„Liquid biopsy“ und microRNA Expression in menschlichen Karzinomen - innovative Biomarker

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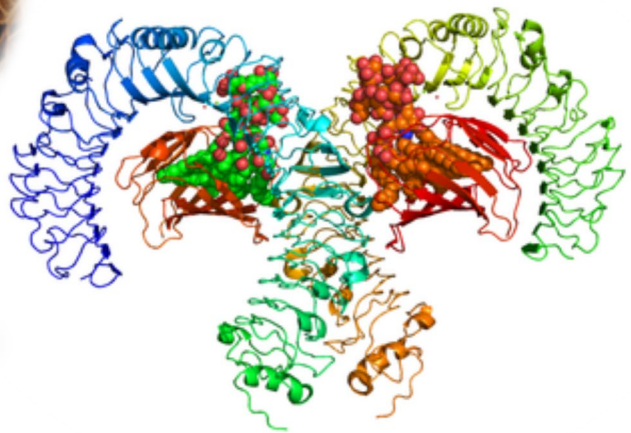
Frühere Forschungsprojekte, *DFG Pr*411/1-12 gefördert:

Karzinogenese im Magen

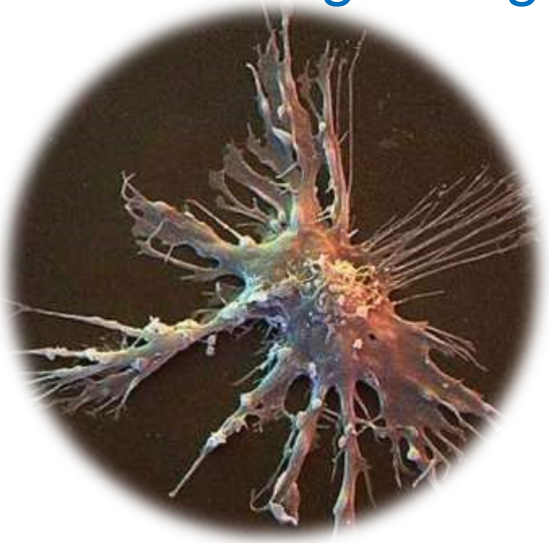
Helicobacter induzierte Karzinogenese

Immunantwort, Toll Rezeptoren und Molekulares Signalling

Helicobacter pylori



Toll-like receptors



dendritic cell

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Bahnbrechende Studien zu neuen Biomarkern von GI Karzinomen:

22nt „MicroRNA Moleküle“ zeigen im *Hierachical Clustering*:
Exzellente Biomarker für GI Karzinome, Lu et al., Nature 2007

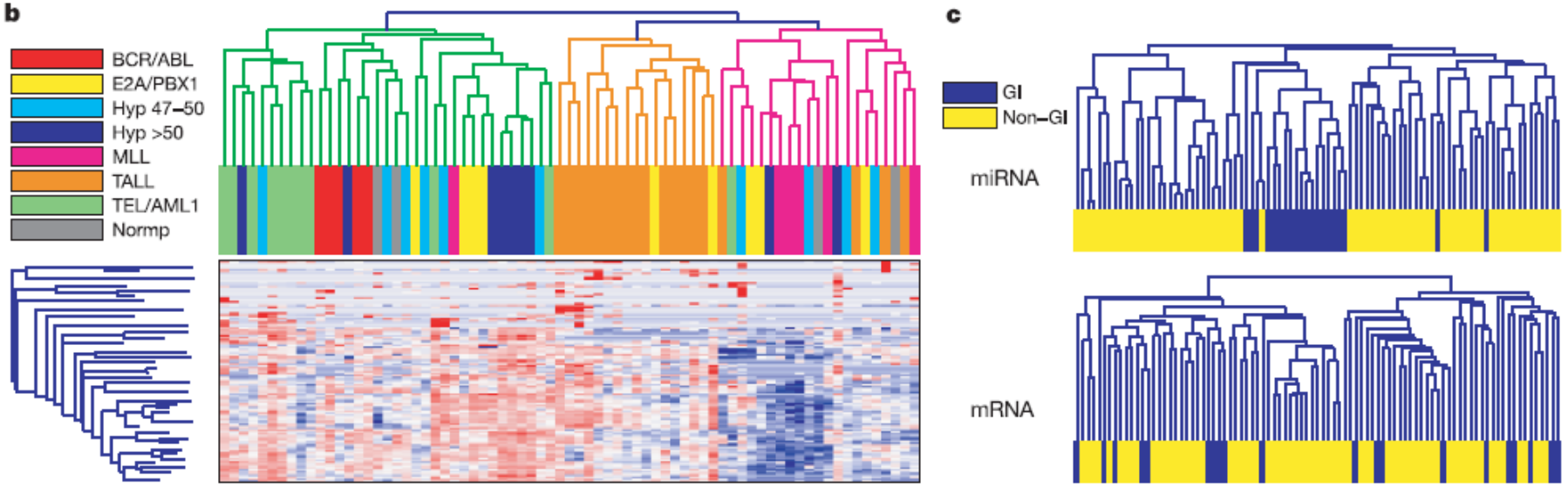
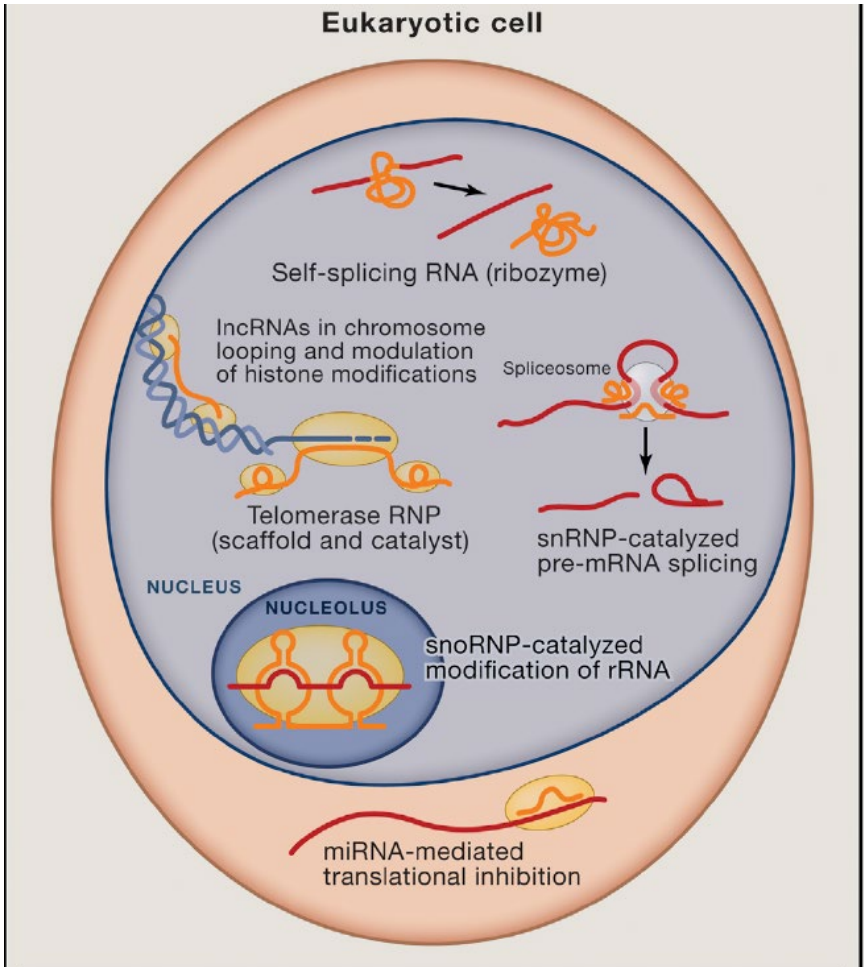


