alterations in their expression patterns, providing an explanation for the increased lipid peroxidation. Alterations of mRNA expression of POR and SLC7A11 levels upon treatment were also examined in primary human gastric cancer tissue cultures.
Discussion & Conclusion: Ferroptosis is involved in the antitumor effects of HDAC inhibitors in gastric cancer while this occurs via downregulating anti-ferroptotic and upregulating pro-ferroptotic enyzmes. We identify the induction of ferroptosis as a new mechanism of action of class-I HDACi in gastric cancer, independent of the genetic background of the cell lines. We therefore introduce lipid peroxidation as a new general effect of HDACi induced anti-tumor effects.

Disclosure Statement: The authors declare no conflict of interest.

Gastrointestinal Cancer: Colorectal

79

Comprehensive profiling of fibroblasts reveals the origin and activation of disease-promoting subtypes in human colorectal cancer

Richard Demmler[1]; Charles G. Anchang[2]; Yong S. Yong[1]; Simon Rauber[3]; Benjamin Schmid[4]; Vera S. Schellerer[5]; Elisabeth Naschberger[1]; Andreas Ramming[3]; Michael Stürzl[1]

[1]Universitätsklinikum Erlangen, Division of Molecular and Experimental Surgery, Erlangen, Deutschland
[2]Vindex GmbH, Potsdam, Deutschland
[3]Universitätsklinikum Erlangen, Department of Medicin 3, Erlangen
[4]Optical Image Centre Erlangen, Erlangen, Deutschland
[5]Universitätsklinikum Greifswald, Department of Visceral Surgery, Pediatric Surgery, Greifswald, Deutschland

Background: Cancer-associated fibroblasts (CAFs) are a major player in the architecture of the tumor microenvironment (TME) and the progression of cancer. CAFs are phenotypically heterogeneous. Several CAF subtypes were proposed, including inflammatory CAFs and myofibroblastic CAFs, but a precise characterization of their stability and function in cancer remains unclear[1]. Buechler et al. proposed a PI16-expressing subtype as the unspecialized normal fibroblast (NAF) state from which different activated phenotypes can arise[2]. The goal of this study is to give a more precise look into the different subtypes of CAFs and their respective functions in colorectal cancer (CRC).
Methods: Bulk/Single-cell RNA Sequencing, Western Blot, qPCR, IHC, ICC
Result: Bulk RNA Sequencing of isolated and cultured fibroblasts of human colorectal cancer (n=6) and healthy colon (n=3) revealed a stable NAF and CAF signature which is preserved *in vitro*. Findings were confirmed by Western Blot, qPCR and Immunohistochemical stainings. Four major subtypes could be identified in normal colon and CRC using a public single-cell RNA Seq dataset of CRC[3]. NAF activation into Myofibroblasts was achieved via TNF-α and TGF-β stimulation and went along with the loss of the NAF signature.
Discussion: Here isolated primary CAFs and corresponding NAFs from human CRC were established to study their role in the disease. Stable subtypes of fibroblasts were preserved in cell culture and portrayed based on their transcriptome and function. The existence of the PI-16 subtype was confirmed in cultured NAFs and further characterized. The activation of this subtype into cancer-promoting subtypes was recreated *in vitro*.
Conclusion: We determined major differences between cultured CAFs and NAFs of human CRC and identified disease-relevant subpopulations originating from an unspecialized normal fibroblast population.

References:
1. Öhlund D. et al., J Exp Med 2017.
2. Buechler M. B. et al., Nature 2021.
3. Lee, H. O. et al., Nat Genet 2020.

Disclosure Statement: The authors declare the following: C.G.Anchang is affiliated with VINDEX GmbH.

91

The patient-derived cancer spheroid model predicts response to chemotherapy in curatively resected patients with high-risk stage II and stage III colon cancer

Barbara Mayer[1]; Isabella Held[1]; Kathrin Halfter[2]; Jens Werner[1]

[1]Department of General, Visceral and Transplantation Surgery, LMU University Hospital, LMU Munich, München, Deutschland
[2]The Institute for Medical Information Processing, Biometry and Epidemiology, LMU Munich, München, Deutschland

