coding (lnc) RNA with complementary sequence to *MACC1*

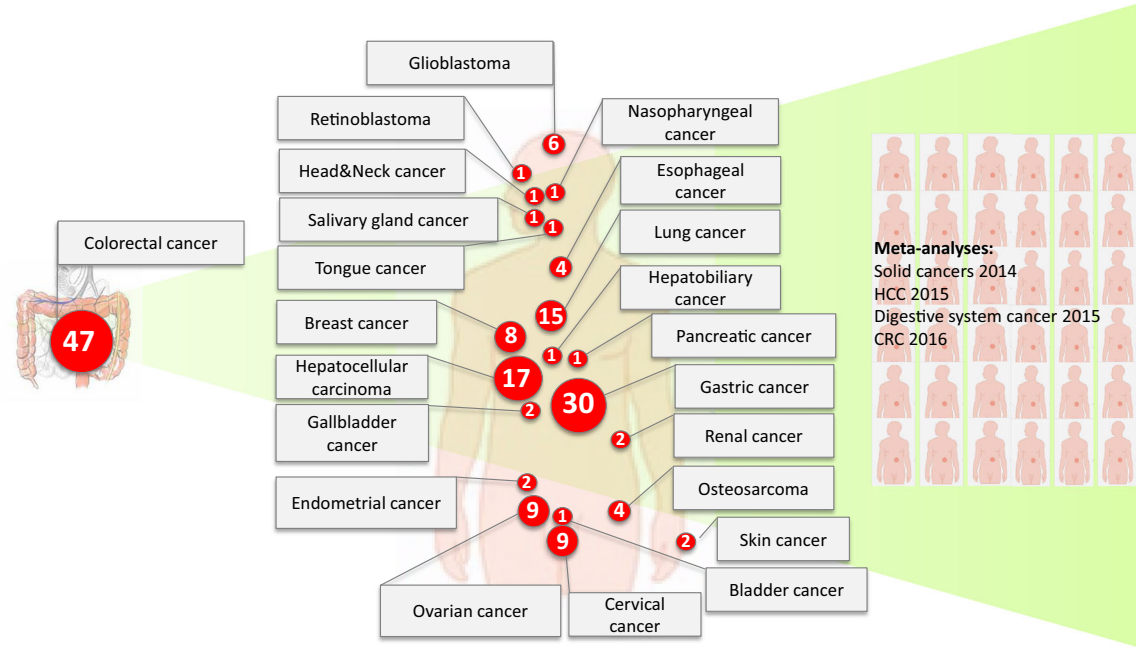

Fig. 2 Overview of published analyses (PubMed) on MACC1 biological functions and clinical significance. The numbers reflect publication frequencies for specific solid tumor entities indicated in red circles. Further meta-analyses prove MACC1 as a prognostic biomarker for solid cancers

[37, 38]. Neighboring regions at chromosome 7p21 comprise other tumorigenic and metastasis associated genes, like Twist neighbor (*TWISTNB*), Twist-related protein 1 (*TWIST1*), and Integrin beta 8 (*ITGB8*) [5].

Transcription of *MACC1* and subsequent splicing generate a 76.8 kbp mRNA, encoding a protein of 852 amino acids (aa). Alternative splicing of *MACC1* has been found in cDNA libraries, but mostly not considered to generate any protein except full length MACC1 with alterations only in the untranslated regions (UTRs) [39].

The 852 aa MACC1 protein shows five predicted structural domains. The most N-terminal protein structures harbor similarities to a domain found in zonula occludens 1 and uncoordinated protein 5 (ZU5) and a domain common in uncoordinated protein 5 (Unc5), p53-induced death domain protein 1, and ankyrins (UPA). More C-terminally, an Src homology 3 (SH3) domain is predicted, followed by a tandem of death domains (DD) [4, 37, 39]. Interestingly, the pattern of ZU5-UPA-DD is found in a variety of proteins with different cellular functions, ranging from cytoskeletal anchors, transmembrane receptors to apoptosis promoting factors. Most similar to MACC1 in domain architecture, but also in nucleic and amino acid sequence is SH3BP4/TTP, which is involved in receptor internalization and recycling [40].

When looking at potential linear protein interaction motifs, the rather unstructured N-terminus of MACC1 contains similar interaction motifs for clathrin mediated endocytosis (clathrin box, NPF, DPF) as seen in the MACC1 homolog SH3BP4/TTP, but also proline-rich motifs (PxPxP, KxxPxxP) located N-terminally of the MACC1-SH3 domain [1, 4].

MACC1 expression is regulated on the transcriptional and post-transcriptional level. The MACC1 promoter (up to 1000 bp from transcription start site, TSS) contains binding elements of the transcription factors AP1, C/EBP, and SP1, which all contributed to the expression of MACC1 [41] (Fig. 3). Additional binding elements for the YB-1 transcription factor have been reported further upstream of the MACC1-TSS in lung cancer cells [42]. Interestingly, intracellular calcium signaling is also involved in MACC1 expression regulation, as the knock-down of key factors of store-operated Ca^{2+} entry resulted in reduced MACC1 levels in gastric cancer [43]. The presence and activity of more distant regulatory elements is not reported so far, but any progress on this topic will contribute to better understand tissue specific- and time-dependent regulation of MACC1 transcription.

Knowledge on post-transcriptional regulation of MACC1 expression emerged in the last years, acting via either stabilization or destabilization of MACC1-mRNA (Fig. 3). Elevated expression of MACC1-AS1, a lncRNA, stabilizes mRNA levels of MACC1 via the AMPK/Lin28 pathway and therefore increases MACC1 protein expression [38]. Similarly, depletion of ZFP36, an RNA destabilizing protein recognizing ARE sequences in the 3′-UTRs of ZEB1, SOX9, and MACC1, stabilized MACC1 mRNA levels [44]. Furthermore, a multitude of microRNAs (miRNA/miR) has been found to strongly reduce MACC1 expression: miR-141 [45], miR-143 [46–48], miR-200a [49], miR-218 [50], miR-338-3p [51–54], miR-433 [55], miR-485 [56], miR-497 [57], miR-574-5p [58], miR-590-3p [34], miR-598 [59], and miR-944 [60, 61]. Epigenetic modifications were described as

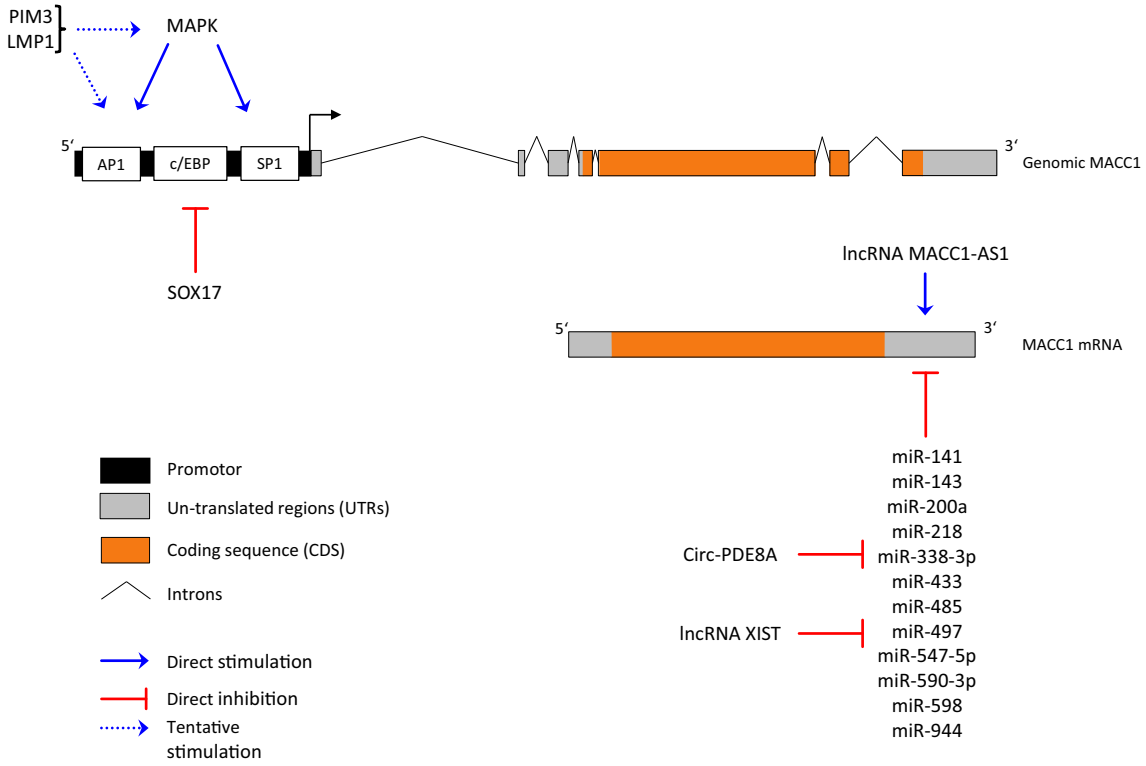

Fig. 3 Schematic representation of MACC1 regulation. MACC1 expression is transcriptionally regulated by the MAPK pathway through its consensus AP1 and SP1 binding sites on MACC1 promotor. SOX17 has been shown to repress MACC1 expression by directly binding to its promotor, whereas PIM3 and LMP1 showed its effect on activating MACC1 expression. MACC1 is post-transcriptionally repressed by plethora of miRNAs (miRs) that bind to its corresponding consensus sequences in the 3′UTR of MACC1. The long non-coding RNA (lncRNA) XIST and exosomal circular RNA (circ-PDE8A) increase MACC1 expression by antagonizing their miR targets miR-497 and miR-338, respectively, whereas lncRNA MACC1-AS1 increases MACC1 expression by stabilizing its mRNA transcript

mechanisms regulating MACC1 expression. DNA methylation arrays, performed with respect to the CRC metastatic potential, revealed MACC1, besides other important genes such as KRAS, genes of the Rho family of GTPases, and c-MET [62]. Further, hypermethylation of MACC1 regulating miR-218 was shown. Consequently, treatment with methyltransferase inhibitor 5-azacytidine induced miR-218 expression leading to inhibition of its target MACC1 [50].

Very recently, the circular RNA PDE8A has been shown to increase MACC1 levels in pancreatic cancer by competitive miR-338 binding, counteracting its inhibitory effect on MACC1 expression [63].

Once translated and folded, MACC1 is highly likely also a target of post-translational modifications (PTM) that regulate its cellular localization, activity, binding affinity of interaction partners, or protein stability. Several sites of PTM, like phosphorylation, glycosylation, or covalent attachment of ubiquitin/-like modifiers, are predicted by current algorithms.

The tight expression regulation of *MACC1* in normal tissues and its deregulated expression in cancer tissues highlight the role of *MACC1* in metastasis formation and support its clinical relevance. Furthermore, its unique pattern of structural domains, linear motifs, and potential PTMs are suggesting a multitude of potential protein interactions, which allows MACC1 to act in many cellular mechanisms, including hallmarks of cancer, like proliferation, invasion, inhibition of apoptosis and treatment resistance [4, 40].

