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Review

Decoding and targeting the molecular basis of MACC1-driven metastatic spread: Lessons from big data mining and clinical-experimental approaches

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ABSTRACT

Metastasis remains the key issue impacting cancer patient survival and failure or success of cancer therapies. Metastatic spread is a complex process including dissemination of single cells or collective cell migration, penetration of the blood or lymphatic vessels and seeding at a distant organ site. Hundreds of genes involved in metastasis have been identified in studies across numerous cancer types. Here, we analyzed how the metastasis-associated gene MACC1 cooperates with other genes in metastatic spread and how these coactions could be exploited by combination therapies: We performed (i) a MACC1 correlation analysis across 33 cancer types in the mRNA expression data of TCGA and (ii) a comprehensive literature search on reported MACC1 combinations and regulation mechanisms. The key genes MET, HGF and MMP7 reported together with MACC1 showed significant positive correlations with MACC1 in more than half of the cancer types included in the big data analysis. However, ten other genes also reported together with MACC1 in the literature showed significant positive correlations with MACC1 in only a minority of 5 to 15 cancer types. To uncover transcriptional regulation

Abbreviations: AKT, AKT serine/threonine kinase; ALDH1, ALDH1A1, aldehyde dehydrogenase 1 family member A1; ALK, anaplastic lymphoma kinase; AP1, activator protein 1; AP2, activating protein 2; APC, APC regulator of Wnt signaling pathway; BCL2, B-cell lymphoma 2 apoptosis regulator; CCL1, CC-chemokine ligand 1; CD44, CD44 molecule; CD133, prominin 1; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; circRNA, circular RNA; CDKN1A, cyclin dependent kinase inhibitor 1; CNV, copy number variation; COAD, colon adenocarcinoma; CRC, colorectal cancer; CYR61, cysteine rich angiogenic inducer 61; DLC3, deleted in liver cancer 3 protein; dMMR, deficient mismatch repair; EF hand, helix-loop-helix structural domain; ELF1, E74 like ETS transcription factor 1; ELK1, ETS transcription factor ELK1; EMT, epithelial-mesenchymal transistion; ERK, extracellular signal-regulated kinase; ETS2, ETS proto-oncogene 2; ETV4, ETS variant 4; FAS, FAS cell surface death receptor; FAK, focal adhesion kinase, protein tyrosine kinase 2; FIGO, International Federation of Gynecology and Obstetrics; FDR, false discovery rate; FOXO4, forkhead box O4; GADD45A, growth-arrest and DNA-damage inducible protein 45A; GO, gene ontology; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; HTS, high throughput screens; IBD, inflammatory bowel disease; KAI1, kangai 1, suppression of tumorigenicity 6; KICH, kidney chromophobe cell cancer; KISS1, KISS1 metastasis suppressor; KIT, KIT proto-oncogene, receptor tyrosine kinase; lncRNA, long non-coding RNA; LNM, lymph-node-metastasis; LOPAC, library of pharmacologically active compounds; LUAD, lung adenocarcinoma; MAPK, mitogen-activated protein kinase; MACC1, metastasis-associated in colon cancer 1; MCL1, induced myeloid leukemia cell differentiation protein 1; MCT1, solute carrier family 16, member 1 (monocarboxylic acid transporter 1); MEK, MAP2K1, mitogen-activated protein kinase kinase 1; MET, MET proto-oncogene, receptor tyrosine kinase; miRNA, microRNA; MMR, mismatch repair; MMP2, matrix metalloproteinase 2; MMP7, matrix metalloproteinase 7; MMP9, matrix metalloproteinase 9; MSigDB, Molecular Signatures Database Broad Institute; MYC, MYC proto-oncogene, BHLH Transcription Factor; Nanog, Nanog homeobox; NFE2L1, nuclear factor, erythroid 2 like 1; NFE2L2, nuclear factor, erythroid 2 like 2; NF-κB, nuclear factor κB; NM23-H1, NME1, nucleoside diphosphate kinase 1; NSCLC, non-small cell lung cancer; Oct4, POU5F1, POU class 5 homeobox 1; Orai1, ORAI calcium release-activated calcium modulator 1; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PI3K, phosphoinositide 3-kinase/serine-threonine kinase; Pim-3, Pim-3 proto-oncogene, serine/threonine kinase; PKB, protein kinase B; pMMR, proficient mismatch repair; PRAD, prostate adenocarcinoma; READ, rectal adenocarcinoma; RET, RET proto-oncogene, tyrosine-protein kinase receptor; RON, MST1R macrophage stimulating 1 receptor; ROS, ROS1 proto-oncogene 1, ROS1, receptor tyrosine kinase; S100A4, S100 calcium binding protein A4; SNP, single nucleotide polymorphism; SOX9, sex determining region Y (SRY)-Box 9; SOX17, sex determining region Y (SRY)-Box 17; Sp1, specificity protein 1; SPON2, spondin 2; STAD, stomach adenocarcinoma; STAT, signal transducer and activator of transcription; TCGA, the cancer genome atlas; TEAD1, TEA domain transcription factor 1; TF, transcription factor; THYM, thymoma; TNM, tumor-node-metastasis; TRAIL, tumor necrosis factor related apoptosis inducing ligand; TWIST, twist family BHLH transcription factor; TWISTNB, TWIST neighbor; ULK-1, Unc-51 like autophagy activating kinase; UVM, uveal melanoma; VEGF-A, vascular endothelial growth factor A; VEGF-C, vascular endothelial growth factor C; VEGF-D, vascular endothelial growth factor D; VEGFR2, VEGF receptor 2; VM, vasculogenic mimicry; Wnt, wingless-related integration site; YB1, Y-box binding protein 1; ZEB1, zinc finger E-box binding homeobox 1; ZEB2, zinc finger E-box binding homeobox 2

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mechanisms that are activated simultaneously with MACC1, we isolated pan-cancer consensus lists of 1306 positively and 590 negatively MACC1-correlating genes from the TCGA data and analyzed each of these lists for sharing transcription factor binding motifs in the promotor region. In these lists, binding sites for the transcription factors TELF1, ETS2, ETV4, TEAD1, FOXO4, NFE2L1, ELK1, SP1 and NFE2L2 were significantly enriched, but none of them except SP1 was reported in combination with MACC1 in the literature. Thus, while some of the results of the big data analysis were in line with the reported experimental results, hypotheses on new genes involved in MACC1-driven metastasis formation could be generated and warrant experimental validation. Furthermore, the results of the big data analysis can help to prioritize cancer types for experimental studies and testing of combination therapies.

1. Introduction

Despite the progress made for treatment of solid cancers, metastasis remains the key issue impacting failure or success of cancer therapies. This is, because metastatic dissemination of primary tumors is directly linked to patient survival representing the most lethal attribute of cancer. Metastatic spread critically limits successful therapy in many tumor entities. This is exemplified by the fact that about 25–30% of all colorectal cancer (CRC) patients are already distantly metastasized when presenting the first time (stage IV). 40–50% of all patients newly diagnosed with CRC without distant metastases (stages I-III) will develop distant metastasis later, metachronously, after primary surgery. This is significantly linked to shorter survival. Patient survival is about 80% in early stages, but below 10%, when distant metastases occurred. This clearly defines the clinical need for reliable and strong biomarkers identifying cancer patients at high risk for metastasis. In an optimal scenario such biomarkers are acting as causal key drivers for metastasis, being involved in signaling pathways, which promote and drive the metastatic phenotype of cancer cells [1–3].

As knowledge on signaling crosstalk in cancer cells is growing, targeting interconnected signaling pathways such as wingless-related integration site (Wnt) pathway, mitogen-activated protein kinase (MAPK) pathway and phosphoinositide 3-kinase/serine-threonine kinase (PI3K) pathway at multiple sites is a rationale to hit alternate routes in cancer cells simultaneously. Such combination therapy approaches have meanwhile reached clinical trials, and holds promise to better intervene in cancer growth and progression and potentially metastasis [4].

The research of the Stein lab is focused on identification of such key molecules for more profound understanding of metastasis. One excellent example during this endeavor is the gene Metastasis Associated in Colon Cancer 1 (MACC1), which was discovered by our group ([5]; Fig. 1). MACC1 was shown to induce cell proliferation, dissemination, migration, invasiveness and metastasis in xenografted and transgenic