Figure 2 | Hierarchical clustering of miRNA expression. **a**, miRNA profiles of 218 samples from several different tissues were clustered (average linkage, correlation similarity). Samples are in columns, miRNAs in rows. Samples of epithelial (EP) origin or derived from the gastrointestinal tract (GI) are indicated. More detail is shown in Supplementary Fig. 4. **b**, Clustering of 73 bone marrow samples from patients with acute lymphoblastic leukaemia (ALL). Coloured bars indicate the different ALL subtypes. **c**, Comparison of miRNA data and mRNA data. For 89 epithelial samples from **a** that had mRNA expression data, hierarchical clustering was performed. Samples of GI origin are shown in blue. GI-derived samples largely cluster together in miRNA expression space, but not in mRNA expression space. Abbreviations used: Bldr, bladder; Brst, breast; Fcc, follicular lymphoma; Kid, kidney; Lvr, liver; Mela, melanoma; Meso, mesothelioma; Pan, pancreas; Prost, prostate; Stom: stomach; Ut, uterus; AML: acute myelogenous leukaemia; BALL, B-cell ALL; LBL, diffuse large-B cell lymphoma; MF, mycosis fungoides; MLL, mixed lineage leukaemia; TALL, T-cell ALL; Hyper 47–50, hyperdiploid with 47–50 chromosomes; Hyper >50, hyperdiploid with over 50 chromosomes; Normp, normal ploidy. Further details can be found in Supplementary Information.

microRNA sind „small non coding RNA Moleküle“

Expression und Wirkung in Zellkernen von eukaryotischen Zellen:

→ Translationale Kontrolle der Protein-Expression



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LIQUID BIOPSIES IN DER GASTROENTEROLOGIE

Viele Körperflüssigkeiten enthalten exosomale microRNAs (miRNAs), die aufgrund der Stabilität von miRNAs in Exosomen eine neue Klasse von Biomarkern für die frühe und minimalinvasive Krebsdiagnose darstellen könnten.

Liquid Biopsies (Flüssigbiopsien) werden zunehmend als Ergänzung zur (festen) Gewebeproben eingesetzt, da sie es ermöglichen, das Fortschreiten der Krankheit Monate vor der klinischen und radiologischen Bestätigung zu erkennen.

In innovativen Studien werden daher exosomale miRNAs (aus Flüssigkeitsbiopsien) als **Biomarker** bei der Diagnose und Prognose verschiedener Krebsarten beschrieben.

Methodik dieser Forschung, Helios-und UWH Unterstützt:

[microRNA Expression in CRC: Weber, Amar und Prinz Oncotarget 2018]

RNA und Blutproben aus menschlichen Colorektalen Karzinomen, n=50 Tumoren und n=50 korrespondierenden Normalgeweben

Illumina Sequenzierung der vollständigen microRNA expression

Expression in **relativer** Hinsicht vs. Normalgewebe (log-xfach)

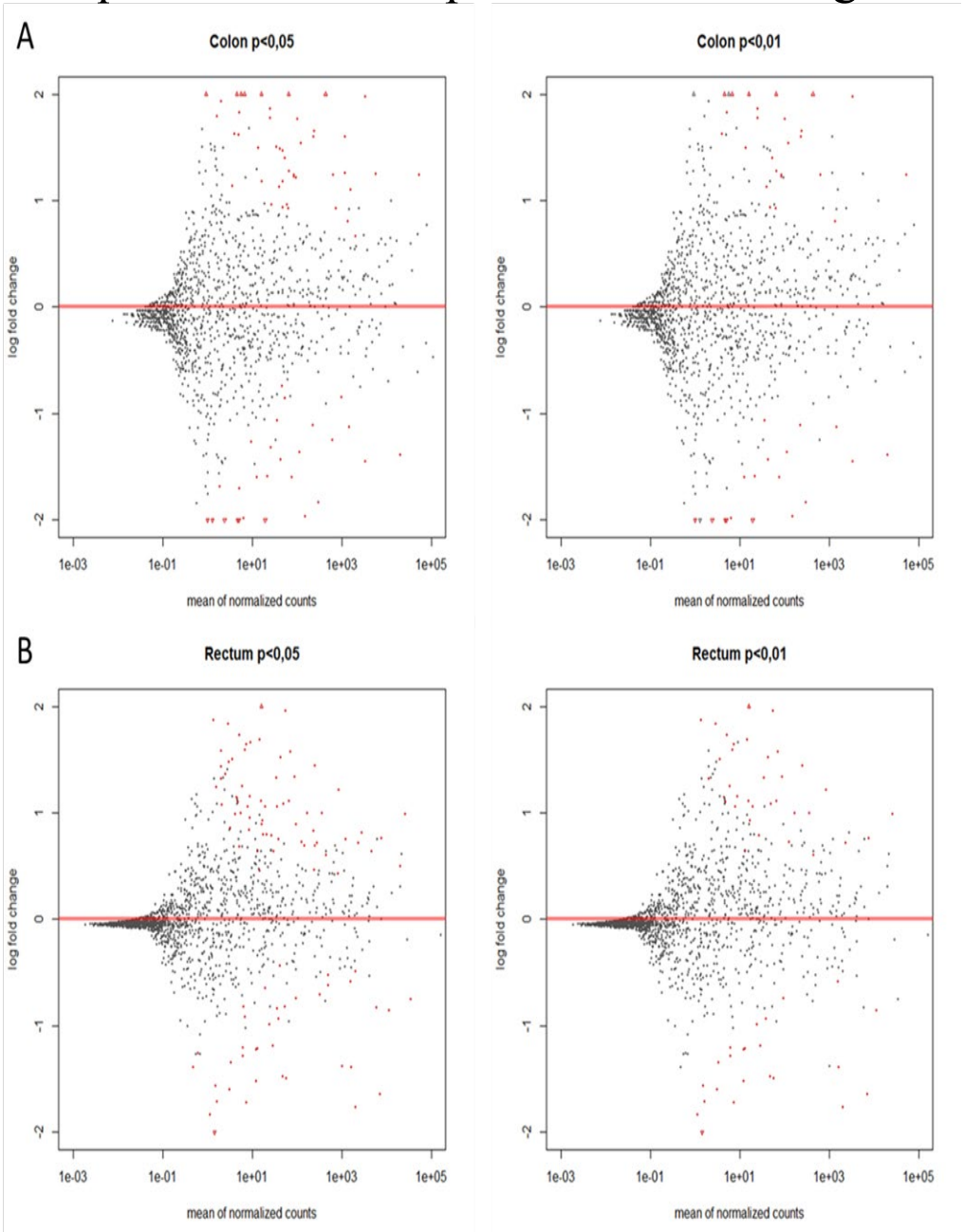
Expression in **absoluter** Hinsicht (Kopienanzahl)