4 The hallmarks of cancer: how a novel gene came into the play

Hanahan and Weinberg's cancer hallmarks provide a comprehensive list of events that outline and dictate the transformation of a normal tissue into an aggressive and malignant tumor [64, 65]. Numerous genes were shown to be essential contributors to the hallmarks of cancer as they influence cell signaling, tumor growth, progression, and metastasis. Here, we describe how the novel gene MACC1 also plays a central role in equipping cells with a malignant phenotype by inducing or promoting the following hallmark capabilities: inducing invasion and metastasis, sustained proliferative signaling, evading growth suppression, resisting cell death, inducing pro-tumor inflammation, preventing immune-attack, inducing tumor angiogenesis, promoting metabolic re-programming, and contributing to replicative immortality and genomic instability (Fig. 4). The molecular mechanisms by which MACC1

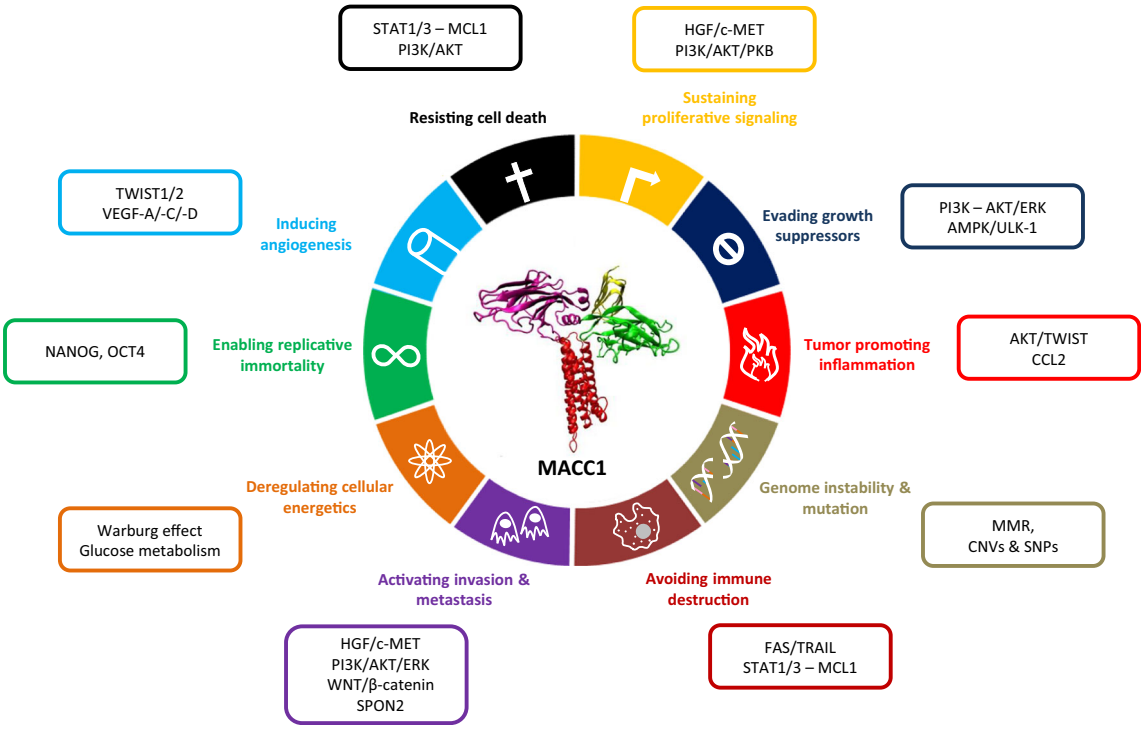

Fig. 4 Schematic representation of MACC1 impact in the hallmarks of cancer. MACC1 elicits and associates with the cancer hallmark characteristics through involvement and activation of various signaling mechanisms and biological features of cancer. The key components through which MACC1 impacts each cancer hallmark are highlighted in uniformly color-coded boxes. The image of MACC1 3D structure was predicted using Protein Homology/ anologY Recognition Engine V 2.0 (Phyre^2)

causally supports these hallmark capabilities are discussed in detail under each section (Fig. 5).

4.1 Activation of invasion and metastasis: the travel agent MACC1

Metastasis is a highly orchestrated process involving cancer cell migration, local invasion, intravasation, systemic dissemination, extravasation, and settlement of secondary tumors in distant organs in virtually all solid tumors [65].

MACC1, frequently overexpressed in primary tumors, has proven to predict metachronous metastasis and reduced recurrence-free, as well as overall survival independently of established clinicopathological criteria in CRC [4] and in many other solid cancer entities (CRC [35, 66]; gastric [67]; lung [22, 68]; HCC [36, 69, 70]; breast [71, 72], renal [73]; bile duct [74]; ovarian [75]; and cervical cancer [76]; as well as GBM [77, 78]; and osteosarcoma [79], reviewed in [6]). MACC1 expression increases as the tumor progresses from adenoma to carcinoma [4, 21, 80, 81], during which the primary tumor loses epithelial features, establishes an invasive front towards the underlying tissue, and eventually disseminates circulating tumor cells (CTCs) into blood and lymphatic vessels. In advanced tumors, MACC1 expression is enriched at the invasive front and tumor buds in CRC [80], as well as in CTCs [81]. As MACC1 induces cell motility [4], its expression at the invasive front and in CTCs strengthens the role of MACC1 as a causative driver of tumor cell invasion and metastasis.

We have observed *in vivo* that transgenic overexpression of MACC1 led to transition of sporadic non-invasive adenomas to carcinomas in the intestine of APC^{Min} mice [82]. The resulting *vil-MACC1/*APC^{Min} tumors were greatly enriched in genes associated with re-modulation of the extracellular matrix (PLAU, MMP7, MMP9), key players driving tissue invasion and metastasis [83]. Further, xenograft models of MACC1-overexpressing CRC cells showed strong increase in number and size of hepatic metastases [4, 84].

Mechanistically, MACC1 is a transcription factor of c-MET, positioning this molecule atop a MACC1/HGF/c-MET axis orchestrating EMT in CRC [4, 85], ovarian cancer [86, 87], Klatskin tumors [74], gastric cancer [88], HCC [89], and GBM [77]. Through c-MET/AKT signaling, MACC1 induces the EMT-associated transcription factors TWIST1 and TWIST2 and promotes migration, invasion, and neovascularization in gastric cancers [90, 91]. The functionality of this MACC1/c-MET/AKT axis is demonstrated in various cancers by miR-598 [59], miR-944 [60, 61] and miR-338-3p, which unequivocally reduced c-MET and pAKT expression by targeting MACC1. miR338-3p, targeting both ZEB2 and MACC1, inhibits EMT in gastric cancer, an effect reversible by exogenous overexpression of either ZEB2 or MACC1, where the latter restored expression of c-MET and pAKT

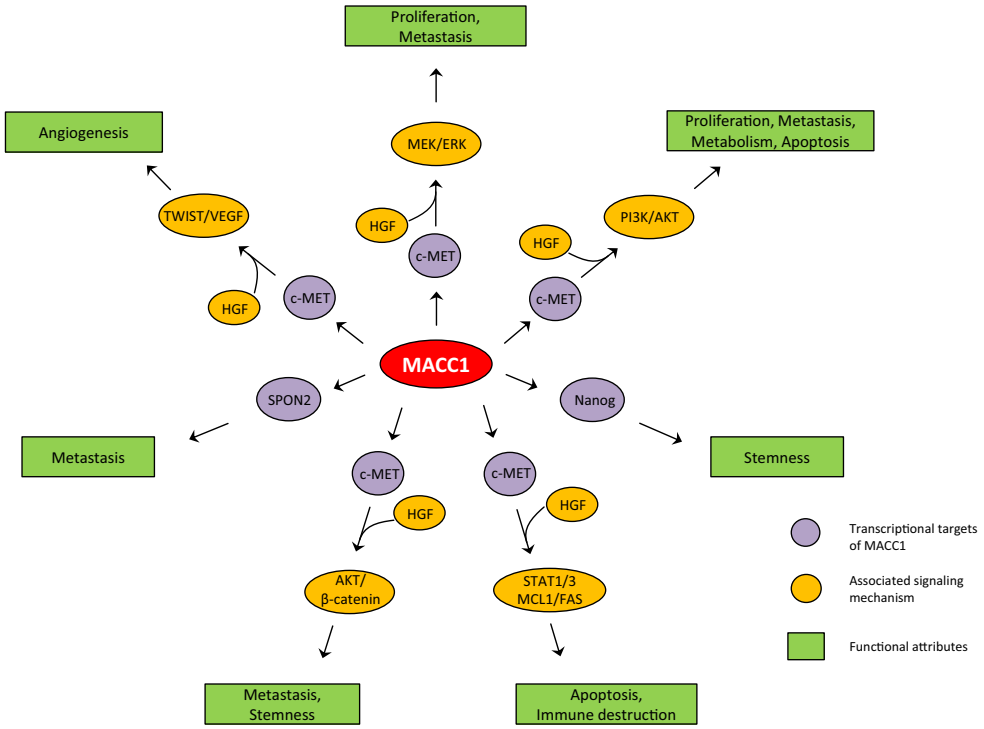

Fig. 5 MACC1 effectors, signaling mechanisms, and biological responses. MACC1 is involved in various cancer hallmark capabilities, such as proliferation, metastasis, metabolic de-regulation, apoptosis resistance, angiogenesis, and stemness through transcriptional activation of its key target molecules c-MET, NANOG, and SPON2. In particular, c-MET upregulation by MACC1 is central in activating various downstream signaling mechanisms, such as MEK/ERK, PI3K/AKT/β-catenin, STAT1/3, and TWIST/VEGF, which results in enhancement of various cellular processes associated with oncogenic transformation, tumor progression, and metastasis. Further, NANOG upregulation induces stemness features and SPON2 induces metastatic dissemination

and promoted EMT-specific gene regulation [51]. Overall, PI3K/AKT signaling emerges as a main hub for the effect of MACC1 on EMT, as increased pAKT was accompanied by markers of mesenchymal differentiation (downregulated E-cadherin, enhanced N-cadherin, α-smooth muscle actin, and vimentin) and matrix remodeling (upregulated MMP2 and MMP9) in several cancer types [76, 89, 92–95]. Potentially, also through inactivation of PTEN, MACC1 expression increased the phosphorylation of AKT in osteosarcoma cells and esophageal cancer [79, 96]. Consistently, in nasopharyngeal cancer, MACC1 overexpression correlated positively with abundance of activated AKT in tumor sections. Additionally, the kinase AKT itself is intimately linked to canonical WNT signaling by stabilizing β-catenin and promoting its nuclear accumulation [92, 97–99]. WNT/β-catenin signaling itself is inappropriately active in many cancers and promotes cell plasticity and motility by direct induction of EMT genes, such as *SNAIL1/2*, *TWIST1/2* and even suppressing *CDH1* (E-cadherin) on a transcriptional level [100–102]. By activation of AKT and subsequent GSK3β inhibition, MACC1 stabilizes β-catenin and enhances migration and invasiveness of cancer cells *in vitro* and *in vivo* [92, 93].

Taken together, critical steps in invasion and metastasis formation of solid cancers are orchestrated by MACC1. Its elevated expression in the primary tumor when benign adenomas turn into carcinomas, its enrichment at the invasive tumor front and CTCs, the MACC1-dependent induction of EMT-associated transcription factors and signaling pathways, and the expression of ECM modulating factors result in increased cellular motility and enhanced tumor invasiveness. This combination drives the lethal spread of tumor cells to local and distant organs, rendering MACC1 a promising target to treat metastasis formation early in tumor development, and thus potentially improves patient outcome.

4.2 Sustained proliferative signaling: MACC1 keeps cancer cells growing

Sustained proliferation is a fundamental feature of cancer whereby cells undergo uncontrolled cell growth and division cycles. Cancer cells fuel proliferative signaling through upregulation of growth factor ligands and activation of receptors or its downstream receptor tyrosine kinase (RTK) signaling [64, 65]. The first study on MACC1 revealed the impact of this gene on cancer cell proliferation, since CRC cells with ectopic overexpression of MACC1 showed increased growth *in vitro* and *in vivo* [4]. More importantly, MACC1 was shown to be the transcriptional activator of c-MET, the receptor tyrosine kinase promoting HGF/c-MET signaling for proliferation. This increased c-MET signaling triggers downstream GAB1-SHP2-ERK/MAPK and PI3K/AKT-axes resulting in increased cell proliferation [4, 103]. Moreover, MACC1 itself is regulated by active ERK signaling via the transcription factors AP1 and SP1 [41, 104, 105]. In this context, the MACC1/HGF/c-MET/ERK/MACC1 positive feed-back loop might represent a self-sustaining proliferation mechanism in cancer thereby contributing to tumor progression.