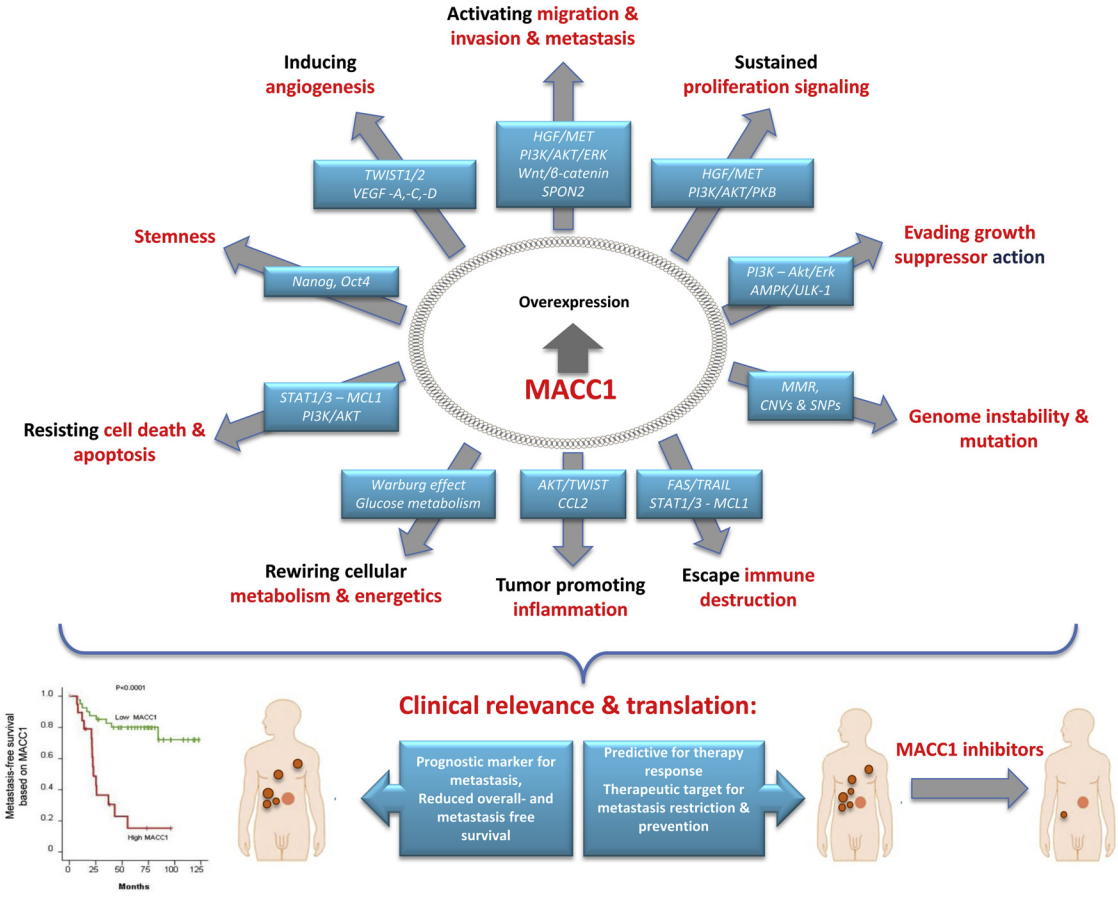

Fig. 1. Schematic representation of MACC1 impact in cancer signaling and its clinical relevance as biomarker and therapeutic target. MACC1 permits and associates with numerous key cancer features via the involvement and activation of various signaling pathways important for migration, invasion, metastasis, proliferation and many other features. The key genes involved/cooperating in these MACC1-mediated functions are indicted in the boxes. This molecular action of MACC1 leads finally to the clinical relevance of the molecule as biomarker and target for selective anti-metastatic therapies.

mice. Meanwhile, MACC1 has been established by us and others as key player, prognostic and predictive biomarker for tumor progression and metastasis in a broad variety of more than 20 solid cancer types, including CRC, gastric, esophageal, pancreatic, hepatocellular/biliary, lung, nasopharyngeal, renal, bladder, ovarian, and breast cancer, as well as glioblastomas and osteosarcomas [6]. Following our initial discovery of MACC1, more than 200 succession papers (PubMed) from research groups worldwide were published until today including meta-analyses of solid cancers, hepatocellular, gastrointestinal cancer, CRC and gastric cancer [7–11]. They strongly confirm the prognostic and predictive value of MACC1 for tumor progression and metastasis in a broad panel of human solid cancer entities, and verify MACC1 as key player for metastasis-associated processes in cell culture, mouse models and cancer patients. High MACC1 levels in the primary tumor or patient blood predict metastasis formation and are linked to shorter patient survival [6]. Taken together, MACC1 has been established as strong metastasis biomarker in tumor tissues and liquid biopsies for clinical disease prognosis and prediction of therapy response in cancer patients.

Nowadays, molecular high-throughput data of ten thousands of tumors comprising multiple cancer types are publicly available via the internet. These data offer the opportunity of a comprehensive data-driven (and thus researcher-unbiased) view on tumor molecular biology. Connecting *in silico* analysis of these molecular data sets with functional annotation such as presence of transcription factor (TF)

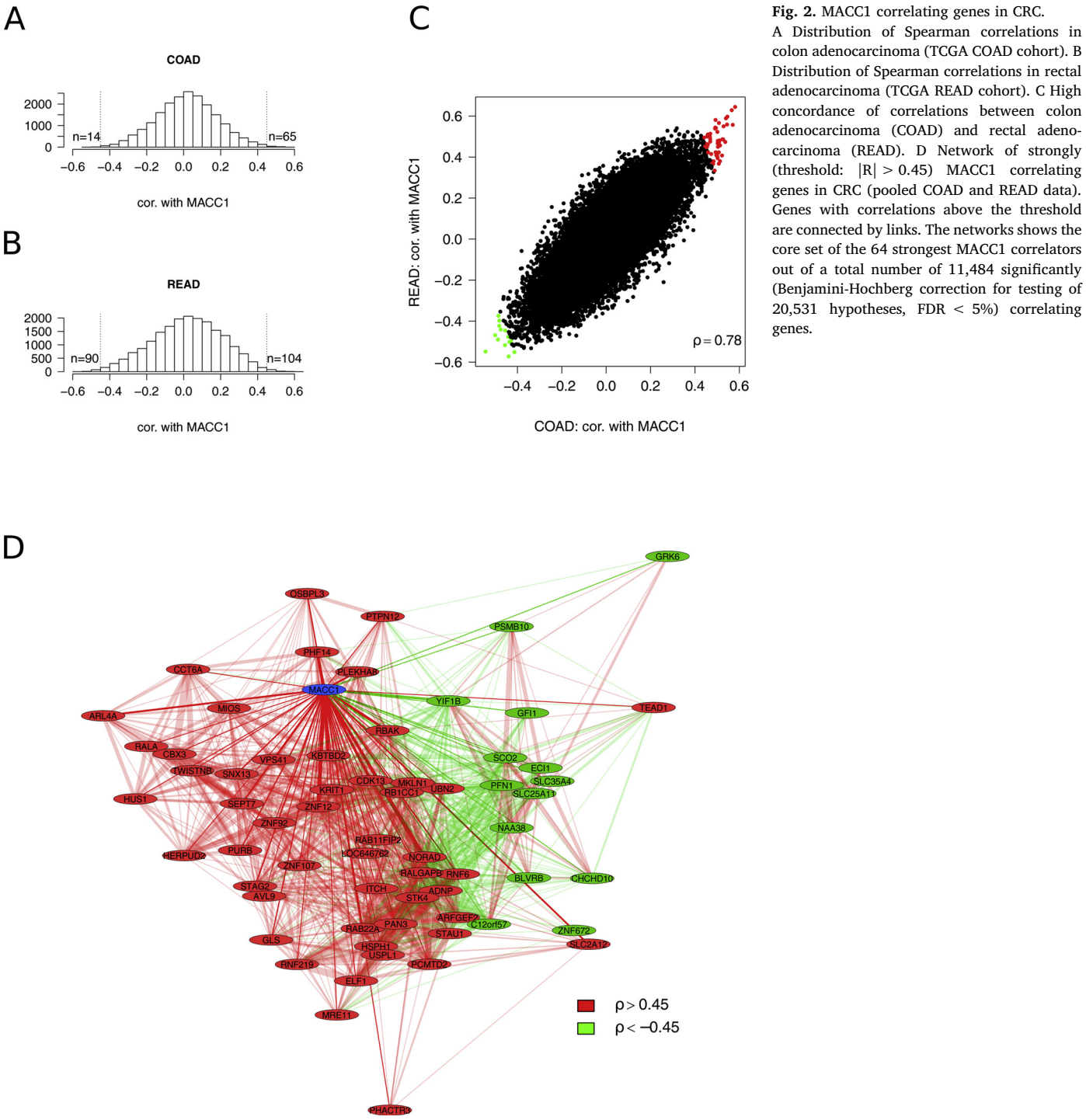

Fig. 2. MACC1 correlating genes in CRC.
A Distribution of Spearman correlations in colon adenocarcinoma (TCGA COAD cohort). B Distribution of Spearman correlations in rectal adenocarcinoma (TCGA READ cohort). C High concordance of correlations between colon adenocarcinoma (COAD) and rectal adenocarcinoma (READ). D Network of strongly (threshold: $|R| > 0.45$) MACC1 correlating genes in CRC (pooled COAD and READ data). Genes with correlations above the threshold are connected by links. The networks shows the core set of the 64 strongest MACC1 correlators out of a total number of 11,484 significantly (Benjamini-Hochberg correction for testing of 20,531 hypotheses, FDR < 5%) correlating genes.

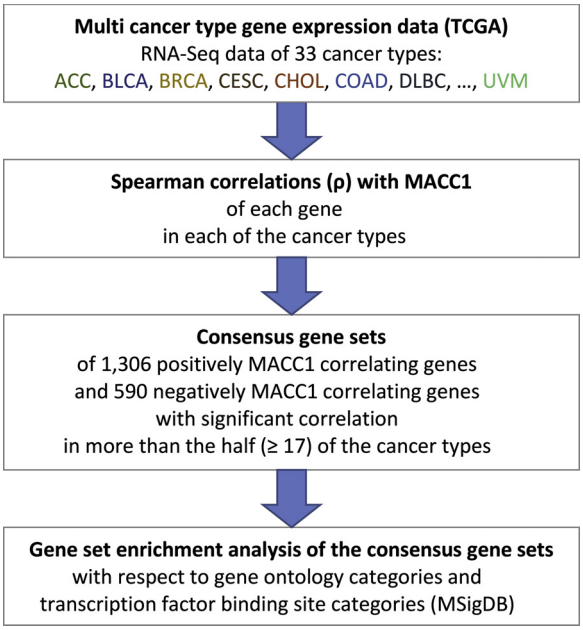

Fig. 3. Workflow of the pan-cancer analysis of MACC1 correlating genes.

binding sites [12], can aid for hypothesis generation and uncovering of possible regulatory mechanisms. Based on this and complementary to the literature search approach, correlation analysis of the gene expression data of 10,000 tumors was performed to generate hypotheses on regulation processes up-steam and down-stream to MACC1.

In summary, we analyzed how MACC1 cooperates with other genes for metastatic spread and how such interactions can be exploited by combination therapies. We performed a MACC1 correlation analysis across 33 cancer types in the mRNA expression data of TCGA and a comprehensive literature search on reported MACC1 combinations and regulation mechanisms.Our comprehensive analytic approach paves the way for useful combinatorial approaches for improved prognosis prediction and novel therapeutic interventions to finally achieve the ultimate goal: to restrict cancer metastasis and thus to prolong patient survival.

2. MACC1 co-expression analysis in CRC

Biological processes involved in cancer progression such as proliferation and epithelial-mesenchymal transition (EMT) contributing to invasion and metastasis formation require the coordinated activation of corresponding gene modules. The classical mechanism of coordinated gene regulation at transcriptional level is comprised of trans-acting transcription factors that bind to cis-regulatory elements in the promoter regions of target genes. Co-expression gene modules can be identified analyzing sample cohorts where the biological process under study is active at different levels. In recent years, thousands of tumor tissues were comprehensively gene molecularly profiled and many of such data sets are publicly available from the internet. These data sets can be exploited for hypothesis generation on the regulatory structure underlying cancer progression.