Background: The prospective SpheroPCT cohort study was conducted to evaluate the chemopredictivity of the patient-derived cancer spheroid model (PDCS) in locally advanced CRC.
Methods: Tumor spheroids were prepared from 48 colorectal cancer patients (R0M0) with UICC-II high-risk and UICC-III tumors for 48 h and treated with guideline-recommended chemotherapy for 72 h. Treatment efficacy was measured by ATP luminescence assay and multivariately correlated with 5-year disease-free survival (DFS).
Result: CRC patients treated according to the most effective test results did not experience tumor recurrence within the 5-year follow-up (32 of 36 patients, 88.9%). In contrast, tumor recurrence occurred in patients who did not receive the best therapy suggested by the PDCS model (7 of 12 patients, 58.3%, p<0.001). Drug testing in the PDCS model proved to be an independent predictor of drug response (HR 0.191, 95% CI 0.045-0.801, p=0.024). Test specificity was calculated to be 86.5% and test sensitivity was calculated to be 74.6%. Consistent with guideline recommendations, drug testing in the PDCS model showed no improvement in treatment efficacy with the addition of irinotecan to 5-FU or cetuximab to 5-FU in combination with oxaliplatin (FO). In six of the 11 relapsed patients (54.5%), the test detected a more effective treatment option than the given one. Two CRC patients were classified as chemoresistant. For nine of 13 patients (69.2%) who required reduction of standard chemotherapy with FO due to severe side effects, the PDCS model identified an equivalent or more effective treatment option.
Discussion: The data suggest that preclinical drug testing in the predictive PDCS model should be translated to clinical practice. This strategy could provide more effective and less toxic therapeutic options for individual cancer patients, resulting in prolonged survival and improved quality of life.
Conclusion: The patient-derived cancer spheroid model supports decision making in personalized cancer therapy.

Disclosure Statement: The authors declare no conflict of interest.

230

Influence of laparoscopic versus open surgery on humoral immunity in patients with colorectal cancer: a systematic review and meta-analysis

Annika Bohne[1]; Elena Grundler[1]; Helge Knüttel[1]; Vinzenz Völkel[3]; Alois Fürst[4]

[1]Universität Regensburg, Regensburg, Deutschland
[2]Tumorzentrum Regensburg, Zentrum für Qualitätssicherung und Versorgungsforschung der Universität Regensburg, Regensburg, Deutschland
[3]Caritas-Krankenhaus St. Josef, Klinik für Allgemein-, Viszeral-, Thoraxchirurgie und Adipositasmedizin, Regensburg, Deutschland

Background: Laparoscopic surgery (LS) and open surgery (OS) are the main surgical treatment options for colorectal cancer (CRC), which might differ in their impact on host immunity so indispensable for anti-infectious and antitumor defence.
Methods: Included in this systematic review and meta-analysis were randomized controlled trials (RCTs) measuring parameters of humoral immunity up to eight days after LS compared to OS in adult patients with CRC of any stage. MEDLINE, Embase, Web of Science (SCI-EXPANDED), Cochrane Library, Google Scholar, ClinicalTrials.gov and ICTRP were systematically searched. Risk of bias (RoB) was assessed using the Cochrane RoB2 tool. Random-effects meta-analysis of mean differences (MD) was performed. Methods were prospectively registered in PROSPERO (CRD42021264324).

Result: Twenty RCTs with 1,131 participants were included. RoB was rated low in five, of some concerns in 13, and high in two studies. Quantitative synthesis found concentrations of parameters to be significantly lower after LS for IL-6 and CRP at 3-9h (CRP MD -1.67 mg/dl 95% CI [-3.25, -0.08] p=0.04, IL-6 -86.71 pg/ml [-125.05, -48.37] p<0.00001), at postoperative day (POD) 1 (CRP -3.68 mg/dl [-5.05, -2.32] p<0.00001, IL-6 -26.88 pg/ml [-31.27, -22.50] p<0.00001) and at POD 2 (IL-6 -11.47 pg/ml [-16.32, -6.63] p<0.00001). IL-8, TNFα and VEGF also showed lower concentrations after LS at 0-2h (IL-8), 3-9h (IL-8, TNFα) and POD 1 (IL-8, VEGF). No meta-analysis yielded results favouring the OS group.
Discussion: The increase in postoperative concentrations of several proinflammatory parameters was significantly less pronounced after LS in the analyses, especially in the early postoperative period up to POD1. The main limitations of the included RCTs were small sample sizes and a heterogenous choice of measuring timepoints.
Conclusion: The summarized evidence favours the laparoscopic approach over the open approach in regard to a milder postoperative proinflammatory reaction, although further research is desirable.