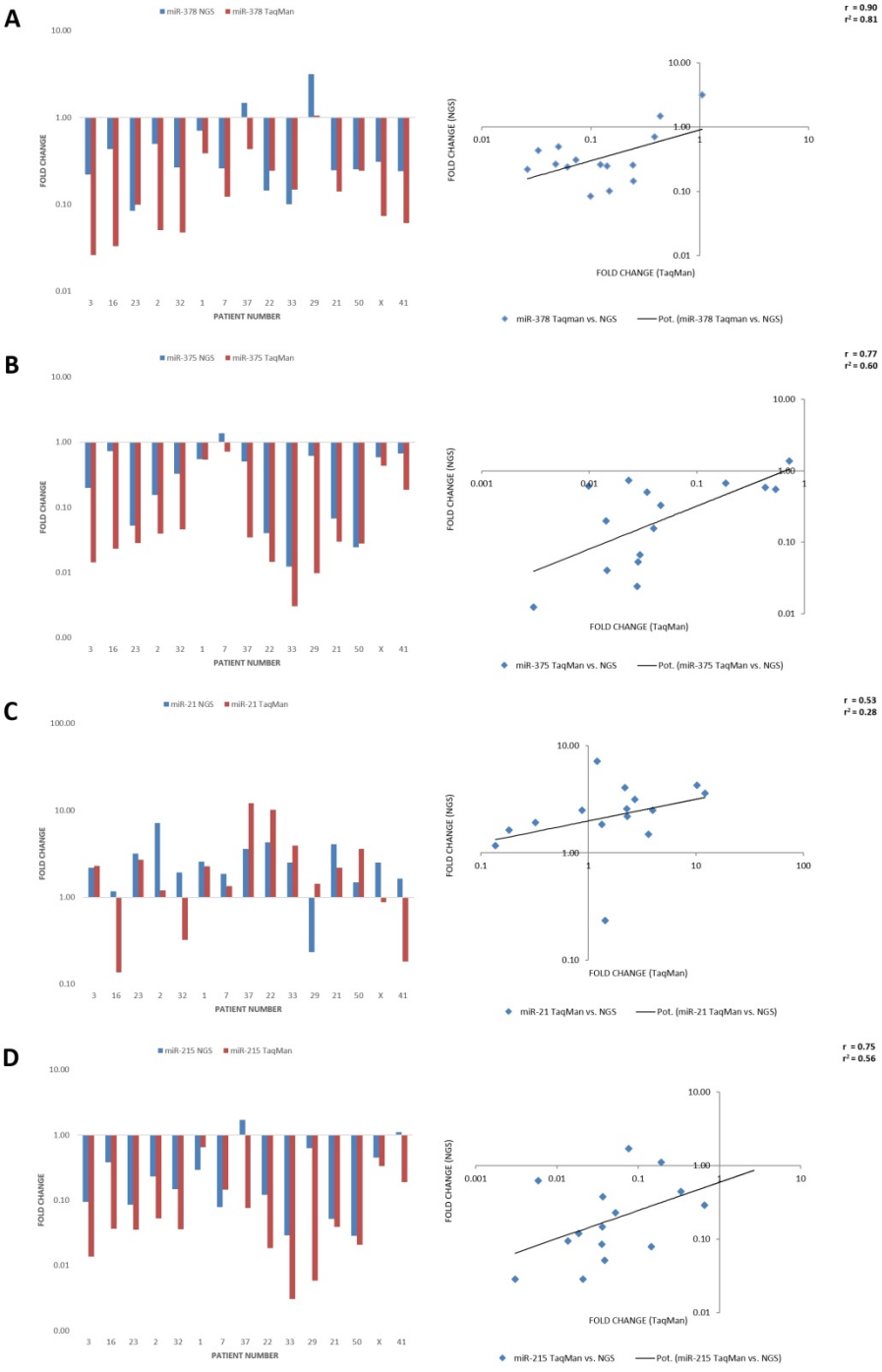
Statistische Auswertung mit Punktgrafiken, Heatmap, relativ.

Absicherung durch TaqMan Analyse

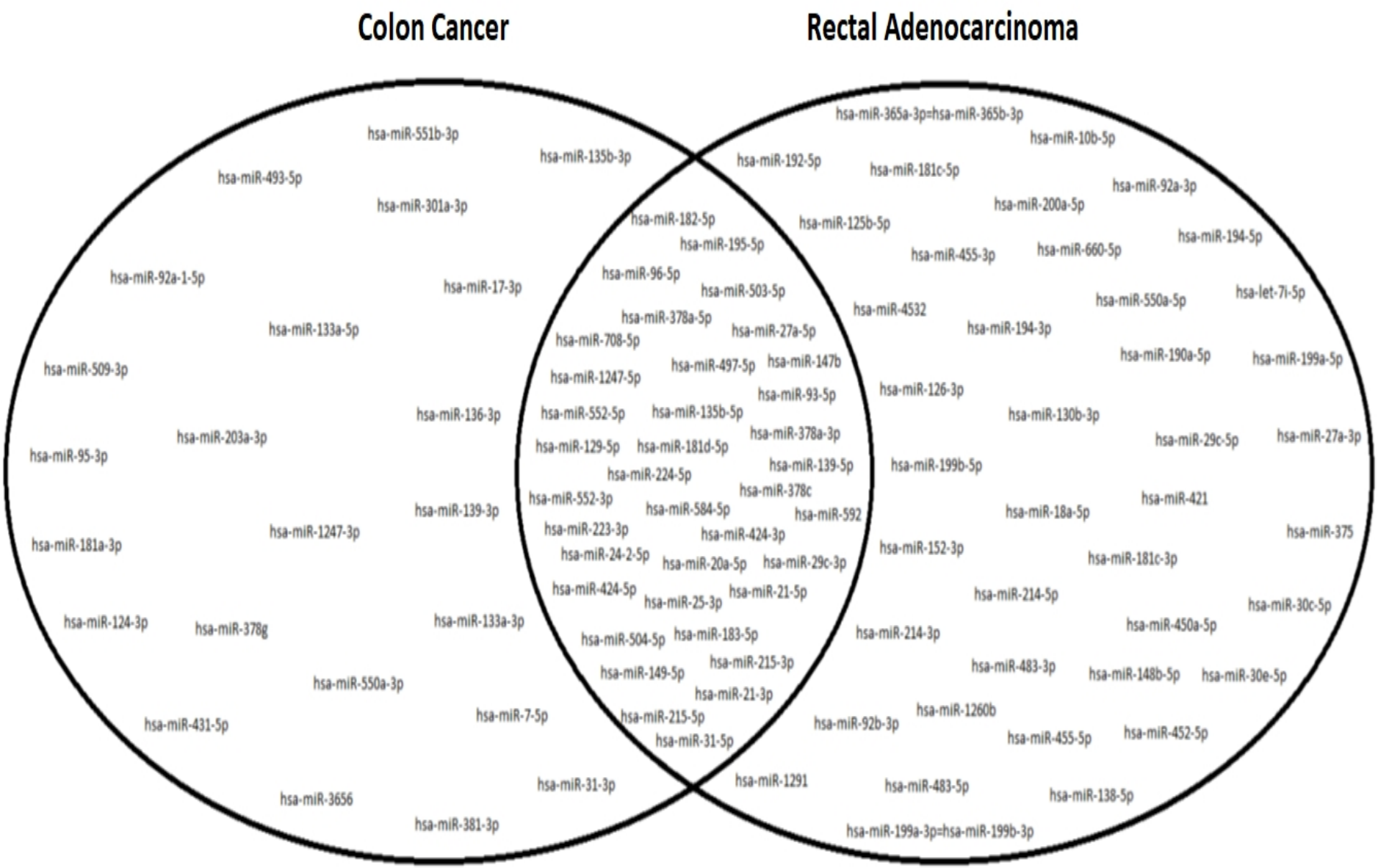
Vorhersage-Wert einzelner microRNA Moleküle mittels ROC Analyse