Here, we exemplify this data-driven strategy to uncover MACC1 co-expression modules analyzing RNA-Seq data of 10 000 tumors of 33 cancer types from TCGA [13]. Separately for each of the cancer types, we calculated the Spearman correlation of each gene with MACC1 and quantified its significances by a p-value. The Benjamini-Hochberg method was used for p-value correction and lists of significantly MACC1 co-expressed genes were generated for each cancer type controlling the false discovery rate (FDR) at 5%.

We compared the MACC1 co-expression patterns in colon cancer (TCGA dataset COAD, n = 452) and in rectal cancer (TCGA dataset READ, n = 160). Controlling the FDR, we detected 10 107 significantly correlating genes in COAD and 6515 significantly correlating genes in READ (Fig. 2A and B). The two lists shared a high number of 5240 genes ($p < 2.2e-16$, exact Fisher test) and the strengths of correlations were similar in COAD and READ across the transcriptome ($\rho = 0.78$, Fig. 2C). The shared co-expression patterns recapitulate the similar molecular biology of these cancer types and at the same time demonstrate reproducibility of the correlation analysis between independent data sets.

Based on this observation, we pooled the COAD and the READ data sets and isolated a core gene set of 64 strongly MACC1-correlating genes in CRC using the threshold $|\rho| > 0.45$ (Suppl. Table S1). The 64 genes were visualized in a correlation network, where genes with correlation above the threshold were interconnected by links (Fig. 2D). The resulting network had a high connectivity with a mean degree of 30. MACC1 was (by definition) connected with all 64 genes in the network, ZNF12 was connected with 56 genes, while the other genes were connected with 6–49 genes. The network included nine transcription factors (gene ontology (GO) term “regulation of transcription by RNA polymerase II”; ADNP, ELF1, PHF14, PURB, RBAK, TEAD1, ZNF107, ZNF12, ZNF92) showing a positive correlation with MACC1 and three transcription factors (GFI1, PFN1, ZNF672) showing a negative correlation with MACC1. Furthermore, it included one gene annotated with the GO term “cell migration” (AVL9), one gene annotated with “positive regulation of cell migration“ and two gens (KTH1, SEPT7) annotated with “negative regulation of cell migration”. Thus, the RNA-Seq data set could be exploited to analyze the correlation structure of MACC1 in CRC and to uncover candidate genes that could be further analyzed in experimental studies for a mechanistic connection to MACC1 and combined targeting.

3. Pan-cancer MACC1 co-expression analysis

We extended the *in silico* correlation analysis to all 33 cancer types analyzed in TCGA (Fig. 3). Lists of significantly (FDR < 5%, Benjamini-Hochberg method) MACC1-correlating genes were isolated separately for each cancer type (Fig. 4A). For the majority of cancer types (23 out of 33) more than 5000 significantly MACC1-correlating genes were detected, while the number of significantly MACC1-correlating genes was very limited in the four cancer types adrenocortical carcinoma (ACC), mesothelioma (MESO), cholangiocarcinoma (CHOL) and diffuse large B-cell lymphoma (DLBC). In the next step, we generated pan-cancer consensus lists of MACC1 positively and of MACC1 negatively correlating genes defined by the criterion of showing a significant ($p < 0.05$) correlation in more than the half (≥ 17) of the cancer types. The consensus lists included 1306 positively MACC1 correlating genes and 590 negatively MACC1 correlating genes, respectively (Suppl. Tables S2 and S3).

The consensus lists of MACC1 correlators were further analyzed using gene set enrichment analysis. In short, a catalog of 836 motif gene sets (collection c3) and a catalog of 15 682 GO categories (collection c5) was obtained from MSigDB [14–16]. Therein the motif gene sets are grouped by short sequence motifs that genes share in their promoters and 3'-UTRs representing potential binding sites for TFs or microRNAs. The GO gene sets are grouped by common molecular function, cellular location or biological processes. The pan-cancer consensus lists were analyzed for enrichment of the gene sets using the exact Fisher test and only gene sets significant after Bonferroni correction of p-values were reported. Enrichment factors (fold enrichment) were calculated as the percentage of genes in the consensus list that are in the gene set divided by the percentage of genes in the genome that are in the gene set.

A high number of 41 GO categories were significantly enriched in the consensus list of positive MACC1 correlators and 17 of these categories were enriched more than two-fold (Fig. 4B). The strongest enrichment (6.3x) was detected for the category “O-glycan processing”:

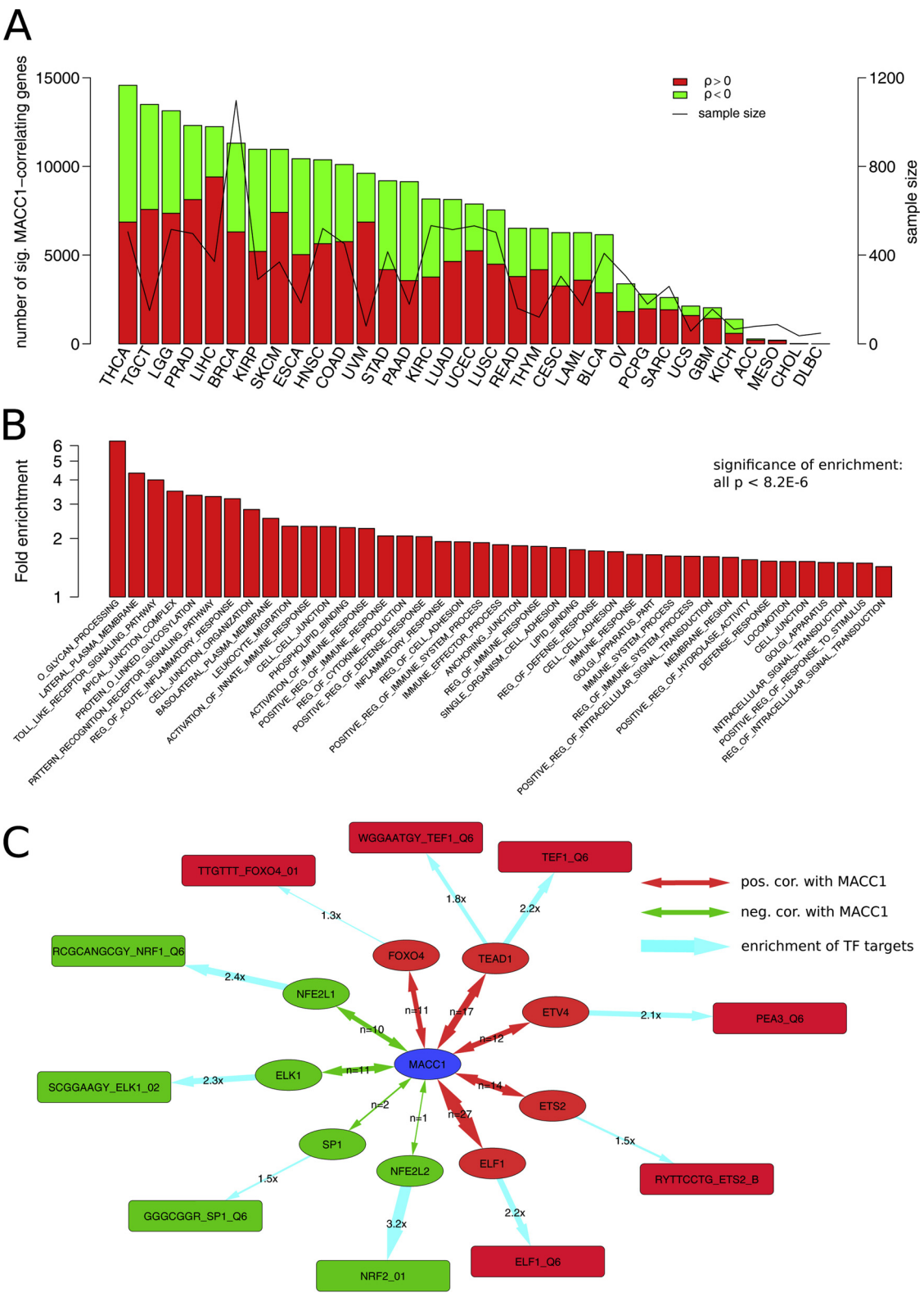

Fig. 4. MACC1 correlating genes across 33 cancer types. A Numbers of genes correlating significantly (Benjamini-Hochberg correction for testing of 20,531 hypotheses, FDR < 5%) with MACC1 (read and green bars) and sample size (black line). B Enrichment of GO categories in the pan-cancer consensus list of positively MACC1-correlating genes. Fold enrichment is defined as the percentage of genes in the consensus list that are in the gene set divided by the percentage of genes in the genome that are in the gene set. REG = regulation. C Explorative analysis of the connection between MACC1 expression and transcription factor activity. Consensus gene set of positively and negatively MACC1-correlating genes across cancer types were analyzed for motif gene sets (catalog C3 of MSigDB, 836 gene sets). Five gene sets were significantly enriched in the consensus list of positively MACC1 correlating genes (red boxes), while four gene sets were significantly enriched in the consensus list of negatively MACC1 correlating genes (green boxes). Red arrows: Number of cancer types with significant and positive MACC1 correlation. Green arrows: Number of cancer types with significant and negative MACC1 correlations. Cyan arrows: Fold enrichment of TF binding motif gene sets.

Twenty of the total of 53 genes in this category (B3GNT2, B3GNT3, B3GNT5, B3GNT7, B4GALT5, C1GALT1, CHST4, GALNT3, GALNT4, GALNT5, GALNT6, GALNT7, GALNT12, GCNT3, MUC1, MUC4, MUC13, MUC15, MUC20, MUC21) were in the list of positive MACC1 correlators. Two other biological themes were observed repeatedly in the consensus list of positive MACC1 correlators: (1) categories related to the cell-cell contact of epithelial cells (such as “lateral plasma membrane”, “cell junction organization” and “regulation of cell adhesion”) and (2) categories related to immune response (such as “toll like receptor signaling”, “regulation of acute inflammatory response”, “leukocyte migration” and “activation of innate immune response”).