MACC1 induced PI3K/AKT signaling increases the expression of WNT target genes, such as c-MYC, cyclin D1/E, MMP2, and MMP9, with concomitant increase in cell proliferation *in vitro* and *in vivo* [30, 76, 79, 88, 89, 92–94, 106, 107]. Consistently, intestine specific MACC1 transgenic mice (*vil-MACC1/APC^{Min}*) showed sporadic development of bigger tumors with strong Ki-67 staining, indicating tumor cell hyper-proliferation. Transcriptomic analysis and validation of tumor tissues from MACC1 transgenic mice showed increased expression of WNT target genes, including VEGF-A and matrix degrading proteases MMP7 and MMP9 [82]. The MMPs are known to induce proliferation by increasing the spatial bioavailability of growth factors whereas VEGF is known to induce tumor cell proliferation in a cell autonomous and angiogenesis-independent manner [65, 108]. By contrast, this MACC1-dependent proliferative signaling was inhibited by RNAi and several MACC1-destabilizing miRNAs [17, 45, 51, 52, 55, 58]. However, MACC1-stabilizing lncRNAs (XIST and MACC1-AS1) and circRNA (PDE8A) induced sustained MACC1-dependent proliferation [38, 57, 63]. Taken together, numerous studies clearly show that MACC1 supports tumor aggressiveness by inducing sustained proliferation in both growth factor dependent and independent manner by modulating different signaling pathways.

4.3 Evading growth suppression: break release by MACC1

Cancer cells develop the ability to circumvent or overcome the strictly controlled mechanisms of cell proliferation which shifts them into a continuous growth state leading to extensive cell expansion and spread [65]. The cell cycle represents one of the essential and tightly regulated mechanisms governed by different upstream cascades including tumor-suppressor proteins (e.g. p53, Rb and PTEN) and further driving or inhibiting factors, such as cyclin-dependent kinases, cyclins, CIP, KIP and c-MYC [109–111]. In this context, MACC1 was shown to induce G_1/S-phase progression in different cancer models, whereas MACC1 silencing led to G_0/G_1 arrest [79, 112, 113]. Cell cycle progression is mediated via MACC1-dependent PI3K/AKT signaling which regulates G_1/S-phase transition and the expression of crucial target genes, such as cyclin B, D1, D2, E, c-MYC, and SPON2 [30, 79, 92–94, 112–114]. Most interestingly, in hepatocellular and nasopharyngeal tumors, a positive correlation between MACC1 and pAKT expression was shown, substantiating the clinical relevance of MACC1-dependent activation of AKT signaling [30, 79, 92, 115]. Consistently, MACC1 silencing increased the expression of PTEN, a well-established tumor suppressor, thereby attenuating the downstream PI3K/AKT signaling and subsequently triggering growth suppression [96]. Taken together, MACC1 enables cancer cells to progress through G_1/S-phase and to evade from growth suppression by inhibiting tumor-suppressor PTEN, thereby activating PI3K/AKT signaling which in turn regulates key cell cycle proteins.

4.4 Resisting cell death: survive with MACC1

Dysregulated apoptosis mechanisms enable cancer cells to acquire resistance towards programmed cell death stimuli of intrinsic and extrinsic origin [64, 65]. Numerous studies have linked MACC1 to cancer escaping from apoptosis. MACC1 silencing *in vitro* increased the number of cells with Annexin-V positivity as well as activation of caspases (caspase 8, 9, 3 and 7) and PARP. Consistently, MACC1 silencing decreased the expression of anti-apoptotic proteins BCL2 and MCL1, whereas the expression of pro-apoptotic proteins BAX and BAD was increased [93, 96, 112, 115–117]. *In vivo*, MACC1 silencing induced the apoptotic phenotype, such as increased cleaved caspase 3 expression and DNA fragmentation in HCC and cervical cancer xenografted tumors [115–117]. In patient-derived tumor specimens of CRC and pancreatic cancer, MACC1 expression positively correlated with that of MCL1. Consistently, MACC1 silencing decreased MCL1 expression thereby inducing apoptosis in cancer cells in a BAX/BAD-dependent manner upon death receptor stimulation by FASL and TRAIL [117]. MACC1 inhibits cell death by inducing pro-survival signaling in a tissue- and context-dependent manner. The MACC1-dependent MCL1 regulation and sensitization to death receptor activation was mediated through STAT1/3 signaling [117]. MACC1 activates PI3K/AKT signaling and regulates the expression of BCL2, BAX, BAD and caspase 3 in CRC, HCC and nasopharyngeal cancer cells [92, 93, 115], whereas in ovarian and pancreatic cells MACC1 induced MEK/ERK pro-survival signaling, thereby regulating the expression of BCL2 and activation of caspase 3, caspase 9 and PARP [17, 86].

Genotoxic stresses originating from reactive oxygen species (ROS) or from therapy-induced DNA adducts eliminate cancer cells by activation of apoptosis. Interestingly, chemotherapy (taxol, 5-FU and cisplatin)-resistant tumors exhibited an enrichment of MACC1 expressing cells, which were re-sensitized by disrupting the HGF/c-MET/AKT pro-survival signaling upon MACC1 silencing [26, 29, 116, 118]. Moreover, MACC1 silencing sensitized pancreatic cancer cells to gemcitabine treatment through inhibition of MEK/ERK signaling [17]. These observations suggest a central role of MACC1 in the regulation of major survival pathways, such as PI3K/AKT, MEK/ERK and STAT, thereby enabling cancer progression via imparting resistance to cell death. Hence, inhibiting MACC1 in combination with chemotherapy or checkpoint inhibitors might present a novel attractive strategy to treat therapy-resistant and –refractory tumors.

4.5 Immune destruction: shielding cancer by MACC1

Immune surveillance controls tumor emergence and also metastatic spread by immune destruction of transformed cells. In turn, tumors develop escape mechanisms to circumvent such destruction. In this regard, MACC1 was found as a modulator of FASL- and TRAIL-mediated apoptosis [117]. FASL and TRAIL are important mediators of immune surveillance and serve as important molecules for the success of checkpoint inhibitor therapy [117, 119, 120]. MACC1-mediated down-regulation of FAS and up-regulation of MCL1 via the STAT1/3 signaling provide first indication for the potential link between this metastasis-promoting gene and immune escape. Other studies also supported the anti-apoptotic activity of MACC1, protecting tumor cells from apoptotic signaling and aiding survival [92]. Furthermore MACC1 might interfere with immune attacks via activation of TIMP1/2, that in turn recruits tumor-associated macrophages (TAMs) [121]. TAMs create a pro-cancerous microenvironment and can support tumor escape from immune destruction by secretion of cytokines (e.g., IL1, IL6, TNF-α) and growth factors (e.g., TGF-β), which dampen T cell activity and T cell-mediated tumor destruction [121–123].

In conclusion, MACC1 not only promotes metastatic spread but might also protect metastasis from immune destruction for their establishment at distant sites. In the light of check-point immune therapies, targeting MACC1 might add to design of new combinatorial concepts to improve immune surveillance of tumors.

4.6 Pro-tumor inflammation: MACC1 conditions microenvironment

Inflammation significantly affects aspects of malignancy, such as proliferation, survival of cancer cells, angiogenesis and metastasis [124]. This is supported by the fact that chronic inflammation promotes development of CRC, particularly patients with inflammatory bowel disease (IBD) show increased risk for CRC [125]. Interestingly, the analyzed regions of genetic alterations in IBD patients mapped one such region to MACC1 [126], providing first clues on the impact of MACC1 in inflammation and cancer development. Recently, MACC1 was associated with IBD by detecting increased MACC1 and c-MET expression in patient tissues with IBD-associated dysplasia [127]. First indications for a function of MACC1 in cancer-promoting inflammation came from the data that MACC1 transcriptionally induces TWIST1/2 [90], genes known to promote macrophage recruitment [128]. In turn, tumor-associated macrophages promote angiogenesis and restructure tumor microenvironment to support metastasis [121]. This indicates that MACC1 not only associates, but actively interacts with key events of cancer-promoting inflammation.

4.7 Genome instability and mutations in cancer: MACC1 loves the defects

Genome instability, an emerging hallmark of cancer [65], is tightly connected to MACC1-induced cancer development, progression and metastasis. Recently, a study on stage II CRC patients revealed that MACC1 together with markers of genomic instability, such as mismatch repair (MMR), predict response to adjuvant 5-FU-based chemotherapy [33]. MACC1 expression stratifies CRC patients with unfavorable pMMR status. Patients with pMMR/MACC1-low tumors have a similar favorable prognosis to those with dMMR. This further indicates potential functional liaisons between MACC1 and genomic instability [66, 80, 129].

Single nucleotide polymorphisms (SNPs) were identified in intronic regions 1, 2, and 6 as well as in the coding region of MACC1 in CRC [130–132], breast cancer (rs1990172, rs975263, rs373515 [72]; rs1990172, rs975263, rs3735615, rs4721888 [133]), and HCC (rs1990172, rs975263, rs3735615, rs4721888, rs2241056 [134]). Some of these SNPs were found to be clinically relevant and were linked to shorter patient survival as well as increased risk for metachronous metastasis for patients younger than 60 years with stage I or II CRC tumors (rs1990172, rs975263), increased risk of recurrence after liver transplantation (rs1990172, rs975263), and increased risk for progression or death in breast cancer (rs1990172, rs975263).

The impact of MACC1 copy number variations (CNVs) was studied in CRCs patients [135]. Increase in CNVs correlated with MACC1 expression levels and unfavorable tumor characteristics, like lesion size, multiple metastases, and detection of intravascular metastatic cells.

Taken together, SNPs and CNVs of MACC1 might have prognostic value for cancer patients and may be used in the future as biomarkers, in addition to the MACC1 expression levels. The combinatorial use of MMR status and MACC1 expression levels might serve as predictive biomarkers for treatment decisions for 5-FU-based chemotherapy of stage II CRC patients.

4.8 Inducing angiogenesis: MACC1 goes with the flow

Tumor angiogenesis is the process by which cancer cells reactivate the angiogenic switch in a constitutive manner, resulting in neo-vascularization to support nutrient as well as oxygen supply and metabolic waste expulsion from the neoplastic tissue [64, 65]. The angiogenic process is tightly regulated by vascular endothelial growth factors (VEGFs),

angiopoietin1, angiopoietin2 and their cognate receptors (VEGFR1, VEGFR2, VEGFR3, and Tie2) that coordinate the differentiation, proliferation and migration of cells to form new blood and lymphatic vessels [136–138]. High MACC1 expression was correlated with increased microvessel density and tumor recurrence in patients with gastric cancer. Molecular analysis showed that MACC1 induces expression of VEGF-A, a key protein involved in vasculogenesis, through upregulated TWIST1 expression [91]. Consistently, MACC1 silencing by miR-338-3p reduced VEGF expression with a concomitant decrease in tube formation *in vitro* and angiogenesis in chorioallantoic membrane (CAM) assay [52]. Therefore VEGF signaling downstream of MACC1 dictates endothelium-dependent tumor angiogenesis [91].

Interestingly, MACC1 also induces endothelium-independent angiogenesis through vasculogenic mimicry, whereby tumor cells form endothelial–like vasculature to maintain blood supply. MACC1 expression correlated with vasculogenic mimicry density and expression of its markers VE-cadherin as well as TWIST1/2 in gastric cancer tissues [90]. Moreover, silencing of MACC1/TWIST1/TWIST2 inhibited vasculogenic mimicry in gastric cancer xenograft models, which was also mimicked by c-MET inhibitor treatment [90]. This suggests a MACC1/HGF/c-MET/TWIST/VEGF signaling axis central to endothelium-dependent and -independent tumor angiogenesis. An auxiliary angiogenic function of MACC1-induced VEGF signaling is lymphogenesis and promotion of lymphatic metastasis through VEGF-C/D upregulation in transplanted tumors, which is also inhibited by c-MET inhibitor treatments. Consistently, MACC1 expression correlated with lymphatic vessel density and VEGF-C/D expression in gastric cancer patients and was associated with tumor recurrence [88].