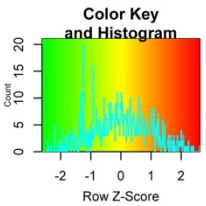
Vollständige microRNA Expressionsanalyse durch Illumina Sequenzierung, relativ und quantitativ zur Expression in Normalgewebe



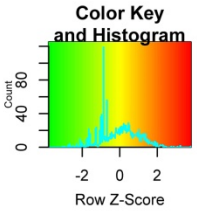


Bestätigung der microRNA Expression nach Illumina Sequenzierung durch TaqMan PCR, relativ und quantitativ zur Expression in Normalgewebe

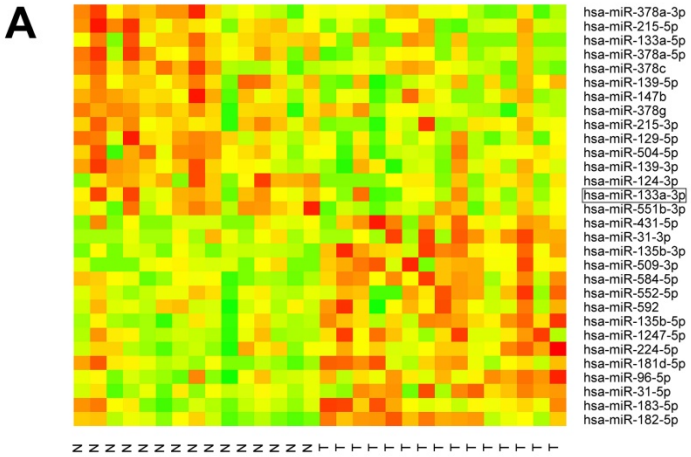

Colon Cancer
Rectal Adenocarcinoma
hsa-miR-551b-3p
hsa-miR-135b-3p
hsa-miR-493-5p
hsa-miR-301a-3p
hsa-miR-92a-1-5p
hsa-miR-17-3p
hsa-miR-133a-5p
hsa-miR-509-3p
hsa-miR-136-3p
hsa-miR-203a-3p
hsa-miR-95-3p
hsa-miR-139-3p
hsa-miR-1247-3p
hsa-miR-181a-3p
hsa-miR-124-3p
hsa-miR-378g
hsa-miR-133a-3p
hsa-miR-550a-3p
hsa-miR-431-5p
hsa-miR-7-5p
hsa-miR-31-3p
hsa-miR-3656
hsa-miR-381-3p
hsa-miR-182-5p
hsa-miR-195-5p
hsa-miR-96-5p
hsa-miR-503-5p
hsa-miR-378a-5p
hsa-miR-27a-5p
hsa-miR-708-5p
hsa-miR-497-5p
hsa-miR-147b
hsa-miR-1247-5p
hsa-miR-93-5p
hsa-miR-552-5p
hsa-miR-135b-5p
hsa-miR-378a-3p
hsa-miR-129-5p
hsa-miR-181d-5p
hsa-miR-139-5p
hsa-miR-224-5p
hsa-miR-378c
hsa-miR-552-3p
hsa-miR-584-5p
hsa-miR-592
hsa-miR-223-3p
hsa-miR-424-3p
hsa-miR-24-2-5p
hsa-miR-20a-5p
hsa-miR-29c-3p
hsa-miR-424-5p
hsa-miR-21-5p
hsa-miR-25-3p
hsa-miR-504-5p
hsa-miR-183-5p
hsa-miR-215-3p
hsa-miR-149-5p
hsa-miR-21-3p
hsa-miR-215-5p
hsa-miR-31-5p
hsa-miR-365a-3p=hsa-miR-365b-3p
hsa-miR-10b-5p
hsa-miR-192-5p
hsa-miR-181c-5p
hsa-miR-92a-3p
hsa-miR-200a-5p
hsa-miR-125b-5p
hsa-miR-194-5p
hsa-miR-455-3p
hsa-miR-660-5p
hsa-miR-550a-5p
hsa-let-7i-5p
hsa-miR-4532
hsa-miR-194-3p
hsa-miR-190a-5p
hsa-miR-199a-5p
hsa-miR-126-3p
hsa-miR-130b-3p
hsa-miR-29c-5p
hsa-miR-27a-3p
hsa-miR-199b-5p
hsa-miR-421
hsa-miR-18a-5p
hsa-miR-375
hsa-miR-152-3p
hsa-miR-181c-3p
hsa-miR-214-5p
hsa-miR-30c-5p
hsa-miR-450a-5p
hsa-miR-214-3p
hsa-miR-483-3p
hsa-miR-148b-5p
hsa-miR-30e-5p
hsa-miR-1260b
hsa-miR-92b-3p
hsa-miR-455-5p
hsa-miR-452-5p
hsa-miR-1291
hsa-miR-483-5p
hsa-miR-138-5p
hsa-miR-199a-3p=hsa-miR-199b-3p