Analyzing the sequence motifs that represent potential TF binding sites, six motif gene sets were enriched in the consensus list of positive MACC1 correlators, while four motif gene sets were enriched in the consensus list of negative MACC1 correlators (Fig. 4C, outer circle). The ten sequence motifs were binding sites for nine TFs (Fig. 4C, inner circle). The figure shows both the number of cancer types with a significant positive or negative correlation between MACC1 and the TF (red and green arrows) as well as the fold enrichment for each of the motif gene sets (cyan arrows). As an example, ELF1 correlated significantly positive with MACC1 in an impressive number of 27/33 cancer types. Among these, the highest correlations were 0.53 in uveal melanoma (UVM), 0.50 in kidney chromophobe cell cancer (KICH), 0.48 in READ, 0.47 in COAD, 0.45 in pheochromocytoma and paraganglioma (PCPG), 0.44 in cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), 0.43 in thymoma (THYM) and 0.40 in PRAD. At the same time, 3.8% of the genes in the list of positive MACC1 correlators contained the binding site V$ELF1_QW6 (with sequence motif RNWMBAGGAART) in their promotor region compared to 1.7% of genes in the genome resulting in a 2.2x enrichment ($p = 8.2E-06$). Thus, a positive correlation of MACC1 and ELF1 as well as between MACC1 and the target genes of ELF1 was found across many cancer types. MACC1 and the nine TF uncovered in this analysis (ELF1, ETS2, ETV4, TEAD1, FOXO4, NFE2L1, ELK1, SP1 and NFE2L2) should be further investigated for a possible functional connection.

4. Clinical-experimental combinations of MACC1 with further genes

4.1. Impact of biomarker combination for improved disease prognosis and prediction of therapy response

Numerous groups reported on molecular networks and axes involved in MACC1-regulated processes for cell proliferation, cell motility and metastasis. Thus, in this review, we will discuss and evaluate a large body of genes/proteins investigated in the context of MACC1 in our lab as well as published by groups worldwide for combinatorial patient prognosis and therapy response prediction. In this chapter, we focus on MACC1 gene combinations, which are repeatedly reported.

4.1.1. How MACC1 impacts MET

The first function unveiled for the newly identified gene MACC1 was to act as transcription factor regulating the transmembranous receptor tyrosine kinase proto-oncogene (MET) [5]. By treatment with its ligand hepatocyte growth factor (HGF), the mainly cytoplasmically localized protein MACC1 translocates into the nuclei, binds to gene promoters, e.g. for MET, and transcriptionally regulates the expression of its target genes. The transcriptional control of MET is driven by the binding of MACC1 to specific transcription factor binding sites, preferentially for the transcription factors specificity protein 1 (SP1) and activating protein 2 (AP2) [17]. Both have been previously described as MET regulators [18,19]. The transcriptional activity of SP1 is dependent by interaction with further proteins, either tumor suppressors or oncogenes. We demonstrated that MACC1 acts via a specific consensus sequence of the MET promoter, described as an SP1 binding site. SP1 binds preferentially to GC-boxes with the consensus sequences 5'-G/T-GGGCGG-G/A-G/A-C/T-3' or 5'-G/T-G/A-GGCG-G/T-G/A-G/A-C/T-3' [20]. This binding of MACC1 to the MET promoter finally results in a positive feedback loop of induced MET expression leading to increased HGF binding, thereby identifying MACC1 as a master regulator of the HGF/MET signaling pathway. The binding of HGF to MET is known to activate the receptor, leading to increased cell survival, cell dissemination, and cell motility like migration and invasion. MET is acknowledged as crucial for metastasis of CRC, and is reported as prognostic marker for early stage invasion and metastasis [21,22]. This MACC1-induced MET-signaling finally results in metastasis formation, which was shown being enhanced by forced ectopic MACC1 expression, and hindered by si/shRNA acting on MACC1 [5,23], as well as later on, by using newly identified MACC1 inhibitors [24].

Galimi and colleagues [25] postulated further transcriptional MACC1 target genes using bioinformatic approaches, by employing motifs in the promoter regions similar to the MET promoter motifs with one or several SP1 sites and an AP2 site, also considering the distance of these sites. The proposed list of 129 putative MACC1 target genes includes 10, being differentially expressed in our microarray analysis, e.g. the extracellular matrix protein SPON2 [26]. SPON2 was also found in a first selection of target genes based exclusively on the presence on SP1 sites. Since the SPON2 promoter region harbors two SP1 sites, but is lacking an AP2 site, it is suggested that MACC1 might interact with the SPON2 promoter via mechanism/protein complexes additional those with the MET gene promoter. Following our paper of MACC1 discovery and showing the link to its target gene MET, a variety of studies in different entities validated this finding. Migliore and colleagues confirmed this MACC1/MET relationship by demonstrating that concomitant miR-1 down-regulation and MACC1 high expression functionally synergize in promoting MET overexpression presumably contributing to metastasis formation [27]. Based on the MACC1 domain composition the group of Kokoszyńska et al. linked MACC1 to MET signaling and apoptosis [28]. This hypothesized link was later experimentally validated by a variety of papers in several cancer types [e.g. 29–31]. By detailed analyses of human colon cancer samples, we could align the induction of MACC1 expression into the adenoma-carcinoma-sequence [32] at the transition from the adenoma to the carcinoma state [33]. This finding was experimentally confirmed with the first generated MACC1 transgenic mouse models. Here we demonstrated the invasive phenotype of carcinomas in vil-MACC1/ APC regulator of Wnt signaling pathway (Apc) MIN mice, but not in ApcMIN mice without transgenic MACC1 expression [34].

The initial link of MACC1 and MET in clinical specimens of CRC was shown in a cohort of CRC patients of stages I, II and III, not yet distantly metastasized [5]. In a study of patients with rectal cancer treated with chemo-radio-therapy followed by surgery, MACC1 and MET expressions were positively co-expressed and associated with reduced relapse-free survival. Patient prognosis was worse when both genes were highly expressed demonstrating that evaluation of MACC1 and MET expression may be useful for predicting prognosis [35]. In inflammatory bowel disease (IBD)-associated colonic neoplasia, Harpaz et al. found a stepwise increase of MACC1 expression from IBD-associated colitis to dysplasia to adenocarcinoma, however, independent of MET [36]. Thus, MACC1 is strongly associated with conventional colitis-associated CRC and may serve as a potential marker for early diagnosis.

The relevance of MACC1 in conjunction with MET was also investigated in further gastrointestinal tumor entities. For gastric cancer, MACC1 protein expression was related to the protein expression of MET. Both expressions correlated to the presence of peritoneal metastasis, lymph node metastasis and hepatic metastasis [37], and thus contributed to a poor prognosis for gastric cancer patients. This finding was confirmed by Ma and colleagues [38], demonstrating that MACC1 and MET expression strongly correlates to gastric cancer stage and degree of malignancy, and is inversely correlated to patient prognosis.

However, although a study by Koh and colleagues showed that MACC1-positive patients had lower overall survival or event-free

survival than MACC1-negative patients, MET positivity itself was not associated with survival [39]. They conclude that MACC1 is an independent prognostic factor in gastric adenocarcinoma, but the prognostic impact of MACC1 may be associated with MACC1 partners other than MET. Furthermore, Dong et al. demonstrated that positive protein expression of MACC1, HGF and MET was significantly higher in human gastric cancer tissues compared with adjacent normal tissues, positively correlated with each other and with tumor size, depth of tumor invasion, lymph node metastasis, tumor-node-metastasis TNM stage, histological differentiation, and overall and disease-free survival [40]. The authors conclude that MACC1, HGF and MET might cooperatively participate in the malignant progression of gastric cancer and that MACC1 might serve as a useful molecular marker for diagnosis prognosis of gastric cancer. The MACC1/MET link was also addressed in pancreatic cancer. Li and colleagues showed the circular RNA PDE8A to promote invasive growth via the miR-338/MACC1/MET pathway [41].

The prognostic value of MACC1 and MET was also shown for lung cancer [42]. Targeting Y-Box Binding Protein 1 (YB1) suppressed lung adenocarcinoma progression through the MACC1/MET pathway, and suggesting high expression of YB1/MACC1 as potential prognostic marker in lung adenocarcinoma [43].

In ovarian cancer, MACC1 may also serve as a potential biomarker. Deregulation of MACC1, HGF and MET proteins synergistically participate in the malignant progression of epithelial ovarian cancer [44]. Further, Sheng and colleagues confirmed MET as the target gene of MACC1 [45]. They demonstrated that attenuation of MACC1 suppresses cell invasion and migration. Since MACC1 may regulate cell metastasis through targeting the expression of MET, inhibition of the MACC1 function may represent a new treatment strategy for ovarian cancer. Li et al. concluded in their study that MACC1 is a predictor of prognosis and a therapeutic target for treatment of ovarian tumors [46]. They recommend the combined detection of MACC1 and HGF/MET for assessing the prognosis of patients with malignant epithelial ovarian tumors. In the same line for cervical cancer, Chen and colleagues summarized their data that HGF, MACC1 and MET are not only involved in malignant cervical tumors occurrence, development and prognosis, but might become potential molecular targets for therapy of cervical cancer [47].

4.1.2. MACC1 and S100A4, a dangerous liaison for metastasis

S100 Calcium Binding Protein A4 (S100A4) belongs to the S100 family, containing 2 specific helix-loop-helix structural domain (EF-hand) calcium-binding motifs. S100A4 has demonstrated its power as prognostic biomarker in metastatic cancer in many different tumor entities, such as colon, gastric, ovarian, lung, and breast cancer. S100A4 is promoting EMT, cell cycle progression and differentiation, cell migration, invasion, angiogenesis, and tubulin polymerization. It was also shown to impact cancer cell signaling leading to the metastatic phenotype of cancer cells. S100A4 serves as molecular marker for prognosis and represents a target for therapeutic targeting [48–51].

Its elevated expression in CRC and further cancer types correlates with poor prognosis. By using isogenic cell line models we were first identifying the well-known metastasis inducer S100A4 as a transcriptional target of Wnt/β-catenin signaling [52]. Importantly, Wnt-signaling and S100A4 were linked as important regulatory axis for cancer progression and metastasis. Thus, intervention targeting the Wnt pathway resulted in reduced S100A4 expression leading to significantly reduced metastasis formation in mice. S100A4 induces cellular processes such as cell migration and invasion, resulting in metastasis. These potentials of S100A4 are enhanced when combined with MACC1.