These observations indicate the role of MACC1 in vasculogenesis and lymphogenesis, thereby supporting tumor progression. Hence targeting MACC1 might restrict tumor metastasis and recurrence by inhibiting angiogenesis and lymphatic dissemination.

4.9 Deregulating cellular energetics: MACC1 and cancer feeding

Reprogramming metabolism is another emerging hallmark of cancer. This redirection of energy metabolism in cancer towards aerobic glycolysis (Warburg effect) is often induced by oncogenes that are involved in programming the core hallmarks of cancer [65].

MACC1 is up-regulated by glucose deprivation-induced metabolic stress via adenosine monophosphate-activated protein kinase (AMPK) signaling in gastric cancer cells. MACC1 in turn enhances the Warburg effect by up-regulating glycolytic enzymes such as hexokinase (HK2), pyruvate dehydrogenase (PDH) kinase, and lactate dehydrogenase (LDH), leading to increased viability, resistance to apoptosis induced by glucose deprivation/nutrient starvation, and increased 18F-deoxyglucose uptake in xenografted mice. In gastric cancer patients, MACC1 correlates with the maximum standardized uptake value of 18F-deoxyglucose [13, 139]. MACC1 was also linked to enhanced Warburg effect via activated PI3K/AKT signaling, which phenotypically results in trastuzumab resistance [140]. LncRNA MACC1-AS1, elevated by metabolic stress, induces metabolic plasticity through MACC1 up-regulation, subsequently enhanced glycolysis with increase in expression of glucose transporter GLUT1, HK2, LDH, and anti-oxidative capabilities, which are mediated via the AMPK/Lin28 pathway. This is linked to poor prognosis in gastric cancer patients [38].

The role of MACC1 in glucose metabolism was also shown for HCC with higher expression of MACC1 and 6-phosphofructo-2-kinase/fructose 2,6-bisphosphatase (PFKFB2) vs. corresponding non-tumor tissues. Simultaneous high MACC1 and PFKFB2 was associated with high Edmondson classification, advanced TNM stage, and lower overall survival [141]. Also in HCC, MACC1 promotes proliferation through enhanced glucose metabolism linked to HK2 expression [142].

MACC1 also promotes lipogenesis by activation of lipogenic enzymes including fatty acid synthase (FASN)/ATP citrate lyase (ACLY) and acetyl-CoA carboxylase (ACC). In gastric cancer patients, high MACC1 correlated with high FASN, more advanced disease, more frequent post-operative recurrence, more metastases, and higher mortality [143].

In summary, the crucial impact of MACC1 for tumor initiation, progression and metastasis has to be contemplated with respect to MACC1-induced re-wiring of metabolic pathways. This provides new options for metabolism-based diagnosis as well as for therapeutic interventions.

4.10 Replicative immortality and cancer stemness: MACC1 for rejuvenation

Cancer cells sustain unlimited replication in order to form macroscopic tumors which are supported by telomerase activity that prevents telomere attrition thereby maintaining chromosomal integrity [144, 145]. Telomerase and its protein subunit hTERT have also non-canonical roles [146, 147] like induction of WNT signaling via the interaction of hTERT with β-catenin/LEF transcription factor complex [148]. Consistently, stem cell factors CD117, OCT4, and SOX2 are regulated by hTERT in cancer cells, contributing to their stemness and immortal properties [149–151].

MACC1 promotes stemness by regulating stem cell markers OCT4 and NANOG. Intestinal overexpression of

MACC1 in APC^{Min} mice results in not only more invasive phenotype but also increased expression of cancer stem cell (CSC) markers as well as WNT target genes [82]. It correlates with stem cell gene expression, such as ALDH1, CD133 and CD44, in cell culture and patient samples in head and neck cancer, non-small cell lung cancer, ovarian carcinoma and retinoblastoma. These tumors were characterized by their higher invasive potential and poor prognosis [152–155]. Mechanistically, MACC1 promoted CSC-like properties, specifically chemoresistance and sphere formation by activating EMT through PI3K/AKT/β-catenin and RAS/ERK signaling pathways [28, 30, 32, 34, 44].

Regulation of stem cell markers [82] and the correlation of MACC1 expression with cancer stem cell genes in different tumor entities [152–155] highlight its role in maintaining cancer cell immortality. One possible mechanism might be synergistic regulation of WNT signaling via MACC1/PI3K/AKT/GSK3β axis-dependent β-catenin stabilization followed by direct interaction of hTERT with β-catenin, increasing its nuclear retention [148, 151] and target gene expression [32, 34, 51, 92, 93]. Alternatively, hTERT might function upstream of MACC1, inducing WNT/β-catenin signaling and transcription of its target genes, such as *NANOG* and *c-MET,* where binding of MACC1 to the promoter is required [4, 82]. However, further studies are required to shed light on the direct function of MACC1 in cancer stemness and replicative immortality and to elucidate the role of MACC1 in therapy response in patients with cancer recurrence.

5 MACC1 as new target for therapies to restrict tumor progression and metastasis

MACC1 has emerged as a protein that enables hallmark properties of cancer, making it a promising new target for intervention strategies to restrict tumor progression and more importantly, cancer metastasis. In this context, downregulating MACC1 by shRNA, siRNA, or miRNA approaches has clearly shown that reduced MACC1 restricts invasion, migration, promotes apoptosis, and increases chemosensitivity of tumor cells *in vitro* and *in vivo* [4, 28, 31, 34, 45–61, 84, 86, 92, 93, 115]. Such studies indicate that targeting MACC1 is of therapeutic value. Hence, interfering with MACC1 expression and function at transcriptional or post-transcriptional level particularly with novel or repositioned small molecule inhibitors will be of clinical relevance. Identification of the human MACC1 promoter has enabled high throughout screens (HTS) for transcriptional MACC1 inhibitors [41]. By this, rottlerin and lovastatin were identified, which reduced MACC1 expression, cell invasion, and migration *in vitro* and reduced tumor growth and metastasis *in vivo* [156]. More extended HTS will reveal additional, novel MACC1 inhibitors for efficient tumor growth inhibition and metastasis restriction. In fact, such MACC1 inhibitors can be used in combination with other drugs that interfere in signaling pathways, which are also impacted by MACC1 action, as they have been discussed in the previous sections. In particular, combinations with conventional drugs (e.g., 5-FU, cisplatin, taxol, gemcitabine) for which MACC1 causes resistance could be of clinical value [17, 28, 30, 32, 116, 118]. The concept of combination therapies can certainly be extended to checkpoint inhibitor and death receptor agonist therapies in which MACC1 inhibition might promote apoptosis induction by sensitizing tumor cells.

The knowledge that MACC1 harbors predicted phosphorylation sites as well as protein-protein interaction domains, will be the basis for targeting such functional moieties for selective post-translational intervention to interfere with MACC1 function.

Taken together, MACC1 will develop to a valuable clinically relevant therapeutic target, either as sole molecular target or by hitting multiple targets in its signaling context via combination therapies. In fact MACC1-targeted therapies hold promise not only for anti-tumoral and anti-metastatic but also for metastasis prevention therapies. This will be complemented by MACC1-based patient stratification for metastasis intervention or even prevention in a more personalized therapy approach.

6 Conclusion

A decade-long research on MACC1 has continuously highlighted its predictive value as a biomarker for metastasis and its prognostic potential in the clinical setting. This review presents evidence that MACC1 promotes tumor progression by enabling various cancer hallmark features that could be prevented by blocking MACC1 expression or its function. Hence, MACC1 has the potential to become a therapeutic target for metastasis restriction or even prevention. The growing body of knowledge on MACC1 brings about novel functions of MACC1 in carcinogenesis, such as in cancer stemness, induction of pro-tumor inflammation and autophagy. However, there is a dearth of understanding on its physiological role. To date, the only available insight in this regard is the role of MACC1 on craniofacial development in zebrafish based on a morpholino screen [157]. The recent advancements in gene-editing technologies, such as CRISPR-Cas9 system, will allow us to better understand the physiological and developmental roles of MACC1. More studies are also required to define how MACC1 is specifically activated during cancer progression but is kept to the basal level in normal tissues. This might in part be explained by the tumor-suppressors and tumor-suppressor miRNA-dependent regulation of MACC1 expression in tumor tissues. However the benefits of inhibiting MACC1 for restricting

tumor progression and metastasis strongly suggest its clinical potential. In this regard, the recent developments in search of MACC1 targeting small molecules and therapies might prove to be beneficial in cancer care. Additionally, elucidation of MACC1 structure will open up new possibilities for post-translational targeting of MACC1 and its oncogenic functions.

Taken together, the combination of MACC1's predictive potential for patient stratification, combinatorial therapies targeting MACC1, and conventional treatment regimens might help in the development of personalized interventions for improving patient survival.

Funding Information Work in Prof. Ulrike Stein's lab is supported by the German Cancer Consortium (DKTK).