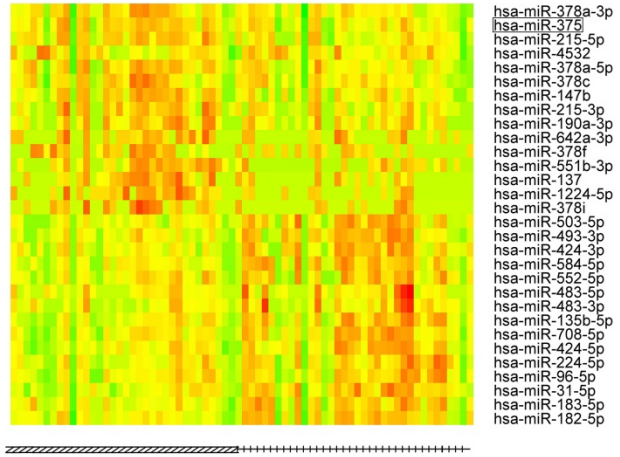


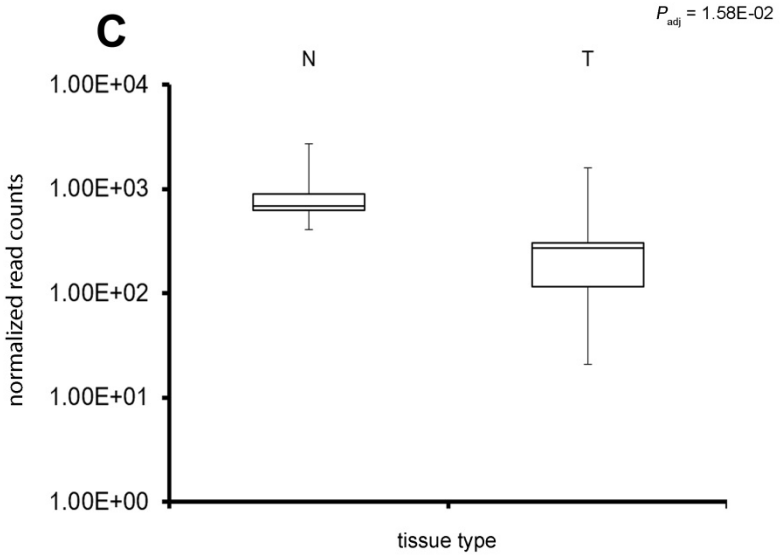
miRNA-133a-3p Kolonkarzinome

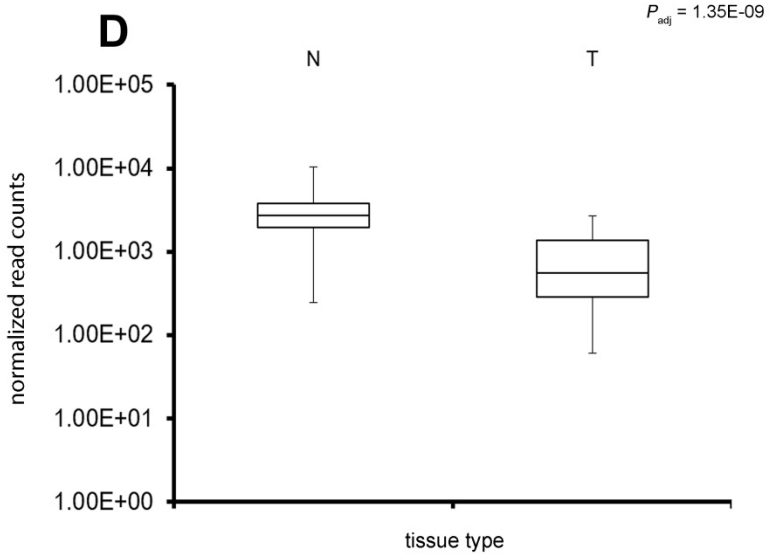


miRNA-375 Rektumkarzinome



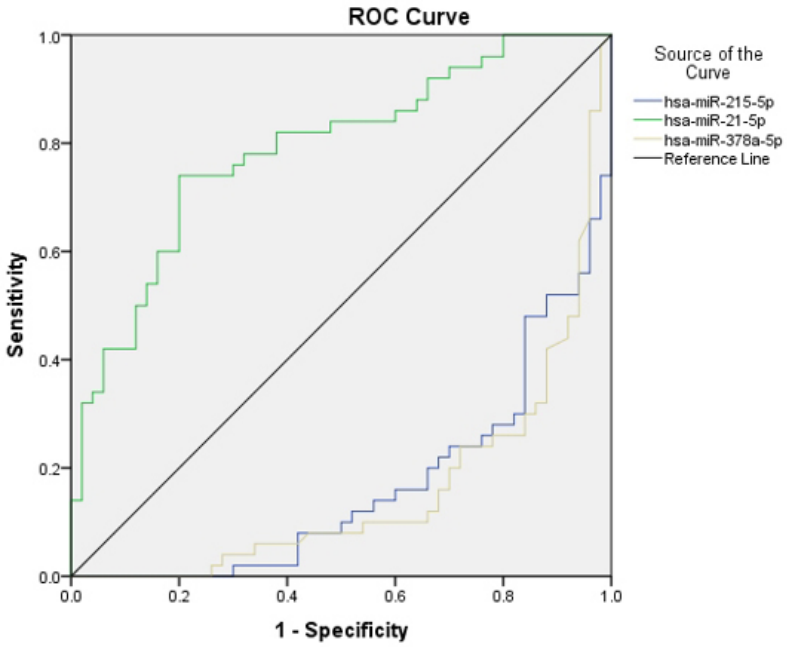






ROC Kurven für KRK gesamt

A



Diagonal segments are produced by ties.

Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
hsa-miR-215-5p	.166	.039	.000	.089	.242
hsa-miR-21-5p	.788	.045	.000	.700	.877
hsa-miR-378a-5p	.158	.040	.000	.079	.236

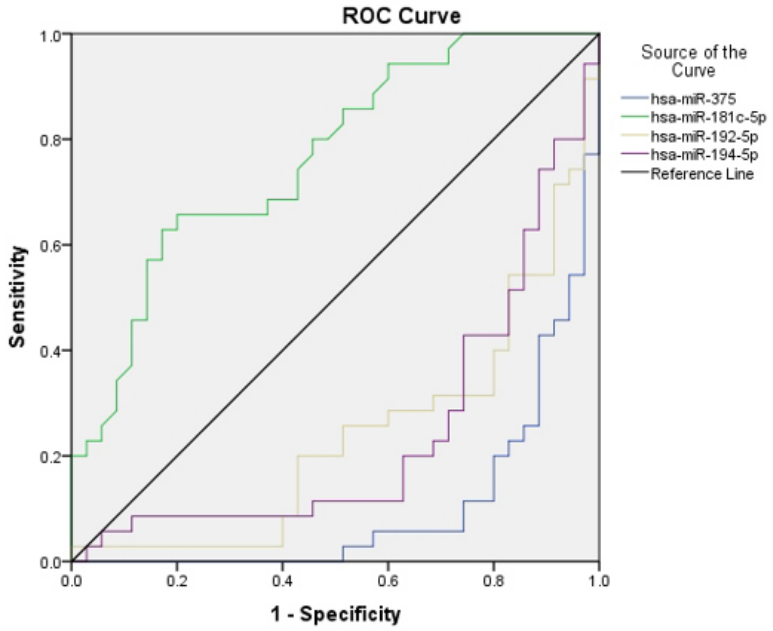
The test result variable(s): hsa-miR-378a-5p has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

ROC Kurven für Rektumkarzinome

B



Diagonal segments are produced by ties.

Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
hsa-miR-375	.100	.037	.000	.028	.172
hsa-miR-181c-5p	.765	.056	.000	.655	.875
hsa-miR-192-5p	.239	.058	.000	.126	.352
hsa-miR-194-5p	.242	.060	.000	.125	.360

The test result variable(s): hsa-miR-181c-5p has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Ergebnisse und Zusammenfassung: microRNA Expression in humanen kolorektalen Karzinomen (TU vs. Normalgewebe)

Weber-D, Amar-L und Prinz-C, Oncotarget 2018:

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(1)microRNA-375 exzellenter Marker für Rektumkarzinome (ebenso im Serum)
(2)miRNA 133a-3p exzellenter Marker für Kolonkarzinome (ebenso im Serum)

Weber D, Amar L, Gödde D, Prinz C. Extensive screening of microRNA populations identifies hsa-miR-375 and hsa-miR-133a-3p as selective markers for human rectal and colon cancer. Oncotarget. 2018 Jun 5;9(43):27256-27267. doi: 10.18632/oncotarget.25535. – IF 3.7

www.oncotarget.com Oncotarget, 2020, Vol. 11, (No. 10), pp: 894-904

Research Perspective

MicroRNA (miR) dysregulation during *Helicobacter pylori*-induced gastric inflammation and cancer development: critical importance of miR-155

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Keywords: Helicobacter pylori; gastric inflammation; gastric cancer; microRNA; miR-155

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ABSTRACT

Dysregulation of noncoding microRNA molecules has been associated with immune cell activation in the context of *Helicobacter pylori* induced gastric inflammation as well as carcinogenesis, but also with downregulation of mismatch repair genes, and may interfere with immune checkpoint proteins that lead to the overexpression of antigens on gastric tumor cells. Numerous miR-molecules have been described as important tools and markers in gastric inflammation and cancer development —including miR-21, miR-143, miR-145, miR-201, and miR-335— all of which are downregulated in gastric tumors, and involved in cell cycle growth or tumor invasion. Among the many microRNAs involved in gastric inflammation, adenocarcinoma development and immune checkpoint regulation, miR-155 is notable in that its upregulation is considered a key marker of chronic gastric inflammation that predisposes a patient to gastric carcinogenesis. Among various other miRs, miR-155 is highly expressed in activated B and T cells and in monocytes/macrophages present in chronic gastric inflammation. Notably, miR-155 was shown to downregulate the expression of certain MMR genes, such as MLH1, MSH2, and MSH6. In tumor-infiltrating miR-155-deficient CD8⁺ T cells, antibodies against immune checkpoint proteins restored the expression of several derepressed miR-155 targets, suggesting that miR-155 may regulate overlapping pathways to promote antitumor immunity. It may thus be of high clinical impact that gastric pathologies mediated by miR-155 result from its overexpression. This suggests that it may be possible to therapeutically attenuate miR-155 levels for gastric cancer treatment and/or to prevent the progression of chronic gastric inflammation into cancer.

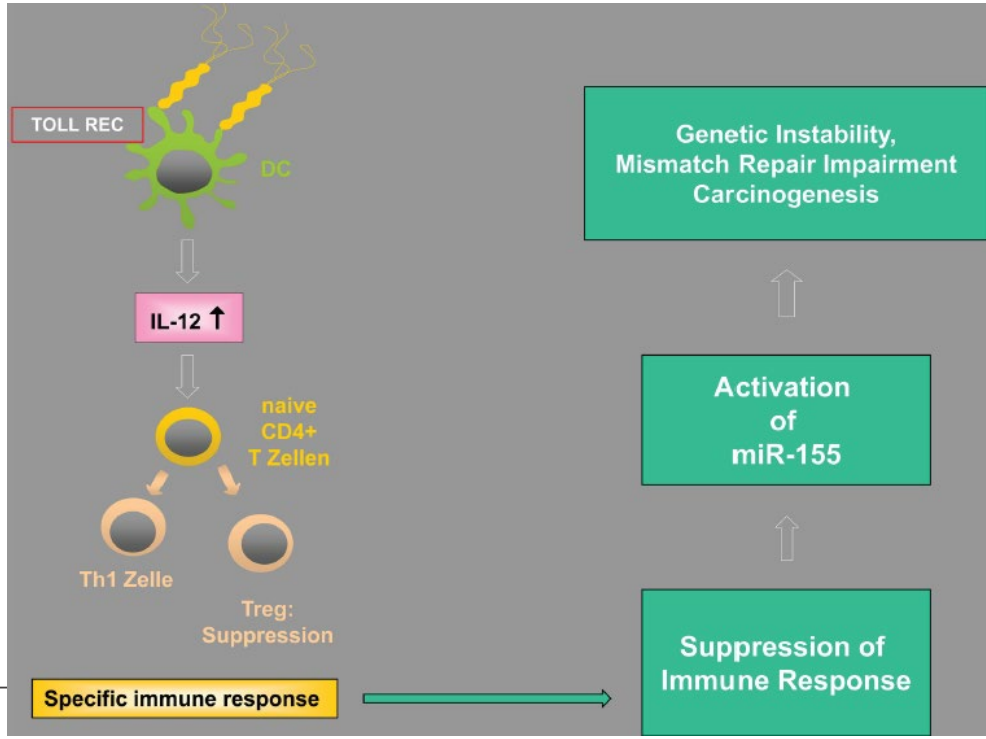
INTRODUCTION: MICRORNA DYSREGULATION AND GASTRIC CANCER

Increasing evidence suggests that microRNA (miRNA) dysregulation has critical impacts on development, as well as inflammation and cancer development [1, 2]. Notably, it seems that human gastrointestinal cancer can be better classified using miRNA expression profiles than mRNA or protein expression profiles [3]. MicroRNAs are non-protein-coding RNAs of ~22 nucleotides, which induce translational repression and/or degradation of their mRNA targets. In complex with argonaute (AGO) proteins, miRNAs can use seed sequences near the 5′ end to base pair with a target mRNA, inducing deadenylation and decay or translational regulation [2]. Consequences of miRNA expression can include post-transcriptional silencing of targeted genes and thereby blocked translation of their target transcripts, and may also prevent apoptosis by binding to promoter units involved in cell cycle regulation. The functional roles of miRNAs are pleiotropic—for example, Let-7 miRNAs play key roles in development, stem cells, and cancer [4].