For CRC, Barbazan and colleagues analyzed MACC1 and S100A4 in non-invasive and invasive parts of primary tumors and in metastases [53]. They showed higher expression of both genes at the tumor invasive front and in the metastases, vs. non-invasive samples. Further, Barbazan and colleagues reported the prognostic relevance of a S100A4/MACC1 cluster in circulating tumor cells for progression-free and overall survival of patients with metastatic CRC. Further, for both molecular markers, blood-based assays were developed to non-invasively evaluate the risk for metachronous metastasis formation: the usefulness for cell free-RNA of S100A4 as biomarker was shown for colon, rectal, gastric, bladder and breast cancer patients [54–57], the usefulness for cell free-RNA of MACC1 as biomarker was shown in colon, rectal, gastric, lung, ovarian cancer and glioblastoma [56,58–61] and for MACC1 protein as biomarker in patient blood via ELISA in breast and pancreatic cancer [62,63]. The combination of circulating MACC1 and S100A4 transcripts improved the prognosis for cancer patients. This combinatorial benefit of MACC1 together with S100A4 was shown for colon and rectal cancer patients [56], for gastric cancer patients [58], and very recently, for patients with ovarian cancer [60]. Thus, simultaneous high expression of MACC1 and S100A4 best identifies those CRC patients at high risk for metastasis linked to shorter survival. For these patients, a combinatorial simultanous treatment with inhibitors targeting MACC1 AND S100A4 would be a fantastic option.

4.1.3. Angiogenesis, MACC1 and VEGF-signaling

Members of the Vascular Endothelial Growth Factor VEGF family are signaling protein contributing to vasculogenesis, angiogenesis and vasculogenic mimicry. These molecules induce cell proliferation and migration, and eventually metastasis. They are up-regulated in many tumors, correlating to tumor stage and progression.

Sun and colleagues reported that MACC1 not only promoted lymphangiogenesis and tube formation in gastric cancer, but also increased the expression of VEGF-C/VEGF-D. These functions were reversible by using MET inhibitors [64]. Wang et al. demonstrated in gastric cancer patients that MACC1 expression correlated with increased microvessel density and tumor recurrence. It also induced endothelium-dependent angiogenesis using nude mice with gastric cancer xenografts. These processes are in conjunction with MACC1-up-regulated Twist Family BHLH Transcription Factor 1 (TWIST1), but also with elevated VEGF-A [65]. Peng and colleagues showed that MACC1 promotes angiogenesis also in cholangiocarcinoma by up-regulating VEGF-A [66]. They also suggest MACC1 as an independent predictor of overall survival and facilitates angiogenesis in cholangiocarcinoma by upregulating of VEGF-A.

4.1.4. MACC1, metastasis and MMPs

Matrix metalloproteinases (MMP) like MMP2, MMP7 and MMP9 are involved in degradation of the extracellular matrix in normal physiological processes and in disease processes such as regulation of vascularization and metastasis.

Gao and colleagues reported that knockdown of MACC1 expression reduced cell migration and invasion together with down-regulation of MMP2, MMP9, and MET proteins in hepatocellular carcinoma (HCC) cells [67]. They conclude that localization of MACC1 protein to the nucleus may predict HCC progression, and that knockdown of MACC1 inhibiting MMP2, MMP9 and MET warrants further evaluation as a novel therapeutic strategy for control of hepatocellular carcinoma. Dong et al. demonstrated higher protein expression of MACC1, HGF and MET in human gastric cancer tissues compared with adjacent normal tissues [68]. This correlated with tumor size, depth of tumor invasion, lymph node metastasis, TNM stage, histological differentiation, and overall (5 years) and disease-free survival (5 years). Interestingly, overexpression of MACC1 induced not only cell migration and invasion, but also HGF, MMP2, and MMP9 expression levels. The authors stated that MACC1 might serve as a useful molecular target for diagnosis, treatment and prognosis of gastric cancer

Our group generated the first transgenic MACC1 mouse models [34]. Using transcriptomics of tumors from ApcMIN mice vs. vil-MACC1/ApcMIN mice, we found the Wnt signaling and pluripotency pathway significantly enriched in the double transgenic mice vs. the ApcMIN controls harboring e.g. different extracellular matrix

modulators, MMP7 and MMP9. Additionally, we also found VEGF-A to be upregulated in the small intestine tumors of vil-MACC1/ApcMIN mice.

4.1.5. MACC1 interplay with TWIST1

The transcription factor TWIST1 is known to play an important role in cranial suture closure during skull development, neural tube closure, and limb development. Interestingly, Melvin and colleagues reported about craniofacial malformation of zebrafish following knockdown of MACC1 [69]. Further, among the nearest neighbors of MACC1 on chromosome 7 (GeneLoc map region 18,146,776–22,223,538 bp) are genes such as TWIST neighbor (TWISTNB), and TWIST homolog 1 (TWIST1) [70]. These genes are known to be involved in signal transduction and regulation of cell adhesion and motility and contribute to tumorigenesis and metastasis of CRC [71,72].

Further, because cancer metastasis requires a sufficient blood supply, usually provided by neovascularization, alternative tumor blood supply sources independent of blood vessel endothelium were identified, named vasculogenic mimicry (VM) [73]. VM is formed by cancer cells (not by endothelial cells) and is strongly associated with EMT, TWIST1 activation and tumor progression. Wang et al. reported for tumors of patients who died of gastric cancer that vasculogenic mimicry density was increased and correlated with MACC1 protein expression [74]. Patients with tumors showing high MACC1 and high vasculogenic mimicry density had a very strongly reduced survival compared to patients whose tumors were negative for both MACC1 and VM. Nuclear expression of MACC1, TWIST1, and TWIST2 was upregulated in gastric cancer tissues vs. matched adjacent non-tumorous tissues ($p < 0.05$). MACC1 overexpression enhanced TWIST1/2 promoter activity, increased TWIST1/2 expression leading to VM in xenografted mice and cell lines. HGF increased the nuclear translocation of MACC1, TWIST1, and TWIST2, while a MET inhibitor reduced these effects, confirming our initial data. Thus, the pathway HGF/MET/TWIST1/2 may represent a potential new therapeutic target for gastric cancer.

Wang and colleagues also analyzed MACC1 and TWIST1 also in the context of endothelium-dependent angiogenesis in gastric cancer [65]. They found that MACC1 expression correlated with increased microvessel density, tube formation, as well as increased expression of TWIST1 and VEGF-A. The authors again suggested potential prognostic and therapeutic value for MACC1 in gastric cancer.

Zhu and colleagues found MACC1 and TWIST1 increased in colon adenocarcinomas vs. normal colon mucosa [75]. High expressions of MACC1 and TWIST1 were positively correlated with invasion, tumor grades, and lymph-node-metastasis stages and tumor-node-metastasis stages as well as with shorter overall survival for patients with colon adenocarcinomas. Both, MACC1 and TWIST1, were identified as independent predictors of prognosis in patients with colon adenocarcinomas and were suggested by the authors as useful biomarkers and therapeutic targets.

4.1.6. MACC1 and more: further EMT genes

MACC1 is also linked to the process of EMT. EMT is not only essential for developmental processes, but also, in the context here, for initiation of metastasis in cancer progression. There a variety of publications demonstration the relevance of MACC1 within this process.

For example, Ding and colleagues demonstrated that silencing of MACC1 restricted cell mobility, migration and invasion in melanoma cells [76]. Further, knockdown of MACC1 up-regulated E-cadherin, and down-regulated N-cadherin and vimentin. These findings suggest MACC1 might serve as a new molecular target for the treatment of melanoma by a novel mechanism underlying the metastasis of melanoma cells.

Montorsi et al. demonstrated in CRC, that the tumor suppressor and mRNA-destabilizing protein ZFP36 impairs EMT [77]. ZFP36 inhibits the expression of three key transcription factors involved in EMT: Zinc Finger E-Box Binding Homeobox 1 (ZEB1), Sex Determining Region Y-Box 9 (SOX9), and MACC1.

For gastric cancer, miR-338-3p influenced the expression of EMT-associated proteins by up-regulating the epithelial marker E-cadherin and down-regulating the mesenchymal markers, N-cadherin, fibronectin, and vimentin by directly targeting Zinc Finger E-Box Binding Homeobox 2 (ZEB2) and MACC1 [78]. In conclusion, miR-338-3p inhibited the EMT progression in GC cells by targeting ZEB2 and MACC1/MET/Akt signaling. Inverse correlations were observed of miR-338-3p expression and ZEB2 or MACC1 in human gastric cancer tissue samples. Pan et al. showed in the same cancer type that miR-944 acts as an inhibitor of EMT and metastasis by targeting MACC1 [79].

4.1.7. Effects of MACC1 on stemness

MACC1 was identified as transcriptional regulator of metastasis inducing genes, involved in signaling pathways like the MAPK and Wnt signaling. Examples are transcriptional MACC1 targets such as MET and SPON2, which are able to induce metastasis in xenografted and genetically modified mouse models by themselves and are correlating to metastasis formation in cancer patients [5,26]. Besides all the very important new molecular insights, these gene/protein networks are also useful for improved cancer patient prognosis by biomarker combinations, as verified by many groups. Interestingly, when we compared the tumors of vil-MACC1/ApcMIN mice vs. ApcMIN mice, we found the Wnt and pluripotency pathways most elevated [34]. Further, novel MACC1 transcriptional targets were identified belonging to the group of stemness-related genes, like Nanog Homeobox (Nanog) and POU5F1, POU Class 5 Homeobox 1 (Oct4). However, although these gene expressions significantly correlate with each other and with MACC1 in CRC tumors, the combination of these stemness genes with MACC1 is not improving patient prognosis.

Wang and colleagues confirmed the relevance of MACC1 for stemness [80]. They showed that by depletion of MACC1 sphere formation and the expression levels of pluripotent markers such as CD44 molecule (CD44), prominin 1 (CD133) and Nanog were reduced. In addition, the phosphoinositide 3-kinase/protein kinase B (PI3K/PKB) signaling pathway may be associated with 5-fluorouracil resistance and cancer stem cell like properties via MACC1. Positive expression of MACC1 and CD44 as well TWIST1 also correlated with invasion, tumor grades, and lymph-node-metastasis (LNM) stages and TNM stages for patients with colon adenocarcinoma [75]. Overexpression of MACC1, CD44 and TWIST1 were independent predictors of prognosis in patients with CRC, and are related to patients` overall survival. Thus, all three genes may be useful as biomarkers as well as therapeutic targets in this tumor entity.