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Stein, U., & Schlag, P. M. (2007). Clinical, biological, and molecular aspects of metastasis in colorectal cancer. *Recent results in cancer research. Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer, 176*, 61–80.
2. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a Cancer Journal for Clinicians*. https://doi.org/10.3322/caac.21492.
3. Goldberg, R. M., Rothenberg, M. L., Van Cutsem, E., Benson, A. B., 3rd, Blanke, C. D., Diasio, R. B., et al. (2007). The continuum of care: a paradigm for the management of metastatic colorectal cancer. *Oncologist, 12*(1), 38–50. https://doi.org/10.1634/theoncologist.12-1-38.
4. Stein, U., Walther, W., Arlt, F., Schwabe, H., Smith, J., Fichtner, I., et al. (2008). MACC1, a newly identified key regulator of HGF-MET signaling, predicts colon cancer metastasis. *Nature Medicine, 15*, 59. https://doi.org/10.1038/nm.1889.
5. Stein, U., Dahlmann, M., & Walther, W. (2010). MACC1 - more than metastasis? Facts and predictions about a novel gene. *J Mol Med (Berl), 88*(1), 11–18. https://doi.org/10.1007/s00109-009-0537-1.
6. Stein, U. (2013). MACC1 - a novel target for solid cancers. *Expert Opinion on Therapeutic Targets, 17*(9), 1039–1052. https://doi.org/10.1517/14728222.2013.815727.
7. Zlobec, I. (2013). Novel biomarkers for the prediction of metastasis in colorectal cancer. *Expert Opinion on Medical Diagnostics, 7*, 137–146. https://doi.org/10.1517/17530059.2013.753054.
8. Weidle, U. H., Birzele, F., & Kruger, A. (2015). Molecular targets and pathways involved in liver metastasis of colorectal cancer. *Clinical & Experimental Metastasis, 32*(6), 623–635. https://doi.org/10.1007/s10585-015-9732-3.
9. Kopczyńska, E. K. (2016). The potential therapeutic applications and prognostic significance of metastasis associated in colon cancer 1 (MACC1) in cancers. *Współczesna Onkologia, 4*, 273–280. https://doi.org/10.5114/wo.2016.61846.
10. Wu, Z.-Z., Chen, L.-S., Zhou, R., Bin, J.-P., Liao, Y.-L., & Liao, W.-J. (2016). Metastasis-associated in colon cancer-1 in gastric cancer: beyond metastasis. *World Journal of Gastroenterology, 22*, 6629. https://doi.org/10.3748/wjg.v22.i29.6629.
11. Mudduluru, G., Ilm, K., Dahlmann, M., & Stein, U. (2017). MACC1, a novel player in solid cancer carcinogenesis. In *Mechanisms of molecular carcinogenesis – volume 1* (pp. 11–38). Cham: Springer International Publishing.
12. Wang, G., Fu, Z., & Li, D. (2015). MACC1 overexpression and survival in solid tumors: a meta-analysis. *Tumour Biology, 36*(2), 1055–1065. https://doi.org/10.1007/s13277-014-2736-9.
13. Wu, Z., Zhou, R., Su, Y., Sun, L., Liao, Y., & Liao, W. (2015). Prognostic value of MACC1 in digestive system neoplasms: a systematic review and meta-analysis. *BioMed Research International, 2015*, 252043. https://doi.org/10.1155/2015/252043.
14. Sun, D.-W., Zhang, Y.-Y., Qi, Y., Liu, G.-Q., Chen, Y.-G., Ma, J., et al. (2015). Prognostic and clinicopathological significance of MACC1 expression in hepatocellular carcinoma patients: a meta-analysis. *International Journal of Clinical and Experimental Medicine, 8*, 4769–4777.
15. Zhao, Y., Dai, C., Wang, M., Kang, H., Lin, S., Yang, P., et al. (2016). Clinicopathological and prognostic significance of metastasis-associated in colon cancer-1 (MACC1) overexpression in colorectal cancer: a meta-analysis. *Oncotarget, 7*(39), 62966–62975. https://doi.org/10.18632/oncotarget.11287.
16. Stein, U., Burock, S., Herrmann, P., Wendler, I., Niederstrasser, M., Wernecke, K.-D., et al. (2012). Circulating MACC1 Transcripts in Colorectal Cancer Patient Plasma Predict Metastasis and Prognosis. *PLoS ONE, 7*(11), e49249. https://doi.org/10.1371/journal.pone.0049249.
17. Wang, G., Kang, M. X., Lu, W. J., Chen, Y., Zhang, B., & Wu, Y. L. (2012). MACC1: A potential molecule associated with pancreatic cancer metastasis and chemoresistance. *Oncology Letters, 4*(4), 783–791. https://doi.org/10.3892/ol.2012.784.
18. Burock, S., Herrmann, P., Wendler, I., Niederstrasser, M., Wernecke, K.-D., & Stein, U. (2015). Circulating metastasis associated in colon cancer 1 transcripts in gastric cancer patient plasma as diagnostic and prognostic biomarker. *World Journal of Gastroenterology, 21*, 333. https://doi.org/10.3748/wjg.v21.i1.333.
19. Wang, Z., Cai, M., Weng, Y., Zhang, F., Meng, D., Song, J., et al. (2015). Circulating MACC1 as a novel diagnostic and prognostic biomarker for nonsmall cell lung cancer. *Journal of Cancer Research and Clinical Oncology, 141*(8), 1353–1361. https://doi.org/10.1007/s00432-014-1903-0.
20. Tan, W., Xie, X., Li, L., Tang, H., Ye, X., Chen, L., et al. (2016). Diagnostic and prognostic value of serum MACC1 in breast cancer patients. *Oncotarget, 7*(51), 84408–84415. https://doi.org/10.18632/oncotarget.12910.
21. Ashktorab, H., Hermann, P., Nouraie, M., Shokrani, B., Lee, E., Haidary, T., et al. (2016). Increased MACC1 levels in tissues and blood identify colon adenoma patients at high risk. *Journal of Translational Medicine, 14*(1), 215. https://doi.org/10.1186/s12967-016-0971-0.
22. Shimokawa, H., Uramoto, H., Onitsuka, T., Chundong, G., Hanagiri, T., Oyama, T., et al. (2011). Overexpression of MACC1 mRNA in lung adenocarcinoma is associated with postoperative recurrence. *The Journal of Thoracic and Cardiovascular Surgery, 141*, 895–898. https://doi.org/10.1016/j.jtcvs.2010.09.044.
23. Isella, C., Mellano, A., Galimi, F., Petti, C., Capussotti, L., De Simone, M., et al. (2013). MACC1 mRNA levels predict cancer recurrence after resection of colorectal cancer liver metastases. *Annals of Surgery, 257*, 1089–1095. https://doi.org/10.1097/SLA.0b013e31828f96bc.
24. Gao, S., Lin, B.-Y., Yang, Z., Zheng, Z.-Y., Liu, Z.-K., Wu, L.-M., et al. (2014). Role of overexpression of MACC1 and/or FAK in predicting prognosis of hepatocellular carcinoma after liver

transplantation. *International Journal of Medical Sciences, 11*, 268–275. https://doi.org/10.7150/ijms.7769.

25. Li, H. F., Liu, Y. Q., Shen, Z. J., Gan, X. F., Han, J. J., Liu, Y. Y., et al. (2015). Downregulation of MACC1 inhibits invasion, migration and proliferation, attenuates cisplatin resistance and induces apoptosis in tongue squamous cell carcinoma. *Oncology Reports, 33*(2), 651–660. https://doi.org/10.3892/or.2014.3612.
26. Shang, C., Hong, Y., Guo, Y., Liu, Y. H., & Xue, Y. X. (2015). Influence of the MACC1 gene on sensitivity to chemotherapy in human U251 glioblastoma cells. *Asian Pacific Journal of Cancer Prevention, 16*(1), 195–199. https://doi.org/10.7314/APJCP.2015.16.1.195.
27. Chen, Z. M., Shi, H. R., Li, X., Deng, Y. X., & Zhang, R. T. (2015). Downregulation of MACC1 expression enhances cisplatin sensitivity in SKOV-3/DDP cells. *Genetics and Molecular Research, 14*, 17134–17144. https://doi.org/10.4238/2015.December.16.13.
28. Zhang, R., Shi, H., Ren, F., Li, X., Zhang, M., Feng, W., et al. (2016). Knockdown of MACC1 expression increases cisplatin sensitivity in cisplatin-resistant epithelial ovarian cancer cells. *Oncology Reports, 35*(4), 2466–2472. https://doi.org/10.3892/or.2016.4585.
29. Wang, C., Wen, Z., Xie, J., Zhao, Y., Zhao, L., Zhang, S., et al. (2017). MACC1 mediates chemotherapy sensitivity of 5-FU and cisplatin via regulating MCT1 expression in gastric cancer. *Biochemical and Biophysical Research Communications, 485*(3), 665–671. https://doi.org/10.1016/j.bbrc.2017.02.096.
30. Zhang, Q., Zhang, B., Sun, L., Yan, Q., Zhang, Y., Zhang, Z., et al. (2018). Cisplatin resistance in lung cancer is mediated by MACC1 expression through PI3K/AKT signaling pathway activation. *Acta Biochimica et Biophysica Sinica Shanghai, 50*(8), 748–756. https://doi.org/10.1093/abbs/gmy074.
31. Duan, J., Chen, L., Zhou, M., Zhang, J., Sun, L., Huang, N., et al. (2017). MACC1 decreases the chemosensitivity of gastric cancer cells to oxaliplatin by regulating FASN expression. *Oncology Reports, 37*, 2583–2592. https://doi.org/10.3892/or.2017.5519.
32. Wang, J., Wang, W., Cai, H., Du, B., Zhang, L., Ma, W., et al. (2017). MACC1 facilitates chemoresistance and cancer stem celllike properties of colon cancer cells through the PI3K/AKT signaling pathway. *Molecular Medicine Reports, 16*(6), 8747–8754. https://doi.org/10.3892/mmr.2017.7721.
33. Rohr, U. P., Herrmann, P., Ilm, K., Zhang, H., Lohmann, S., Reiser, A., et al. (2017). Prognostic value of MACC1 and proficient mismatch repair status for recurrence risk prediction in stage II colon cancer patients: the BIOGRID studies. *Annals of Oncology, 28*(8), 1869–1875. https://doi.org/10.1093/annonc/mdx207.
34. Zhou, W., Liu, L., Xue, Y., Zheng, J., Liu, X., Ma, J., et al. (2017). Combination of endothelial-monocyte-activating polypeptide-II with temozolomide suppress malignant biological behaviors of human glioblastoma stem cells via miR-590-3p/MACC1 inhibiting PI3K/AKT/mTOR signal pathway. *Frontiers in Molecular Neuroscience, 10*, 68. https://doi.org/10.3389/fnmol.2017.00068.
35. Kawamura, M., Saigusa, S., Toiyama, Y., Tanaka, K., Okugawa, Y., Hiro, J., et al. (2012). Correlation of MACC1 and MET expression in rectal cancer after neoadjuvant chemoradiotherapy. *Anticancer Research, 32*(4), 1527–1531.
36. Yang, Y. P., Qu, J. H., Chang, X. J., Lu, Y. Y., Bai, W. L., Dong, Z., et al. (2013). High intratumoral metastasis-associated in colon cancer-1 expression predicts poor outcomes of cryoablation therapy for advanced hepatocellular carcinoma. *Journal of Translational Medicine, 11*, 41. https://doi.org/10.1186/1479-5876-11-41.
37. Zerbino, D. R., Achuthan, P., Akanni, W., Amode, M. R., Barrell, D., Bhai, J., et al. (2018). Ensembl 2018. *Nucleic Acids Research, 46*(D1), D754–D761. https://doi.org/10.1093/nar/gkx1098.
38. Zhao, Y., Liu, Y., Lin, L., Huang, Q., He, W., Zhang, S., et al. (2018). The lncRNA MACC1-AS1 promotes gastric cancer cell metabolic plasticity via AMPK/Lin28 mediated mRNA stability of MACC1. *Molecular Cancer, 17*(1), 69. https://doi.org/10.1186/s12943-018-0820-2.
39. Thierry-Mieg, D., & Thierry-Mieg, J. (2006). AceView: a comprehensive cDNA-supported gene and transcripts annotation. *Genome Biology, 7*(Suppl 1, S12), 11–14. https://doi.org/10.1186/gb-2006-7-s1-s12.
40. Kokoszyńska, K., Kryński, J., Rychlewski, L., & Wyrwicz, L. S. (2009). Unexpected domain composition of MACC1 links MET signaling and apoptosis. *Acta Biochimica Polonica, 56*, 317–323.
41. Juneja, M., Ilm, K., Schlag, P. M., & Stein, U. (2013). Promoter identification and transcriptional regulation of the metastasis gene MACC1 in colorectal cancer. *Molecular Oncology, 7*, 929–943. https://doi.org/10.1016/j.molonc.2013.05.003.
42. Guo, T., Zhao, S., Wang, P., Xue, X., Zhang, Y., Yang, M., et al. (2017). YB-1 regulates tumor growth by promoting MACC1/c-Met pathway in human lung adenocarcinoma. *Oncotarget, 8*, 48110–48125. https://doi.org/10.18632/oncotarget.18262.
43. Xia, J., Wang, H., Huang, H., Sun, L., Dong, S., Huang, N., et al. (2016). Elevated Orai1 and STIM1 expressions upregulate MACC1 expression to promote tumor cell proliferation, metabolism, migration, and invasion in human gastric cancer. *Cancer Letters, 381*, 31–40. https://doi.org/10.1016/j.canlet.2016.07.014.
44. Montorsi, L., Guizzetti, F., Alecci, C., Caporali, A., Martello, A., Atene, C. G., et al. (2016). Loss of ZFP36 expression in colorectal cancer correlates to wnt/ ss-catenin activity and enhances epithelial-to-mesenchymal transition through upregulation of ZEB1, SOX9 and MACC1. *Oncotarget, 7*(37), 59144–59157. https://doi.org/10.18632/oncotarget.10828.
45. Li, S., Zhu, J., Li, J., Li, S., & Li, B. (2018). MicroRNA-141 inhibits proliferation of gastric cardia adenocarcinoma by targeting MACC1. *Archives of Medical Science, 14*, 588–596. https://doi.org/10.5114/aoms.2017.68757.
46. Zhang, Y., Wang, Z., Chen, M., Peng, L., Wang, X., Ma, Q., et al. (2012). MicroRNA-143 targets MACC1 to inhibit cell invasion and migration in colorectal cancer. *Molecular Cancer, 11*, 23. https://doi.org/10.1186/1476-4598-11-23.
47. Tokarz, P., & Blasiak, J. (2012). The role of microRNA in metastatic colorectal cancer and its significance in cancer prognosis and treatment. *Acta Biochimica Polonica, 59*, 467–474.
48. Wang, G., Gu, J., & Gao, Y. (2016). MicroRNA target for MACC1 and CYR61 to inhibit tumor growth in mice with colorectal cancer. *Tumour Biology, 37*(10), 13983–13993. https://doi.org/10.1007/s13277-016-5252-2.
49. Feng, J., Wang, J., Chen, M., Chen, G., Wu, Z., Ying, L., et al. (2015). miR-200a suppresses cell growth and migration by targeting MACC1 and predicts prognosis in hepatocellular carcinoma. *Oncology Reports, 33*(2), 713–720. https://doi.org/10.3892/or.2014.3642.
50. Ilm, K., Fuchs, S., Mudduluru, G., & Stein, U. (2016). MACC1 is post-transcriptionally regulated by miR-218 in colorectal cancer. *Oncotarget, 7*(33), 53443–53458. https://doi.org/10.18632/oncotarget.10803.
51. Huang, N., Wu, Z., Lin, L., Zhou, M., Wang, L., Ma, H., et al. (2015). MiR-338-3p inhibits epithelial-mesenchymal transition in gastric cancer cells by targeting ZEB2 and MACC1/Met/Akt signaling. *Oncotarget, 6*(17), 15222–15234. https://doi.org/10.18632/oncotarget.3835.
52. Zhang, T., Liu, W., Zeng, X.-c., Jiang, N., Fu, B.-s., Guo, Y., et al. (2016). Down-regulation of microRNA-338-3p promoted angiogenesis in hepatocellular carcinoma. *Biomedicine &*