Lu et al. [3] recently reported that certain microRNAs can be used to profile tumors or tissues especially in gastrointestinal tumors, which have critical functions across various biological processes. Using a new

MicroRNA Expression miR-155 auch relevanter Parameter für die Entstehung von Magenkarzinomen

Helicobacter pylori und EBV assoziierte Karzinome haben vollständig unterschiedliches Profil



Prinz C, Weber D. MicroRNA (miR) dysregulation during Helicobacter pylori-induced gastric inflammation and cancer development: critical importance of miR-155. Oncotarget. 2020 Mar 10;11(10):894-904. doi: 10.18632/oncotarget.27520. – IF: 3,3

Prinz C, Mese K, Weber D. MicroRNA Changes in Gastric Carcinogenesis: Differential Dysregulation during Helicobacter pylori and EBV Infection. Genes (Basel). 2021 Apr 19;12(4):597. doi: 10.3390/genes12040597. – IF 4.1

Wirkung und therapeutischer Ausblick der miR-155 beim Adenokarzinom des Magens

Bei miR-155-T-Zell-bedingten KO-Mäusen wurde die Antitumorimmunität durch Immun-Checkpoint-blockierende (ICB) Antikörper gegen das programmierte Zelltodprotein 1/den programmierten Todesliganden 1 (PD-1/PD-L1) und zytotoxische T-Lymphozyten wiederhergestellt (assoziiertes Protein 4 CTLA-4).
Darüber hinaus stellten Antikörper gegen Immun-Checkpoint-Proteine in tumorinfiltrierenden miR-155-defizienten CD8+-T-Zellen die Expression mehrerer dereprimierter miR-155-Ziele wieder her, was darauf hindeutet, dass miR-155 und ICB überlappende Signalwege regulieren, um die Antitumorimmunität zu fördern.
Insgesamt unterstreichen diese Ergebnisse die starke Fähigkeit von miR-155, die **Antitumorimmunität von T-Zellen zu fördern**, und legen nahe, dass eine Steigerung der miR-155-Expression möglicherweise die Immuntherapien gegen Krebs verbessern könnte

genes

MDPI

Review

Emerging Role of microRNA Dysregulation in Diagnosis and Prognosis of Extrahepatic Cholangiocarcinoma

Christian Prinz [1,2,*], Robin Frese [1,2], Mashiba Grams [1,2] and Leonard Fehring [1,2]

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[2] Lehrstuhl für Innere Medizin 1 der, University of Witten gGmbH, 42283 Wuppertal, Germany
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Abstract: Extrahepatic cholangiocarcinomas, also called bile duct carcinomas, represent a special entity in gastrointestinal tumors, and histological specimens of the tumors are often difficult to obtain. A special feature of these tumors is the strong neovascularization, which can often be seen in the endoluminal endoscopic procedure called cholangioscopy, performed alone or in combination with laserscanning techniques. The additional analysis of microRNA expression profiles associated with inflammation and neovascularization in bile duct tumors or just the bile duct fluid of these patients could be of enormous additional importance. In particular, the dysregulation of microRNA in these cholangiocarcinomas (CCA) was previously reported to affect epigenetics (reported for miR-148, miR-152), inflammation (determined for miR-200, miR-125, and miR-605), and chemoresistance (miR-200b, 204) in patients with cholangiocarcinoma. More importantly, in the context of malignant neovascularization, well-defined microRNAs including miR-141, miR-181, miR-191, and miR-200b have been found to be dysregulated in cholangiocarcinoma and have been associated with an increased proliferation and vascularization in CCA. Thus, a panel of these microRNA molecules together with the clinical aspects of these tumors might facilitate tumor diagnosis and early treatment. To our knowledge, this is the first review that outlines the unique potential of combining macroscopic findings from cholangioscopy with microRNA expression.

Keywords: microRNA; cholangiocellular carcinoma; cholangioscopy; neovascularisation; angiogenetic pathways

check for updates

Citation: Prinz, C.; Frese, R.; Grams, M.; Fehring, L. Emerging Role of microRNA Dysregulation in Diagnosis and Prognosis of Extrahepatic Cholangiocarcinoma. *Genes* 2022, 13, 1479. https://doi.org/10.3390/genes13081479

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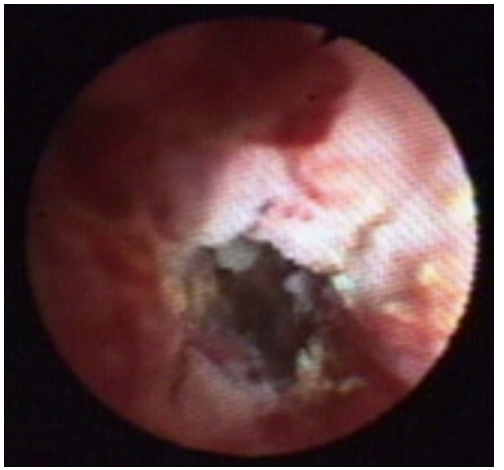
1. Cholangiocarcinoma—Clinical Background

Cancers of the biliary tract, also called cholangiocarcinomas (CCA, CCC, or CC) [1], are tumors of the extrahepatic (eCCA) or intrahepatic (iCCA) bile duct system. The worldwide mortality has increased dramatically during the past years, according to the WHO and other Health Organization databases, for different locations in the U.S.A., in Europe, but especially in East Asia [2]. CCA mortality has been reported to be higher in men than women worldwide, and Asian individuals were reported to have a high mortality (2.81 per 100,000 men in Japan). However, in the USA, an increased mortality was found between 2004 and 2014 for African American individuals (45%), followed by Asian (22%) and white (20%) individuals [3]. In Japan, the age-standardized incidence rates (ASRs) per 100,000 person-years for iCCA are higher than for eCCA (e.g., Japan: ASR for ICC, 0.95; ASR for ECC, 0.83) [4].

Based on the anatomical origin, CCAs can be classified as intrahepatic (iCCAs), perihilar (pCCAs), or distal (dCCAs) [1]. There are also some cases of combined hepatocellular cholangiocarcinoma [5]. The risk factors may vary depending on the location [6]. iCCAs are associated with overweight/obesity and chronic liver diseases involving cirrhosis and/or viral hepatitis; pCCAs are associated with primary sclerosing cholangitis; and dCCAs are associated with choledocholithiasis [7]. pCCAs and dCCAs often develop in the setting of prolonged inflammation and/or cholestasis, which contribute to carcinogenesis, especially



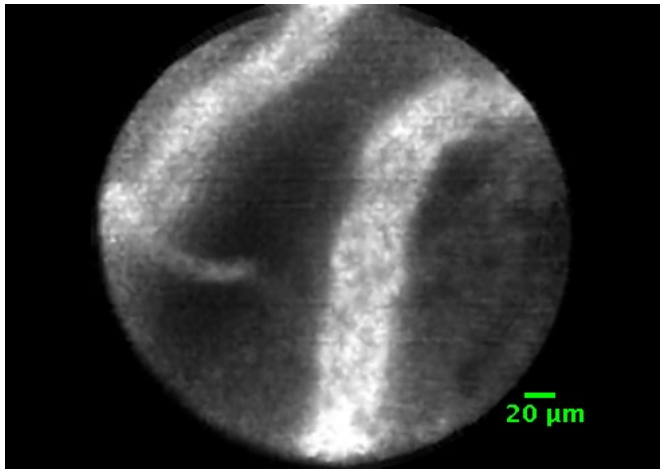


Abb.1: Cholangioskopie eines CCC mit real-time Bioluminescence der starken Neovaskularisation, ein diagnostischer und prognostischer (therapeutischer) Marker.