Yu et al. analyzed the relevance of MACC1 together with the stemness-associated gene aldehyde dehydrogenase 1 family member A1 (ALDH1, ALDH1A1) for ovarian cancer disease prognosis and prediction for metastasis formation [81]. Expression levels of ALDH1 and MACC1 were higher in tumor tissues vs. benign ovary tumors, and high levels correlated with tumor/lymph node/metastasis, grade, implantation, and International Federation of Gynecology and Obstetrics (FIGO) stage, and with patients' overall survival. The authors conclude that MACC1 and ALDH1 represent promising markers for metastasis and prognosis, and potential therapeutic targets for epithelial ovarian cancer. Zhou et al. analyzed this combination in non-small cell lung cancer (NSCLC) and found higher expression levels vs. normal lung tissues [82]. Both, high MACC1 and ALDH1 expressions showed correlations to tumor grade, lymph node metastasis, and tumor node metastasis. Patients high in these independent prognostic tumor markers demonstrated shorter overall survival. Thus, MACC1 and ALDH1 serve as promising metastatic and prognostic biomarkers and potential therapeutic targets for NSCLC as well.

4.1.8. Interplay of metastasis suppressor genes and MACC1

Metastasis Suppressor (KISS1) belongs to the group of metastasis

suppressor genes, inhibiting metastasis formation by e.g. affecting invasion via regulation of cell-matrix adhesion without inhibiting tumorigenicity. Dong and colleagues reported on KISS1 expression together with MACC1 and the transcriptional repressor Snail in specimens of infiltrating breast carcinoma. KISS1 expression is higher in normal tissues and lower in infiltrating breast cancer, reciprocally to MACC1 expression [83]. KISS1 positive patients showed a longer survival vs. KISS1 negative patients. MACC1, Snail and KISS1 were evaluated as independent risk factor for this tumor entity. This finding, here in the context of MACC1 and ALDH1, was also confirmed by Yu et al. for epithelial ovarian cancer [81]. Zhu and colleagues also analyzed KISS1 levels in colon adenocarcinomas together with MACC1, CD44 and TWIST1 [75]. They summarized that the levels of the biomarkers investigated here are related to patient overall survival. All of these genes might by suitable as biomarker and therapeutic target in these tumors.

Another metastasis inhibiting factor is the nucleoside diphosphate kinase 1 NM23-H1 (NME1), which is down-regulated in metastasizing cells. Ozturk et al. analyzed this gene expression in the context with MACC1 in early-stage colon cancer [84]. They reported higher MACC1 and lower NM23-H1 expression in patients with recurrence during the 5-year follow-up vs. Non-recurrent patients. Coexistence of high MACC1 and low NM23-H1 was linked to short overall survival. They authors conclude that the combination of MACC1 and NM23-H1 are promising biomarkers for the prediction of recurrence and may aid the stratification of patients with stage II colon cancer for adjuvant chemotherapy.

4.1.9. Somatic mutations combined with MACC1

We also tested for combinations of gene mutations of other genes, together with MACC1 expression. For example, we investigated the MACC1 in the context of mismatch repair (MMR) status, mutant KRAS (KRAS G12, KRAS G13) and BRAF (V600). Only high MACC1 expression and KRAS G13 mutation were independent prognostic markers for shorter metastasis-free survival. Patients with high MACC1 expression and KRAS G13 mutation exhibited the worst prognosis and the highest risk for metachronous metastases formation. Thereby we could identify a highly relevant prognostic signature for CRC patients who are at very high risk for metastasis formation [85].

Further, we identified the prognostic value of MACC1 and proficient mismatch repair (pMMR) status for recurrence risk prediction in stage II colon cancer patients, using the BIOGRID cohorts [86]. Therefore, we analyzed the combination of MMR status (deficient MMR (dMMR) vs. pMMR) together with MACC1 expression in CRC patient tumor tissues. Remarkably, we found that patients with pMMR (unfavorable) but MACC1 low have a comparatively good prognosis, such as dMMR patients. These patients might not benefit from 5-fluorouracil-based chemotherapy.

4.2. Employment of biomarker inhibition for novel combinatorial treatment options

4.2.1. The therapeutic target MACC1

In order to develop combinatorial therapeutic strategies connecting treatments targeting MACC1 and associated genes simultaneously, MACC1 inhibitors have to be generated. As proof of concept we and others identified and tested miRNAs targeting MACC1 as post-transcriptional MACC1 inhibitors. It was shown, that CRC tumors demonstrated an inverse correlation of MACC1 and corresponding miRNA. Restoration of MACC1 miRNAs abrogated MACC1 expression and function [6,87].

We already identified the first MACC1 transcriptional inhibitors [24]. By performing human MACC1 promoter-based high throughput screens (HTS), we identified FDA-approved small molecule drugs such as lovastatin and rottlerin as transcriptional inhibitors of MACC1. These compounds impaired the binding of the transcription factors c-Jun/AP1 to the human MACC1 promoter, which resulted in reduced MACC1 level in treated cells. By this, both compounds inhibited cell motility in vitro, and more importantly, restricted metastasis development in vivo. These data provide strong evidence, that therapeutic targeting of MACC1 has impact on tumor growth and more importantly on metastasis formation. In this regard, great potential lays in the combined attack of MACC1 and other genes, which show correlation with MACC1 as prognostic biomarkers and which ideally are functionally linked in the process of metastasis formation as either MACC1 target genes or by cooperating with MACC1 mediated signaling. Such genes could be MET, S100A4 and others, used as additional targets in combinatorial settings to treat solid cancers.

4.2.2. Hitting twice: MACC1 and MET inhibition

MACC1 is a key regulator of MET, which creates the basis for combined intervention targeting the MET-regulator MACC1 and MET itself. This is supported by the fact that the most frequent event in cancers for MET activation is the overexpression of the structurally unaltered receptor protein, whereas genetic alterations of this receptor molecule are relatively rare events [88]. This overexpression leads to the overactivation of the MET-mediated cell signaling, which is associated with aggressive tumor growth and poor prognosis of patients. Here, the link between MACC1 as transcriptional regulator and MET as target comes into play. In this context, inhibiting MACC1 as key trigger of MET overexpression would represent one component in combination therapies and MET inhibition will be the second component. Such MET inhibition will then affect all downstream signaling pathways, such as MAPK, PI3K/AKT, signal transducer and activator of transcription (STAT), and also nuclear factor κB (NF- κB) signaling, as these are tightly regulated by MET [89]. Thus, concerted inhibition of both molecules might lead to more effective and pronounced inhibition of tumor cell growth and metastasis formation.

For the interference of MET signaling numerous inhibitors came into focus, which aim at different levels of MET activation: interfering with the MET ligand HGF, to prevent receptor activation, MET receptor antagonists (e.g. rilotumumab), and receptor tyrosin kinase inhibitors (e.g crizotinib, tivantinib etc.).

The interference with HGF as the MET ligand has been shown to affect the downstream signaling of MET. Such inhibition has been achieved with HGF binding antibodies in solid cancers (e.g. gastric, lung cancer, myeloma), such as ficlatuzumab or rilotumumab. These have already entered clinical phase 1 or phase 2 trials showing improved overall survival and progression-free survival, particularly if combined with erlotinib (for ficlatuzumab), a EGFR tyrosine kinase inhibitor, or combined with capecitabine (for ritolumumab), a 5-fluorouracil anti-metabolite prodrug [90,91].

Another strategy aims directly at the MET receptor molecule, as this has been done by using anti-MET antagonists, represented by onartuzumab. This antibody has been tested in numerous clinical phase 2 and 3 trials in different solid cancer entities (gastric, lung, breast cancer) as monotherapy and in combination, mainly with erlotinib [92,93]. For both, the anti-HGF as well as the anti-MET antibody therapies showed best efficacies in MET overexpressing tumors and, if combined with other small molecule inhibitors, acting on additional signaling pathways to prevent signaling escape of the tumor cells.

The small molecule MET-specific class I inhibitors tivantinib (ARQ197) and savolitinib (AZD6094), which act on the ATP binding site, show good activity in vitro and in vivo. Similarly, the non-selective (multi-target) class II inhibitors crizotinib (an anaplastic lymphoma kinase (ALK), proto-oncogene 1, receptor tyrosine kinase (ROS), macrophage stimulating 1 receptor MST1R (RON) and MET inhibitor) and cabozantinib (a VEGFR2, KIT proto-oncogene receptor tyrosine kinase (KIT), RET proto-oncogene tyrosine-protein kinase receptor (RET) and MET inhibitor) exert their therapeutic potential via MET tyrosine kinase inhibition. Clinical testing of tivantinib and savolitinib demonstrated progression free survival and partial responses in a variety of solid cancers, where patients with MET overexpression and in the context of

KRAS mutational status show highest benefit of these therapies [94,95]. The multi-target inhibitors crizotinib and carbozantinib exerted their activity in MET overexpressing and exon 14 skipping mutation (results in delayed MET degradation and prolonged signaling) harboring patients of different solid tumor types [96]. These kinase inhibitors thereby do have potential of being combined in anti-MACC1 and MET therapies.

Therefore, identifying patients with high levels of MET or HGF expression and of MACC1 overexpression are primary candidates for combining MACC1 and HGF/MET therapies for improved therapeutic outcome, since the HGF/MET signaling axis is one of the most prominent signaling pathways driving tumor genesis, disease progression, metastatic spread and also resistance to anticancer treatment.

4.2.3. Therapeutic targeting of MACC1 and S100A4

The causal role of such biomarkers like MACC1 and S100A4 consequently leads to the approach of metastasis intervention by targeting these molecules. However, despite the overwhelming acknowledgement of the role of MACC1 and also S100A4 in solid cancers, inhibitors for these molecules are still under-investigated. Using a human S100A4 promoter-based HTS employing the library of pharmacologically active compounds (LOPAC) we already identified first transcriptional inhibitors of the metastasis gene S100A4. Among the best candidates, we identified the FDA-approved NSAID sulindac, the anti-biotic calcimycin and the anti-helminthic drug niclosamide. Interestingly, all of these drugs intervene in the Wnt/β-catenin signaling pathway, reduced cell motility in vitro, and more importantly, significantly restricted metastasis formation in mice [97–99]. Translation of these preclinical findings on metastasis inhibition by repositioning of small molecule drugs is currently underway with the FDA-approved anti-helminthic drug niclosamide by a clinical phase II trial: Drug trial to investigate the safety and efficacy of niclosamide tablets in patients with metastases of a CRC progressing after therapy; EudraCT 2014-005151-20, NCT02519582; recruiting patients since 8/2015 [100]. Drug-induced S100A4 modulation is monitored for therapy response using our blood-based S100A4 assay in conjunction with HPLC determination of niclosamide in patient blood.