Pharmacotherapy, 84, 583–591. https://doi.org/10.1016/J.BIOPHA.2016.09.056.

53. Shang, C., Hong, Y., Guo, Y., & Xue, Y. X. (2016). Mir-338-3p inhibits malignant biological behaviors of glioma cells by targeting MACC1 gene. *Medical Science Monitor, 22*, 710–716. https://doi.org/10.12659/MSM.897055.
54. Hua, F.-F., Liu, S.-S., Zhu, L.-H., Wang, Y.-H., Liang, X., Ma, N., et al. (2017). MiRNA-338-3p regulates cervical cancer cells proliferation by targeting MACC1 through MAPK signaling pathway. *European Review for Medical and Pharmacological Sciences, 21*, 5342–5352.
55. Li, J., Mao, X., Wang, X., Miao, G., & Li, J. (2017). miR-433 reduces cell viability and promotes cell apoptosis by regulating MACC1 in colorectal cancer. *Oncology Letters, 13*(1), 81–88. https://doi.org/10.3892/ol.2016.5445.
56. Wang, S., Zhang, Y., Yuan, S., & Ji, X. (2018). MicroRNA485 targets MACC1 and inhibits cervical cancer cell proliferation and invasion. *Molecular Medicine Reports, 18*(2), 2407–2416. https://doi.org/10.3892/mmr.2018.9186.
57. Ma, L., Zhou, Y., Luo, X., Gao, H., Deng, X., & Jiang, Y. (2017). Long non-coding RNA XIST promotes cell growth and invasion through regulating miR-497/MACC1 axis in gastric cancer. *Oncotarget, 8*(3), 4125–4135. https://doi.org/10.18632/oncotarget.13670.
58. Cui, Z., Tang, J., Chen, J., & Wang, Z. (2014). Hsa-miR-574-5p negatively regulates MACC-1 expression to suppress colorectal cancer liver metastasis. *Cancer Cell International, 14*, 47. https://doi.org/10.1186/1475-2867-14-47.
59. Wang, N., Zhang, Y., & Liang, H. (2018). microRNA-598 inhibits cell proliferation and invasion of glioblastoma by directly targeting metastasis associated in colon cancer-1. *Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics*. https://doi.org/10.3727/096504018X15185735627746.
60. Pan, T., Chen, W., Yuan, X., Shen, J., Qin, C., & Wang, L. (2017). miR-944 inhibits metastasis of gastric cancer by preventing the epithelial-mesenchymal transition via MACC1/Met/AKT signaling. *FEBS Open Bio, 7*(7), 905–914. https://doi.org/10.1002/2211-5463.12215.
61. Wen, L., Li, Y., Jiang, Z., Zhang, Y., Yang, B., & Han, F. (2017). miR-944 inhibits cell migration and invasion by targeting MACC1 in colorectal cancer. *Oncology Reports, 37*(6), 3415–3422. https://doi.org/10.3892/or.2017.5611.
62. Tokarz, P., Pawlowska, E., Bialkowska-Warzecha, J., & Blasiak, J. (2017). The significance of DNA methylation profile in metastasis-related genes for the progression of colorectal cancer. *Cellular and Molecular Biology (Noisy-le-Grand, France), 63*, 79–87.
63. Li, Z., Yanfang, W., Li, J., Jiang, P., Peng, T., Chen, K., et al. (2018). Tumor-released exosomal circular RNA PDE8A promotes invasive growth via the miR-338/MACC1/MET pathway in pancreatic cancer. *Cancer Letters, 432*, 237–250. https://doi.org/10.1016/j.canlet.2018.04.035.
64. Hanahan, D., & Weinberg, R. A. (2000). The hallmarks of cancer. *Cell, 100*(1), 57–70. https://doi.org/10.1016/S0092-8674(00)81683-9.
65. Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. *Cell, 144*(5), 646–674. https://doi.org/10.1016/j.cell.2011.02.013.
66. Nitsche, U., Rosenberg, R., Balmert, A., Schuster, T., Slotta-Huspenina, J., Herrmann, P., et al. (2012). Integrative marker analysis allows risk assessment for metastasis in stage II colon cancer. *Annals of Surgery, 256*(5), 763–771; discussion 771. https://doi.org/10.1097/SLA.0b013e318272de87.
67. Shirahata, A., Sakata, M., Kitamura, Y., Sakuraba, K., Yokomizo, K., Goto, T., et al. (2010). MACC 1 as a marker for peritoneal-disseminated gastric carcinoma. *Anticancer Research, 30*(9), 3441–3444.
68. Wang, Z., Li, Z., Wu, C., Wang, Y., Xia, Y., Chen, L., et al. (2014). MACC1 overexpression predicts a poor prognosis for non-small cell lung cancer. *Medical Oncology, 31*(1), 790. https://doi.org/10.1007/s12032-013-0790-6.
69. Qiu, J., Huang, P., Liu, Q., Hong, J., Li, B., Lu, C., et al. (2011). Identification of MACC1 as a novel prognostic marker in hepatocellular carcinoma. *Journal of Translational Medicine, 9*, 166. https://doi.org/10.1186/1479-5876-9-166.
70. Xie, C., Wu, J., Yun, J., Lai, J., Yuan, Y., Gao, Z., et al. (2013). MACC1 as a prognostic biomarker for early-stage and AFP-normal hepatocellular carcinoma. *PLoS ONE, 8*(5), e64235. https://doi.org/10.1371/journal.pone.0064235.
71. Huang, Y., Zhang, H., Cai, J., Fang, L., Wu, J., Ye, C., et al. (2013). Overexpression of MACC1 and Its significance in human Breast Cancer Progression. *Cell & Bioscience, 3*(1), 16. https://doi.org/10.1186/2045-3701-3-16.
72. Muendlein, A., Hubalek, M., Geller-Rhomberg, S., Gasser, K., Winder, T., Drexel, H., et al. (2014). Significant survival impact of MACC1 polymorphisms in HER2 positive breast cancer patients. *European Journal of Cancer, 50*(12), 2134–2141. https://doi.org/10.1016/j.ejca.2014.05.007.
73. Hu, H., Tian, D., Chen, T., Han, R., Sun, Y., & Wu, C. (2014). Metastasis-associated in colon cancer 1 is a novel survival-related biomarker for human patients with renal pelvis carcinoma. *PLoS ONE, 9*(6), e100161. https://doi.org/10.1371/journal.pone.0100161.
74. Lederer, A., Herrmann, P., Seehofer, D., Dietel, M., Pratschke, J., Schlag, P., et al. (2015). Metastasis-associated in colon cancer 1 is an independent prognostic biomarker for survival in Klatskin tumor patients. *Hepatology, 62*(3), 841–850. https://doi.org/10.1002/hep.27885.
75. Li, H., Zhang, H., Zhao, S., Shi, Y., Yao, J., Zhang, Y., et al. (2015). Overexpression of MACC1 and the association with hepatocyte growth factor/c-Met in epithelial ovarian cancer. *Oncology Letters, 9*(5), 1989–1996. https://doi.org/10.3892/ol.2015.2984.
76. Zhou, X., Xu, C.-J., Wang, J.-X., Dai, T., Ye, Y.-P., Cui, Y.-M., et al. (2015). Metastasis-associated in colon cancer-1 associates With poor prognosis and promotes cell invasion and angiogenesis in human cervical cancer. *International Journal of Gynecological Cancer, 25*, 1353–1363. https://doi.org/10.1097/IGC.0000000000000524.
77. Hagemann, C., Fuchs, S., Monoranu, C. M., Herrmann, P., Smith, J., Hohmann, T., et al. (2013). Impact of MACC1 on human malignant glioma progression and patients unfavorable prognosis. *Neuro-Oncology, 15*(12), 1696–1709. https://doi.org/10.1093/neuonc/not136.
78. Yang, T., Kong, B., Kuang, Y. Q., Cheng, L., Gu, J. W., Zhang, J. H., et al. (2014). Overexpression of MACC1 protein and its clinical implications in patients with glioma. *Tumour Biology, 35*(1), 815–819. https://doi.org/10.1007/s13277-013-1112-5.
79. Zhang, K., Tian, F., Zhang, Y., Zhu, Q., Xue, N., Zhu, H., et al. (2014). MACC1 is involved in the regulation of proliferation, colony formation, invasion ability, cell cycle distribution, apoptosis and tumorigenicity by altering Akt signaling pathway in human osteosarcoma. *Tumour Biology, 35*(3), 2537–2548. https://doi.org/10.1007/s13277-013-1335-5.
80. Koelzer, V. H., Herrmann, P., Zlobec, I., Karamitopoulou, E., Lugli, A., & Stein, U. (2015). Heterogeneity analysis of metastasis associated in colon cancer 1 (MACC1) for survival prognosis of colorectal cancer patients: a retrospective cohort study. *BMC Cancer, 15*, 160. https://doi.org/10.1186/s12885-015-1150-z.
81. Barbazan, J., Dunkel, Y., Li, H., Nitsche, U., Janssen, K. P., Messer, K., et al. (2016). Prognostic impact of modulators of G

proteins in circulating tumor cells from patients with metastatic colorectal cancer. *Scientific Reports, 6*, 22112. https://doi.org/10.1038/srep22112.