Prinz C, Frese R, Grams M, Fehring L. Emerging Role of microRNA Dysregulation in Diagnosis and Prognosis of Extrahepatic Cholangiocarcinoma. Genes (Basel). **2022** Aug 19;13(8):1479. doi: 10.3390/genes13081479. – IF: 4,1

Prinz et al., *Genes* 2022 (review): MicroRNA expression in Cholangiocarcinoma „Besondere Bedeutung für Neovaskularisation“

MiRNA dysregulation in biliary tract cancers and Potential Targets	
miR-9	useful diagnostic marker for CCA, induces cell arrest of carcinoma cells, downregulated in CCC [17]
miR-141	highly overexpressed in CCA cells, correlating with multifocal cholangiocarcinoma and vascular invasion [49]
miR-145	useful diagnostic markers for Biliary tract cancer, involved in vascular invasion [17]
miR-181	therapeutic targets for the treatment of various diseases. Targets MKP-5 and regulating the p38 MAPK activation[50], and regulates NDRG2 to influence carcinogenesis and metastasis [51]
miR-191	miR-191 acts a potential therapeutic target [52]
miR-200b	highly overexpressed in CCA cells, inhibition of miR-200b is associated with sensitivity to gemcitabine [49]
miR-412	differed significantly between patients with PSC and PSC/CCA, regulates angiogenesis, leading to de novo angioinvasion [18, 53)

cells

MDPI

Review

MicroRNAs as Indicators of Malignancy in Pancreatic Ductal Adenocarcinoma (PDAC) and Cystic Pancreatic Lesions

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Abstract: The dysregulation of microRNAs has recently been associated with cancer development and progression in pancreatic ductal adenocarcinoma (PDAC) and cystic pancreatic lesions. In solid pancreatic tumor tissue, the dysregulation of miR-146, miR-196a/b, miR-198, miR-217, miR-409, and miR-490, as well as miR-1290 has been investigated in tumor biopsies of patients with PDAC and was reported to predict cancer presence. However, the value of the predictive biomarkers may further be increased during clinical conditions suggesting cancer development such as hyperinsulinemia or onset of diabetes. In this specific context, the dysregulation of miR-486 and miR-196 in tumors has been observed in the tumor tissue of PDAC patients with newly diagnosed diabetes mellitus. Moreover, miR-1256 is dysregulated in pancreatic cancer, possibly due to the interaction with long non-coding RNA molecules that seem to affect cell-cycle control and diabetes manifestation in PDAC patients, and, thus, these three markers may be of special or "sentinel value". In blood samples, Next-generation sequencing (NGS) has also identified a set of microRNAs (miR-20a, miR-31-5p, miR-24, miR-25, miR-99a, miR-185, and miR-191) that seem to differentiate patients with pancreatic cancer remarkably from healthy controls, but limited data exist in this context regarding the prediction of cancer presences and outcomes. In contrast to solid pancreatic tumors, in cystic pancreatic cancer lesions, as well as premalignant lesions (such as intraductal papillary neoplasia (IPMN) or mucinous-cystic adenomatous cysts (MCAC)), the dysregulation of a completely different expression panel of miR-31-5p, miR-483-5p, miR-99a-5p, and miR-375 has been found to be of high clinical value in differentiating benign from malignant lesions. Interestingly, signal transduction pathways associated with miR-dysregulation seem to be entirely different in patients with pancreatic cysts when compared to PDAC. Overall, the determination of these different dysregulation "panels" in solid tumors, pancreatic cysts, obtained via fine-needle aspirate biopsies and/or in blood samples at the onset or during the treatment of pancreatic diseases, seems to be a reasonable candidate approach for predicting cancer presence, cancer development, and even therapy responses.

Keywords: microRNA; pancreatic cyst; pancreatic ductal adenocarcinoma; hyperinsulinemia; dysregulation; anti-apoptotic pathways

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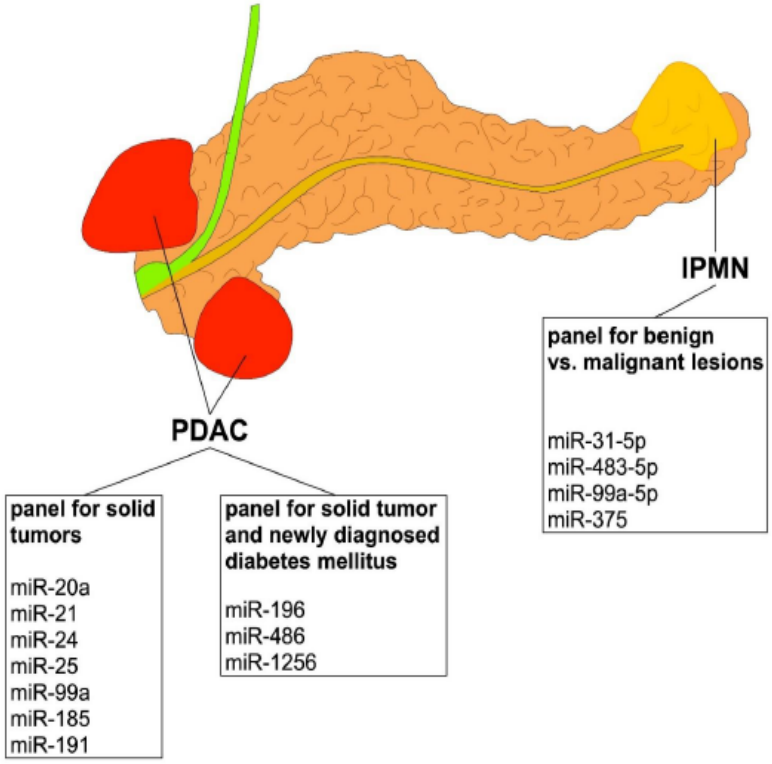
1. Introduction

MicroRNA Dysregulation Shows Different Patterns in Pancreatic Ductal Adenocarcinoma (PDAC) and Pancreatic Cysts (PC)

Pancreatic cancer is increasingly frequent in Western countries and among the top seven leading causes of cancer-related deaths worldwide [1]. Pancreatic cancer remains one of the most lethal malignant neoplasms, causing 432,242 new deaths in 2018 worldwide, with 355,317 new cases estimated to occur by 2040. Local infiltrative growth, peritoneal carcinosis, and liver metastases determine operability, and local resectability criteria are based in particular on tumor growth in the surrounding vessels [2]. Painless jaundice is a characteristic sign of pancreatic cancer, but it is frequently associated with an advanced

REVIEW: MicroRNA Expression in Pankreatischen Tumoren



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Bedeutung der microRNA in Serum-Panels

Bei Patienten mit neu aufgetretenem Diabetes mellitus und Verdacht auf Pankreas-Raumfoderung kann die Bestimmung eines Serum-Panels mit den MicroRNA Molekülen hilfreich in der Detektion eines Pankreas-Karzinoms sein. Patente sind entwickelt.

Innovative Forschungsansätze in Wuppertal

(n=78 Pankreaskarzinome de novo pro Jahr)

Etablierung von Biobanken und Korrelation mit klinischen Entwicklungen (5-Jahres Überleben, PFS)

Kooperation mit Forschenden Pharmaunternehmen, hier: ROCHE-Kooperation

Validierung bes. Biomarker (Ca-19-9) bei der täglichen Entscheidungs-Findung; hier: HOLIPANC Studie

Validierung und Vergleich mit bekannten klinischen Risikokonstellationen, hier: HbA1C Expression.