The crucial roles of MACC1 and S100A4 as prognostic biomarkers as well as their combinatorial assessment in patients are currently investigated. We demonstrate in tumors as well as in patient blood the beneficial role of combining both biomarkers for improved prognosis for CRC [56], gastric [58] and ovarian cancer [60] patients. Therefore we hypothesize a significant benefit for the patients when being simultaneously treated with drug combinations acting on both molecules, MACC1 and S100A4.

We developed strategies for molecularly targeting MACC1 and also S100A4 for metastasis restriction at the transcriptional level. HTS identified small molecule inhibitors for these two proteins, which inhibit their transcription leading then to reduced cell migration and invasion in vitro and, more importantly, to metastasis restriction in vivo: For MACC1, lovastatin and rottlerin [24], for S100A4 niclosamide and calcimycin [98,99]. For both genes, we developed intervention strategies, which have shown to significantly inhibit biomarker-induced metastasis in mouse models, when applied as monotherapy.

Since the ultimate goal is the restriction of solid cancer metastasis, novel molecularly targeted therapies using FDA-approved drugs are of highest clinical relevance. Such combinatorial approaches are hitting causal metastasis inducing genes, which might result in additive or even synergistic metastasis restriction or prevention. Finally, the development of combinatorial personalized interventions for restriction and prevention of cancer progression and metastasis might improve patient survival.

4.2.4. Combination of anti-angiogenic and MACC1 therapy

MACC1 was shown to upregulate VEGF-A and VEGF-C/D expression and signaling, thereby promoting angiogenesis by the vasculogenic mimicry of tumors, which in turn leads to accelerated tumor growth [64,65]. Combined inhibition by either specific antibodies that act on the ligand VEGF (e.g. bevacizumab, ramucirumab) or receptor tyrosine kinase inhibitors (e.g. apatinib, sorafenib) might improve therapeutic efficacies.

Bevacizumab (avastin) is selectively binding to VEGF-A and inhibits its receptor binding, thereby preventing the growth and maintenance of tumor blood vessels and impairing tumor growth [101,102]. VEGF-A is upregulated in a wide range of human tumors and has been associated with a worse prognosis and an increased incidence of disease recurrence. Phenotypic changes associated with angiogenesis inhibition include changes in vessel structure, vascular permeability, partial pressure of oxygen and a decrease in interstitial fluid and in tumor blood perfusion and volume. Monotherapies with anti-angiogenic antibodies have only shown limited efficacies, whereas combination treatments with chemotherapeutic drugs improved therapeutic outcomes [102,103]. Hitting MACC1 and its expression target VEGF-A will most probably be of value for increased anti-tumoral efficacy and might contribute to interfere with metastasis establishment via inhibition of metastatic vascularization.

Apart from the therapeutic targeting of VEGF with specific antibodies, use of inhibitors, which target both, VEGFR tyrosine kinase and the MET tyrosine kinase (such as altiratinib) will also be of value, since such inhibitors are acting on different signaling pathways, which are also linked to MACC1 action [104].

Other rather non-selective VEGF inhibitors of value in combinations with anti-MACC1 therapies might be axitinib, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib and sunitinib. These approved small molecule inhibitors have anti-angiogenic activities, but do also hit alternative targets such as FGF and PDGF signaling. In fact, anti-angiogenic inhibitors with multiple molecular targets could be more promising as pan-target drugs to better prevent escape mechanisms of tumors [105].

4.2.5. Inhibiting MACC1 and TWIST

The tight connection between MACC1 and TWIST1 has been shown for the two molecules acting as valuable prognostic biomarker pair but also as causative players for tumor vascularization in the process of vascular mimicry. Regarding cancer therapy, TWIST1 is also associated with cancer resistance, which adds to the value of this protein as therapeutic target to improve therapy efficacies [106]. In this regard, inhibiting TWIST1 and MACC1 might represent a useful strategy to interfere in metastasis formation, angiogenesis and drug resistance. The major drawback here is the limited availability of TWIST1 inhibitors. Tamoxifen was found to accelerate proteasomal degradation of TWIST1 in vitro [107]. Further, paclitaxel was shown to decrease TWIST1 expression in Hep-2 cells in vitro and quercetin reduced TWIST presence in association with reduced cell migration [108]. Although currently the inhibitory repertoire of TWIST inhibitors is rather small, the combined TWIST and MACC1 inhibition will have potential for novel combination therapies to treat solid cancers and their metastasis.

4.2.6. Combined therapies against MACC1 and Wnt signaling

The Wnt/β-catenin pathway has importance for normal development and its deregulation leads to neoplastic transformation and tumor progression in association with overexpression of target genes such as MYC or cyclin D1 [109]. Our results from vil-MACC1/ApcMIN transgenic mice showed the cooperation of the Wnt-signaling-pathway and MACC1 action for tumor formation [34]. Molecular analysis revealed increased Wnt and pluripotency signaling and a upregulation of the pluripotency markers Oct4 and Nanog in the tumors of vil-MACC1/ApcMin mice. The relation between MACC1 and Wnt/β-catenin signaling was further supported by the study of Meng et al., where the functional relationship of β-catenin, MET expression, and MACC1 was shown to be decisive for tumor growth and metastasis formation in nasopharyngeal carcinoma [110]. Thus, Wnt-inhibitors targeting Wnt

signaling and thereby exerting effects on Wnt target genes will provide new therapeutic options to interfere with the MACC1/Wnt/β-catenin signaling axis. Such Wnt inhibitors will then serve as potential combinatorial drugs for anti-tumoral and anti-metastatic therapies.

For Wnt-pathway directed therapies drugs have already been developed, which act at the level of Wnt ligand secretion (O-acyltransferase/porcupine inhibitors), at the level of Wnt ligand binding (fusion protein of truncated frizzled receptor 8 and antibody Fc, anti-Wnt antibody) or at the level of β-catenin (small molecules or peptide mimetic). The porcupine inhibitors ETC-159 and LGK974 are currently in clinical testing in patients suffering from different advanced solid cancers and show some first effectiveness [111,112]. Similarly, the inhibitors ipafricept (OMP-54F28) and vantictumab (OMP-18R5) are effective in reducing metastasis and reducing cancer stem cell frequencies, improve chemosensitivity and are currently tested in clinical phase I studies in refractory solid cancers [113,114]. These inhibitors, which act at the Wnt receptor/ligand level of signaling, demonstrate the effectiveness of inhibiting Wnt-signaling for cancer therapy at this particular upstream pathway-level. Inhibition of further downstream signaling mediated by β-catenin is another promising approach. Here, the small molecule inhibitor PRI-724 is in focus, which inhibits the interaction of β-catenin and the CREB-binding protein, which leads to cancer stem cell differentiation and increased sensitivity towards chemotherapeutics [115,116]. The peptide mimetic CWP232291 (CWP291) interferes with β-catenin transcriptional activity lowering expression of its target genes survivin and cyclin D1. Both inhibitors are also in clinical testing.

Another promising approach for Wnt-inhibition is the use of repurposing drugs such as the NSAID celecoxib, sulindac or the anti-helminthic niclosamide [97,99,117,118]. In pre-clinical studies celecoxib showed suppression of cancer stem cell renewal, inhibited EMT and improved chemosensitivity. The NSAID sulindac increases β-catenin degradation and thereby interferes with Wnt-signaling. Niclosamide is acting on formation of the TCF4/β-catenin complex, which in turn reduced expression of β-catenin target genes, including S100A4 as one key metastasis gene [99].

In summary, different levels of Wnt-inhibition provide a feasible rationale for combined therapies aiming at Wnt-signaling and at MACC1 signaling to effectively interrupt this malicious interplay.

4.2.7. Targeting MACC1 and PI3K signaling

Knockdown experiments of MACC1 have demonstrated that PI3K/AKT signaling can be activated by MACC1 in esophageal cancer [119] as well as in osteosarcoma, since MACC1 knockdown led to increased activity of the PI3K antagonist PTEN. Additionally, activation of PI3K/AKT signaling by MACC1 induces EMT and expression of its target genes MYC, cyclin D1/E, MMP2 and MMP9 [120,121]. In fact, such data show, that the interconnection of different key signaling pathways such as PI3K, but also Wnt and MET signaling provokes the design of combinatorial treatments in conjunction with MACC1.

5. Comparison of reported combinations of MACC1 with co-expression in the pan-cancer analysis

We checked whether the genes reported in clinical-experimental studies together with MACC1 showed co-expression with MACC1 in the 33 cancer types of TCGA (Table 1). Only three of these genes correlated significantly with MACC1 in more than the half of the investigated cancer types: MMP7 (24 cancer types), MET (19 cancer types) and HGF (18 cancer types). MET represents the firstly discovered regulatory target of MACC1 and was confirmed in numerous studies supporting this results at a high level of evidence [5,17–25,27,28,35–47]. In line with the clinical-experimental studies, co-expression of MET and MACC1 was observed in 19 cancer types of TCGA including all six types of adenocarcinoma investigated. However, although CRC represents the most frequently studied entity in this context, the correlation of MET mRNA and MACC1 mRNA - although highly significant - was only moderate in this cancer type (COAD: $\rho = 0.31$, READ: $\rho = 0.37$). Stronger correlations of MET and MACC1 were detected in other cancer types including thyroid carcinoma ($\rho = 0.84$), prostate adenocarcinoma ($\rho = 0.80$), testicular germ cell tumors ($\rho = 0.63$), kidney papillary carcinoma ($\rho = 0.59$), uveal melanoma ($\rho = 0.58$), pancreatic adenocarcinoma ($\rho = 0.54$) and further cancer types. Thus, while there is a strong correspondence between the big data analysis and the mechanistic studies in this case, the big data analysis can help to prioritize cancer types for experimental investigation of the relationship of MET and MACC1 in future.