82. Lemos, C., Hardt, M. S., Juneja, M., Voss, C., Forster, S., Jerchow, B., et al. (2016). MACC1 induces tumor progression in transgenic mice and colorectal cancer patients via increased pluripotency markers Nanog and Oct4. *Clinical Cancer Research, 22*(11), 2812–2824. https://doi.org/10.1158/1078-0432.CCR-15-1425.
83. Jiang, W. G., Sanders, A. J., Katoh, M., Ungefroren, H., Gieseler, F., Prince, M., et al. (2015). Tissue invasion and metastasis: molecular, biological and clinical perspectives. *Seminars in Cancer Biology, 35*, S244–S275. https://doi.org/10.1016/j.semcancer.2015.03.008.
84. Pichorner, A., Sack, U., Kobelt, D., Kelch, I., Arlt, F., Smith, J., et al. (2012). In vivo imaging of colorectal cancer growth and metastasis by targeting MACC1 with shRNA in xenografted mice. *Clinical & Experimental Metastasis, 29*(6), 573–583. https://doi.org/10.1007/s10585-012-9472-6.
85. Stein, U., Smith, J., Walther, W., & Arlt, F. (2009). MACC1 controls Met: what a difference an Sp1 site makes. *Cell Cycle, 8*(15), 2467–2469. https://doi.org/10.4161/cc.8.15.9018.
86. Zhang, R., Shi, H., Chen, Z., Wu, Q., Ren, F., & Huang, H. (2011). Effects of metastasis-associated in colon cancer 1 inhibition by small hairpin RNA on ovarian carcinoma OVCAR-3 cells. *Journal of Experimental & Clinical Cancer Research, 30*, 83. https://doi.org/10.1186/1756-9966-30-83.
87. Sheng, X. J., Li, Z., Sun, M., Wang, Z. H., Zhou, D. M., Li, J. Q., et al. (2014). MACC1 induces metastasis in ovarian carcinoma by upregulating hepatocyte growth factor receptor c-MET. *Oncology Letters, 8*(2), 891–897. https://doi.org/10.3892/ol.2014.2184.
88. Sun, L., Duan, J., Jiang, Y., Wang, L., Huang, N., Lin, L., et al. (2015). Metastasis-associated in colon cancer-1 upregulates vascular endothelial growth factor-C/D to promote lymphangiogenesis in human gastric cancer. *Cancer Letters, 357*, 242–253. https://doi.org/10.1016/j.canlet.2014.11.035.
89. Gao, J., Ding, F., Liu, Q., & Yao, Y. (2013). Knockdown of MACC1 expression suppressed hepatocellular carcinoma cell migration and invasion and inhibited expression of MMP2 and MMP9. *Molecular and Cellular Biochemistry, 376*(1-2), 21–32. https://doi.org/10.1007/s11010-012-1545-y.
90. Wang, L., Lin, L., Chen, X., Sun, L., Liao, Y., Huang, N., et al. (2015). Metastasis-associated in colon cancer-1 promotes vasculogenic mimicry in gastric cancer by upregulating TWIST1/2. *Oncotarget, 6*(13), 11492–11506. https://doi.org/10.18632/oncotarget.3416.
91. Wang, L., Zhou, R., Zhao, Y., Dong, S., Zhang, J., Luo, Y., et al. (2016). MACC-1 promotes endothelium-dependent angiogenesis in gastric cancer by activating TWIST1/VEGF-a signal pathway. *PLoS ONE, 11*(6), e0157137. https://doi.org/10.1371/journal.pone.0157137.
92. Meng, F., Li, H., Shi, H., Yang, Q., Zhang, F., Yang, Y., et al. (2013). MACC1 down-regulation inhibits proliferation and tumourigenicity of nasopharyngeal carcinoma cells through Akt/beta-catenin signaling pathway. *PLoS ONE, 8*(4), e60821. https://doi.org/10.1371/journal.pone.0060821.
93. Zhen, T., Dai, S., Li, H., Yang, Y., Kang, L., Shi, H., et al. (2014). MACC1 promotes carcinogenesis of colorectal cancer via beta-catenin signaling pathway. *Oncotarget, 5*(11), 3756–3769. https://doi.org/10.18632/oncotarget.1993.
94. Chen, S., Zong, Z. H., Wu, D. D., Sun, K. X., Liu, B. L., & Zhao, Y. (2017). The role of metastasis-associated in colon cancer 1 (MACC1) in endometrial carcinoma tumorigenesis and progression. *Molecular Carcinogenesis, 56*(4), 1361–1371. https://doi.org/10.1002/mc.22599.
95. Ding, Y., Li, X., Hong, D., Jiang, L., He, Y., & Fang, H. (2016). Silence of MACC1 decreases cell migration and invasion in human malignant melanoma through inhibiting the EMT. *Bioscience Trends, 10*(4), 258–264. https://doi.org/10.5582/bst.2016.01091.
96. Qian, L. Q., Li, X. Q., Ye, P. H., Su, H. Y., Wang, G., Liu, Y., et al. (2017). Downregulation of MACC1 inhibits the viability, invasion and migration and induces apoptosis in esophageal carcinoma cells through the phosphatase and tensin homolog/phosphoinositide 3-kinase/protein kinase B signaling pathway. *Oncology Letters, 14*(4), 4897–4905. https://doi.org/10.3892/ol.2017.6790.
97. Fukumoto, S., Hsieh, C. M., Maemura, K., Layne, M. D., Yet, S. F., Lee, K. H., et al. (2001). Akt participation in the Wnt signaling pathway through Dishevelled. *The Journal of Biological Chemistry, 276*(20), 17479–17483. https://doi.org/10.1074/jbc.C000880200.
98. Fang, D., Hawke, D., Zheng, Y., Xia, Y., Meisenhelder, J., Nika, H., et al. (2007). Phosphorylation of beta-catenin by AKT promotes beta-catenin transcriptional activity. *The Journal of Biological Chemistry, 282*(15), 11221–11229. https://doi.org/10.1074/jbc.M611871200.
99. Lee, G., Goretsky, T., Managlia, E., Dirisina, R., Singh, A. P., Brown, J. B., et al. (2010). phosphoinositide 3-kinase signaling mediates β-Catenin activation in intestinal epithelial stem and progenitor cells in colitis. *Gastroenterology, 139*, 869–881.e869. https://doi.org/10.1053/j.gastro.2010.05.037.
100. Stein, U., Arlt, F., Walther, W., Smith, J., Waldman, T., Harris, E. D., et al. (2006). The metastasis-associated gene S100A4 is a novel target of beta-catenin/T-cell factor signaling in colon cancer. *Gastroenterology, 131*(5), 1486–1500. https://doi.org/10.1053/j.gastro.2006.08.041.
101. Klaus, A., & Birchmeier, W. (2008). Wnt signalling and its impact on development and cancer. *Nature Reviews Cancer, 8*, 387–398. https://doi.org/10.1038/nrc2389.
102. Gonzalez, D. M., & Medici, D. (2014). Signaling mechanisms of the epithelial-mesenchymal transition. *Science Signaling, 7*, re8. https://doi.org/10.1126/scisignal.2005189.
103. Birchmeier, C., Birchmeier, W., Gherardi, E., & Vande Woude, G. F. (2003). Met, metastasis, motility and more. *Nature Reviews. Molecular Cell Biology, 4*(12), 915–925. https://doi.org/10.1038/nrm1261.
104. Zhang, W., & Liu, H. T. (2002). MAPK signal pathways in the regulation of cell proliferation in mammalian cells. *Cell Research, 12*(1), 9–18. https://doi.org/10.1038/sj.cr.7290105.
105. Tan, N. Y., & Khachigian, L. M. (2009). Sp1 phosphorylation and its regulation of gene transcription. *Molecular and Cell Biology, 29*(10), 2483–2488. https://doi.org/10.1128/MCB.01828-08.
106. Wang, H., Wang, H. S., Zhou, B. H., Li, C. L., Zhang, F., Wang, X. F., et al. (2013). Epithelial-mesenchymal transition (EMT) induced by TNF-alpha requires AKT/GSK-3beta-mediated stabilization of snail in colorectal cancer. *PLoS ONE, 8*(2), e56664. https://doi.org/10.1371/journal.pone.0056664.
107. Dong, G., Wang, M., Gu, G., Li, S., Sun, X., Li, Z., et al. (2018). MACC1 and HGF are associated with survival in patients with gastric cancer. *Oncology Letters, 15*(3), 3207–3213. https://doi.org/10.3892/ol.2017.7710.
108. Lichtenberger, B. M., Tan, P. K., Niederleithner, H., Ferrara, N., Petzelbauer, P., & Sibilia, M. (2010). Autocrine VEGF signaling synergizes with EGFR in tumor cells to promote epithelial cancer development. *Cell, 140*(2), 268–279. https://doi.org/10.1016/j.cell.2009.12.046.
109. Malumbres, M., & Barbacid, M. (2009). Cell cycle, CDKs and cancer: a changing paradigm. *Nature Reviews Cancer, 9*, 153–166. https://doi.org/10.1038/nrc2602.
110. Meyer, N., & Penn, L. Z. (2008). Reflecting on 25 years with MYC. *Nature Reviews Cancer, 8*, 976–990. https://doi.org/10.1038/nrc2231.

111. Song, M. S., Salmena, L., & Pandolfi, P. P. (2012). The functions and regulation of the PTEN tumour suppressor. *Nature Reviews. Molecular Cell Biology, 13*(5), 283–296. https://doi.org/10.1038/nrm3330.
112. Sun, L., Li, G., Dai, B., Tan, W., Zhao, H., Li, X., et al. (2015). Silence of MACC1 expression by RNA interference inhibits proliferation, invasion and metastasis, and promotes apoptosis in U251 human malignant glioma cells. *Molecular Medicine Reports, 12*(3), 3423–3431. https://doi.org/10.3892/mmr.2015.3886.
113. Wang, L., Wu, Y., Lin, L., Liu, P., Huang, H., Liao, W., et al. (2013). Metastasis-associated in colon cancer-1 upregulation predicts a poor prognosis of gastric cancer, and promotes tumor cell proliferation and invasion. *International Journal of Cancer, 133*(6), 1419–1430. https://doi.org/10.1002/ijc.28140.
114. Schmid, F., Wang, Q., Huska, M. R., Andrade-Navarro, M. A., Lemm, M., Fichtner, I., et al. (2016). SPON2, a newly identified target gene of MACC1, drives colorectal cancer metastasis in mice and is prognostic for colorectal cancer patient survival. *Oncogene, 35*(46), 5942–5952. https://doi.org/10.1038/onc.2015.451.
115. Yao, Y., Dou, C., Lu, Z., Zheng, X., & Liu, Q. (2015). MACC1 suppresses cell apoptosis in hepatocellular carcinoma by targeting the HGF/c-MET/AKT pathway. *Cellular Physiology and Biochemistry, 35*(3), 983–996. https://doi.org/10.1159/000369754.
116. Chen, X. P., Ren, X. P., Lan, J. Y., Chen, Y. G., & Shen, Z. J. (2014). Analysis of HGF, MACC1, C-met and apoptosis-related genes in cervical carcinoma mice. *Molecular Biology Reports, 41*(3), 1247–1256. https://doi.org/10.1007/s11033-013-2969-5.
117. Radhakrishnan, H., Ilm, K., Walther, W., Shirasawa, S., Sasazuki, T., Daniel, P. T., et al. (2017). MACC1 regulates Fas mediated apoptosis through STAT1/3 - Mcl-1 signaling in solid cancers. *Cancer Letters, 403*, 231–245. https://doi.org/10.1016/j.canlet.2017.06.020.
118. Zhang, X. K., Zhang, L. X., Jia, C. Y., Sun, H. M., Zou, Q. G., Wang, Z., et al. (2017). MACC1 overexpression induces cisplatin resistance in lung adenocarcinoma A549 cells by activating c-Met/Akt pathway. *International Journal of Clinical and Experimental Medicine, 10*(8), 11778–11786.
119. Modiano, J. F., & Bellgrau, D. (2016). Fas ligand based immunotherapy: A potent and effective neoadjuvant with checkpoint inhibitor properties, or a systemically toxic promoter of tumor growth? *Discovery Medicine, 21*, 109–116.
120. Jazirehi, A. R., Lim, A., & Dinh, T. (2016). PD-1 inhibition and treatment of advanced melanoma-role of pembrolizumab. *American Journal of Cancer Research, 6*(10), 2117–2128.
121. Erreni, M., Mantovani, A., & Allavena, P. (2011). Tumor-associated macrophages (TAM) and inflammation in colorectal cancer. *Cancer Microenvironment, 4*(2), 141–154. https://doi.org/10.1007/s12307-010-0052-5.
122. Jedinak, A., Dudhgaonkar, S., & Sliva, D. (2010). Activated macrophages induce metastatic behavior of colon cancer cells. *Immunobiology, 215*, 242–249. https://doi.org/10.1016/j.imbio.2009.03.004.
123. de Aquino, M. T. P., Malhotra, A., Mishra, M. K., & Shanker, A. (2015). Challenges and future perspectives of T cell immunotherapy in cancer. *Immunology Letters, 166*, 117–133. https://doi.org/10.1016/j.imlet.2015.05.018.
124. Balkwill, F., Charles, K. A., & Mantovani, A. (2005). Smoldering and polarized inflammation in the initiation and promotion of malignant disease. *Cancer Cell, 7*(3), 211–217. https://doi.org/10.1016/j.ccr.2005.02.013.
125. Dulai, P. S., Sandborn, W. J., & Gupta, S. (2016). Colorectal cancer and dysplasia in inflammatory bowel disease: a review of disease epidemiology, pathophysiology, and management. *Cancer Prevention Research (Philadelphia, Pa.), 9*(12), 887–894. https://doi.org/10.1158/1940-6207.CAPR-16-0124.
126. Elding, H., Lau, W., Swallow, D. M., & Maniatis, N. (2013). Refinement in localization and identification of gene regions associated with Crohn disease. *American Journal of Human Genetics, 92*(1), 107–113. https://doi.org/10.1016/j.ajhg.2012.11.004.
127. Harpaz, N., Taboada, S., Mabel Ko, H., Yu, J., Yang, Q., Xu, H., et al. (2014). Expression of MACC1 and MET in inflammatory bowel disease-associated colonic neoplasia. *Inflammatory Bowel Diseases, 20*, 703–711. https://doi.org/10.1097/01.MIB.0000442679.39804.48.
128. Low-Marchelli, J. M., Ardi, V. C., Vizcarra, E. A., van Rooijen, N., Quigley, J. P., & Yang, J. (2013). Twist1 induces CCL2 and recruits macrophages to promote angiogenesis. *Cancer Research, 73*(2), 662–671. https://doi.org/10.1158/0008-5472.CAN-12-0653.
129. Ilm, K., Kemmner, W., Osterland, M., Burock, S., Koch, G., Herrmann, P., et al. (2015). High MACC1 expression in combination with mutated KRAS G13 indicates poor survival of colorectal cancer patients. *Molecular Cancer, 14*, 38. https://doi.org/10.1186/s12943-015-0316-2.
130. Lang, A. H., Geller-Rhomberg, S., Winder, T., Stark, N., Gasser, K., Hartmann, B., et al. (2012). A common variant of the MACC1 gene is significantly associated with overall survival in colorectal cancer patients. *BMC Cancer, 12*, 20. https://doi.org/10.1186/1471-2407-12-20.
131. Schmid, F., Burock, S., Klockmeier, K., Schlag, P. M., & Stein, U. (2012). SNPs in the coding region of the metastasis-inducing gene MACC1 and clinical outcome in colorectal cancer. *Molecular Cancer, 11*, 49. https://doi.org/10.1186/1476-4598-11-49.
132. Horvat, M., Potocnik, U., Repnik, K., Kavalar, R., Zadnik, V., Potrc, S., et al. (2017). Single nucleotide polymorphisms in genes MACC1, RAD18, MMP7 and SDF-1a as prognostic factors in resectable colorectal cancer. *Radiology and Oncology, 51*(2), 151–159. https://doi.org/10.1515/raon-2016-0043.
133. Dai, Z.-J., Liu, X.-H., Kang, H.-F., Wang, X.-J., Jin, T.-B., Zhang, S.-Q., et al. (2016). Genetic variation in metastasis-associated in colon cancer-1 and the risk of breast cancer among the Chinese Han population: a STROBE-compliant observational study. *Medicine, 95*, e2801. https://doi.org/10.1097/MD.0000000000002801.
134. Zheng, Z., Gao, S., Yang, Z., Xie, H., Zhang, C., Lin, B., et al. (2014). Single nucleotide polymorphisms in the metastasis-associated in colon cancer-1 gene predict the recurrence of hepatocellular carcinoma after transplantation. *International Journal of Medical Sciences, 11*(2), 142–150. https://doi.org/10.7150/ijms.7142.
135. Galimi, F., Torti, D., Sassi, F., Isella, C., Corà, D., Gastaldi, S., et al. (2011). Genetic and expression analysis of MET, MACC1, and HGF in metastatic colorectal cancer: response to met inhibition in patient xenografts and pathologic correlations. *Clinical Cancer Research, 17*, 3146–3156. https://doi.org/10.1158/1078-0432.CCR-10-3377.
136. Fabris, L., Cadamuro, M., Libbrecht, L., Raynaud, P., Spirli, C., Fiorotto, R., et al. (2008). Epithelial expression of angiogenic growth factors modulate arterial vasculogenesis in human liver development. *Hepatology, 47*(2), 719–728. https://doi.org/10.1002/hep.22015.
137. Sleeman, J. P., & Thiele, W. (2009). Tumor metastasis and the lymphatic vasculature. *International Journal of Cancer, 125*(12), 2747–2756. https://doi.org/10.1002/ijc.24702.
138. Alishekevitz, D., Gingis-Velitski, S., Kaidar-Person, O., Gutter-Kapon, L., Scherer, S. D., Raviv, Z., et al. (2016). Macrophage-induced lymphangiogenesis and metastasis following paclitaxel

chemotherapy is regulated by VEGFR3. *Cell Reports, 17*(5), 1344–1356. https://doi.org/10.1016/j.celrep.2016.09.083.

139. Lin, L., Huang, H., Liao, W., Ma, H., Liu, J., Wang, L., et al. (2015). MACC1 supports human gastric cancer growth under metabolic stress by enhancing the Warburg effect. *Oncogene, 34*(21), 2700–2710. https://doi.org/10.1038/onc.2014.204.
140. Liu, J., Pan, C., Guo, L., Wu, M., Guo, J., Peng, S., et al. (2016). A new mechanism of trastuzumab resistance in gastric cancer: MACC1 promotes the Warburg effect via activation of the PI3K/AKT signaling pathway. *Journal of Hematology & Oncology, 9*(1), 76. https://doi.org/10.1186/s13045-016-0302-1.
141. Ji, D., Lu, Z. T., Li, Y. Q., Liang, Z. Y., Zhang, P. F., Li, C., et al. (2014). MACC1 expression correlates with PFKFB2 and survival in hepatocellular carcinoma. *Asian Pacific Journal of Cancer Prevention, 15*, 999–1003. https://doi.org/10.7314/APJCP.2014.15.2.999.
142. Li, Y., Lu, Z., Liang, Z., Ji, D., Zhang, P., Liu, Q., et al. (2015). Metastasis-associated in colon cancer-1 is associated with poor prognosis in hepatocellular carcinoma, partly by promoting proliferation through enhanced glucose metabolism. *Molecular Medicine Reports, 12*, 426–434. https://doi.org/10.3892/mmr.2015.3416.
143. Duan, J., Sun, L., Zhao, L., Liao, W. W., Liao, Y., Duan Jiangman, S. L., Liang, Z., Liao, W., Jing, L., Liao, Y., & Liao, W. (2014). Participation of metastasis-associated in colon cancer-1 gene on lipogenesis and chemoresistance of gastric cancer. *Journal of Clinical Oncology, 32*, e15026.
144. Shay, J. W., & Wright, W. E. (2000). Hayflick, his limit, and cellular ageing. *Nature Reviews. Molecular Cell Biology, 1*(1), 72–76. https://doi.org/10.1038/35036093.
145. Blasco, M. A. (2005). Telomeres and human disease: ageing, cancer and beyond. *Nature Reviews. Genetics, 6*(8), 611–622. https://doi.org/10.1038/nrg1656.
146. Cong, Y., & Shay, J. W. (2008). Actions of human telomerase beyond telomeres. *Cell Research, 18*(7), 725–732. https://doi.org/10.1038/cr.2008.74.
147. Hannen, R., & Bartsch, J. W. (2018). Essential roles of telomerase reverse transcriptase hTERT in cancer stemness and metastasis. *FEBS Letters, 592*(12), 2023–2031. https://doi.org/10.1002/1873-3468.13084.
148. Park, J. I., Venteicher, A. S., Hong, J. Y., Choi, J., Jun, S., Shkreli, M., et al. (2009). Telomerase modulates Wnt signalling by association with target gene chromatin. *Nature, 460*(7251), 66–72. https://doi.org/10.1038/nature08137.
149. Liu, Z., Li, Q., Li, K., Chen, L., Li, W., Hou, M., et al. (2013). Telomerase reverse transcriptase promotes epithelial-mesenchymal transition and stem cell-like traits in cancer cells. *Oncogene, 32*(36), 4203–4213. https://doi.org/10.1038/onc.2012.441.
150. Yu, L., Liu, S., Zhang, C., Zhang, B., Simoes, B. M., Eyre, R., et al. (2013). Enrichment of human osteosarcoma stem cells based on hTERT transcriptional activity. *Oncotarget, 4*(12), 2326–2338. https://doi.org/10.18632/oncotarget.1554.
151. Zhang, K., Guo, Y., Wang, X., Zhao, H., Ji, Z., Cheng, C., et al. (2017). WNT/beta-Catenin directs self-renewal symmetric cell division of hTERT(high) prostate cancer stem cells. *Cancer Research, 77*(9), 2534–2547. https://doi.org/10.1158/0008-5472.CAN-16-1887.
152. Zhou, L., Yu, L., Zhu, B., Wu, S., Song, W., Gong, X., et al. (2016). Metastasis-associated in colon cancer-1 and aldehyde dehydrogenase 1 are metastatic and prognostic biomarker for non-small cell lung cancer. *BMC Cancer, 16*(1), 876. https://doi.org/10.1186/s12885-016-2903-z.
153. Evran, E., Sahin, H., Akbas, K., Cigdem, S., & Gunduz, E. (2016). Investigation of MACC1 gene expression in head and neck cancer and cancer stem cells. *Clinical and Investigative Medicine, 39*(6), 27506. https://doi.org/10.25011/cim.v39i6.27506.
154. Yu, L., Zhu, B., Wu, S., Zhou, L., Song, W., Gong, X., et al. (2017). Evaluation of the correlation of vasculogenic mimicry, ALDH1, KiSS-1, and MACC1 in the prediction of metastasis and prognosis in ovarian carcinoma. *Diagnostic Pathology, 12*(1), 23. https://doi.org/10.1186/s13000-017-0612-9.
155. Nair, R. M., Balla, M. M., Khan, I., Kalathur, R. K. R., Kondaiah, P., & Vemuganti, G. K. (2017). In vitro characterization of CD133(lo) cancer stem cells in retinoblastoma Y79 cell line. *BMC Cancer, 17*(1), 779. https://doi.org/10.1186/s12885-017-3750-2.
156. Juneja, M., Kobelt, D., Walther, W., Voss, C., Smith, J., Specker, E., et al. (2017). Statin and rottlerin small-molecule inhibitors restrict colon cancer progression and metastasis via MACC1. *PLoS Biology, 15*(6), e2000784. https://doi.org/10.1371/journal.pbio.2000784.
157. Melvin, V. S., Feng, W., Hernandez-Lagunas, L., Artinger, K. B., & Williams, T. (2013). A morpholino-based screen to identify novel genes involved in craniofacial morphogenesis. *Developmental Dynamics, 242*(7), 817–831. https://doi.org/10.1002/dvdy.23969.