The tyrosine kinase MET has been identified as the receptor for HGF [122]. In the big data analysis, significant co-expression of HGF and MACC1 was observed in 18 cancer types. Interestingly, these cancer types were not the same, where MET and MACC1 co-expression was observed. For example, significant HGF and MACC1 co-expression was observed only in three of the six adenocarcinoma types under investigation, while MET and MACC1 were co-expressed in all of them. The strongest positive correlations between HGF and MACC1 was detected in testicular germ cell tumors ($\rho = 0.66$), while correlations in other cancer types were smaller than 0.5.These results are suportive for a scenario where the mechanism of activation of the HGF/MET axis by MACC1 is different in different cancer types.

In a transgenic MACC1 mouse model, differential expression of

Table 1
MACC1 co-expression analysis of thirteen genes that were reported in combination with MACC1 in the literature.

gene	cytoband	cancer types with $\rho > 0$	cancer types with $\rho < 0$	ρ COAD	ρ LUAD	ρ PAAD	ρ PRAD	ρ READ	ρ STAD
MET	7q31.2	19	2	0.31	0.26	0.54	0.8	0.37	0.41
HGF	7q21.11	18	1	0.22	n.s.	−0.23	0.44	0.21	n.s.
SPON2	4p16.3	8	6	n.s.	0.14	n.s.	−0.31	n.s.	−0.15
YBX1	1p34.2	5	11	n.s.	−0.17	n.s.	−0.15	n.s.	−0.13
S100A4	1q21.3	15	3	n.s.	n.s.	0.26	0.29	n.s.	−0.17
VEGFA	6p21.1	11	3	0.17	n.s.	0.28	n.s.	n.s.	0.17
VEGFC	4q34.3	11	7	n.s.	n.s.	−0.16	0.13	0.26	−0.29
VEGFD	Xp22.2	6	9	0.1	0.12	−0.49	n.s.	0.21	−0.21
MMP2	16q12.2	8	5	n.s.	0.13	n.s.	0.36	n.s.	−0.17
MMP7	11q22.2	24	1	n.s.	0.24	0.32	0.62	n.s.	0.1
MMP9	20q13.12	8	8	n.s.	n.s.	n.s.	0.3	n.s.	−0.15
TWIST1	7p21.1	7	8	n.s.	n.s.	n.s.	n.s.	n.s.	−0.17
TWIST2	2q37.3	7	10	n.s.	−0.09	−0.31	0.37	n.s.	−0.28

Numbers of the cancer types (out of a total of 33) exhibiting significant ($p < 0.05$) positive correlations and significant negative correlations of the gene with MACC1. Numerical values of the correlations in six types of adenocarcinomas. ρ = Spearman correlation with MACC1. COAD = colon adenocarcinoma, LUAD = lung adenocarcinoma, PAAD = pancreatic adenocarcinoma, PRAD = prostate adenocarcinoma, READ = rectal adenocarcinoma, STAD = stomach adenocarcinoma.

extracellular matrix modulators including MMP7 and MMP9 was detected compared to control mice [34]. In the big data analysis, we detected significant positive correlations between MMP7 and MACC1 in a high number of 24 out of 33 cancer types (73%). The strongest MMP7-MACC1 correlations were detected in testicular germ cell tumors ($\rho = 0.64$), thyroid carcinoma ($\rho = 0.64$), prostate adenocarcinoma ($\rho = 0.62$), uveal melanoma ($\rho = 0.59$) and liver hepatocellular carcinoma ($\rho = 0.55$), while correlations in other cancer types were smaller than 0.5. Thus, for MMP7 the results of the big data analysis were in line with the results from the mouse model. On the other hand MMP9 was co-expressed with MACC1 in a much smaller number of eight cancer types.

For most of the genes in Table 1 (all except MET, HGF and MMP7), significant co-expression with MACC1 was detected in a minority (5–15) of cancer types. Thus, potential regulatory mechanisms connecting MACC1 and these genes are expected to be active only in a subset of cancer types, but inactive in the majority of cancer types.

Vice versa, we asked if the nine transcription factors (and the corresponding sequence motifs in the gene promoters) from the big data analysis (Fig. 4C) have been experimentally investigated for a mechanistic connection to MACC1. Performing a PubMed search of MACC1 together each of the genes ELF1, ETS2, ETV4, TEAD1, FOXO4, NFE2L1, ELK1, SP1 and NFE2L2, we detected three articles describing binding of MACC1 to SP1 binding sites [17,24,123], but no articles reporting combinations of MACC1 together with any other of the nine genes. In summary the big data analysis generated new hypotheses on connections between specific hubs of transcriptional control and MACC1 expression that warrant future experimental examination.

6. Outlook

The thorough computational correlation analyses and the real-life data presented in this review revealed the great potential of combining prognostic and potentially predictive biomarkers. This was exemplified for the metastasis driver gene MACC1, which was shown to be associated with other genes with function in cancer progression and metastasis formation. More importantly, such analyses do also provide valuable insights into causal links between such genes or gene families, as it was demonstrated for MACC1 and MET interrelation not only as improved biomarker pairing, but also as causative biological link, by which the two functionally complement each other. Based on these bioinformatic analyses new therapeutic intervention points can be clearly defined by which multiple targets are hit for more effective intervention in vital cancer signaling pathways. Exemplified for combination targets like MACC1 and MET or MACC1 and S100A4, such combinatorial therapy will strike at different points of intervention to better prevent metastasis and tumor growth and to better hinder cancer cells of using alternative escape signaling pathways.

The computational analysis might further be applied to gene combinations, which have already been described, but represent only a singularity in their reported appearance. In this regard, MACC1 was once-only described of being correlated as prognostic pairing with MYC, axin (a protein phophatase 1), vasohibin (a tyrosine caroxypeptidase), KAI6 (membrane glycoprotein), FAK tyrosine kinase or SOX17 homeobox protein [124–129]. Further, such combinations are once-only described for use as predictive biomarkers, where MACC1 and the monocarboxylic acid transporter 1 (MCT1) or the apotosis regulators MCL1/Bcl-2 is linked to sensitivity towards chemotherapy (e.g. 5-FU) or apoptotic signaling [29,130]. In this context, MACC1 and biological cooperative partners in migration, invasion and metastasis (ORAI1, STIM1, CYR61, Pim-3) as well as tumor cell metabolism (PFKFB2, DLC3) and its rewiring are published once-only and could also be promising combinations to be further evaluated for their potential by computational analyses [131–135]. Computational analyses might add to the validation of such combinations and improve their overall use and importance.

Another important issue for computational correlation analyses as described here is, that biomarker combinations are unveiled for tumor entities, which were initially not anticipated or in focus. By this, MACC1 and combined other genes will be revealed as useful biomarker combination for additional tumor types, which then broadens their use as cross-entity diagnostic tool. As MACC1 was initially defined and perceived as biomarker in CRC, it meanwhile experiences tremendous extension of use to other solid cancers. For example, the big data analysis revealed very high correlations beween MET and MACC1 in thyroid cancer and in prostate cancer ($\rho \geq 0.8$), while – to our knowledge – MACC1 has not been investigated in experimental or theranostic studies in these cancer types. Thus, the big data analysis can help to prioritize cancer types for future analysis of MACC1 and MACC1 combinations.

The fact that the big data analysis determined nine nine transcription factors (ELF1, ETS2, ETV4, TEAD1, FOXO4, NFE2L1, ELK1, SP1 and NFE2L2), which are linked to MACC1, opens an entirely new area of options. Thereby new genes will be identified, that are transcriptionally regulated by these particular transcription factors. Examples are transcriptional targets of TEAD1, such as the anti-apoptotic protein Livin [136], mesothelin or FOXO4-regulated genes like the growth arrest and DNA-damage inducible protein GADD45A, the cyclin dependent kinase inhibitor 1 CDKN1A, etc. These genes could then further be analyzed for their potential to serve as additional biomarkers and also as therapeutic targets.

It is a strength of omics data analyses to allow a comprehensive data-driven (and thus researcher-unbiased) view on tumor molecular biology. Here, using genome-wide mRNA expression data, many new genes showing strong and recurrent MACC1 correlation across cancer types could be identified. Thus, the MACC1 combinations and the corresponding cancer types that are reported in the present literature might represent only the tip of the iceberg. On the other hand, the interpretation of the big data analysis results is limited by correlation research methodology inherent in this approach. Thus, on the way to translation into clinics, experimental studies are warranted to shed light on the mechanisms behind co-expression of the new genes with MACC1 and possible ways of therapeutic intervention.

Apart from such new gene combinations, other regulatory molecules are of value for biomarker uses. Such molecules are microRNAs (miRNA), circular RNAs (circRNA) and long noncoding RNAs (lncRNA). Such RNAs play important roles in regulation of gene expression and are involved in cancer progression as well as cancer metastasis [137]. For the gene MACC1, a multitude of miRNAs has been identified to significantly reduce MACC1 expression, such as by miR-141, miR-143 [138], miR-200a [139], miR-218 [87], miR-433 [140] miR-485 [141] and many others [6]. Alternatively, lncRNAs such as MACC1-AS1 is acting on MACC1 mRNA stability, which is rather tumor promoting in its function [142]. Alternatively, the circRNA PDE8A was shown to increase MACC1 levels in pancreatic cancer by competitive miR-338 binding, thereby counteracting its inhibitory effect on MACC1 expression [143]. Such listings are short glimpse to a broad class of alternative molecules involved in expression/signalling regulation of cancer genes with great potential as additional biomarkers on one hand and also promising therapeutic targets or even therapeutic tools on the other [144].

Still underrepresented, but nevertheless of potential importance are markers of genetic alterations, which might add to an improved diagnosis for cancer. In this regard, single nucleotide polymorphisms (SNP) and copy number variations (CNV) might gain more interest if exploited in the context of MACC1. MACC1 SNPs were identified in intronic regions 1, 2 and 6 as well as in the coding region of the gene [145,146]. Copy number gain (CNV) and overexpression of MACC1 correlated with unfavorable pathologic characteristics, better than overexpression of MET [25].

In conclusion, we linked big data computational analyses with clinical-experimental approaches and created an overlook on MACC1

co-expression and co-regulation enabling hypothesis generation on metastasis related signaling networks and definition of new biomarkers and therapeutic intervention points.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.semcancer.2019.08.010.

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