Disclosure Statement: The authors declare no conflict of interest.

253

Does the Prognosis of Colorectal Cancer Depend on the Age of Onset?

Caroline Deutschmann; Lutz Mirow; Hagen Rudolph

Allgemein- und Viszeralchirurgie Klinikum, Chemnitz, Deutschland

Background: Colorectal cancer (CRC) is one of the most frequent tumor entities in Germany. Less than 10% of all patients are under 50 years of age. But several studies expect an increase in the incidence rate in this age group.
In this paper I study its prognosis depending on the age of its onset in patients.
Methods: I conducted a retrospective data analysis of all surgical primary cases with colon or rectal carcinoma at Klinikum Chemnitz diagnosed between 01/01/1995 and 12/31/2020. These included the diagnostic codes C18.-, C19 and C20 of ICD-10-GM-2021. Applying an age filter of "50 years or younger" and "70 years or older", I evaluated a number of 1381 cases. The final data for this study was compiled on 11/10/2021.
Result: Patients at 50 years or younger showed a pUICC stage III or IV (57.6%) at the time of diagnosis. The cohort of 70 years or older was mostly diagnosed at pUICC stage I or II (54.2%).
The share of patients in stage R2a (macroscopically discernible residual tumor) was significantly higher in the cohort of up to 50 years (20.5%; ≥70 years: 12.8%).
Noticeably, younger CRC patients showed more general recurrences (≤ 50 years: 31.1%; ≥ 70 years: 13.8%), local recurrences (≤ 50 years: 15,9%; ≥ 70 years: 5.0%) and metastases (≤ 50 years: 51.5%; ≥ 70 years: 28.8%).
Up to this study's reference day, 47.0% of the cohort of 50 years or younger had died. In 32.6% of these cases the tumor was the cause of death. The cohort of 70 years or older showed 69.7% deaths, but only 29.8% were caused by the tumor.
Discussion: Assumed causes for the progressed pUICC stage as well as the higher recurrence and metastasis rates with younger patients are: delayed diagnosis with unspecific symptoms appearing late, more aggressive tumor biology, effects due to the birth cohort with a higher prevalence of antibiotics medication and obesity as well as hereditary syndromes.
Conclusion: The comparatively high rate of death in patients up to 50 years of age caused by a tumor indicates, that younger CRC patients have worse prospects of survival.

Disclosure Statement: The authors declare no conflict of interest.

316

An almost insurmountable immunologic barrier: A detailed view on the interaction of hypermutated colon cancer with autologous T cells

Sandra Schwarz[1]; Su Zhaoran[1]; Mathias Krohn[1]; Markus Löffler[2]; Andreas Schlosser[3]; Michael Linnebacher[1]

[1]Universitätsmedizin Rostock, Klinik und Poliklinik für Allgemein-, Viszeral-, Thorax-, Gefäß- und Transplantationschirurgie, Molekulare Onkologie und Immuntherapie, Rostock, Deutschland
[2]Universität Tübingen, Institut für Zellbiologie, Immunologie, Tübingen, Deutschland
[3]Universität Würzburg, Rudolf-Virchow-Zentrum, Center for Integrative and Translational Bioimaging, Würzburg, Deutschland

Background: The interaction of cancer and immune cells is still not completely resolved. Thus, we selected two colon cancer cases with patient-derived cell lines, peripheral and tumor-infiltrating T cells available for detailed investigation.
Methods: Prior to co-culture, T cell populations were characterized regarding immune checkpoint (PD-1, CTLA-4, LAG-3) expression and the amount of regulatory T cells. Tumor cell line analysis covered tumor mutational burden, antigen processing and presentation, and immune checkpoint ligands (PD-L1, CD80/86). After co-culture experiments, a degranulation assay determined tumor cell recognition.
Result: T cells co-cultured with autologous tumor cells showed only low levels of pro-inflammatory cytokines and failed at tumor recognition. Since antigen presentation was not affected in tumor cells, we assumed active immunosuppressive tumor cell mechanisms. Yet, the treatment of co-cultures with immune checkpoint inhibitors (ICI) did not boost anti-tumor immune responses. Only pre-stimulation of T cells with tumor-specific peptides significantly increased tumor cell recognition. Above all, this effect was higher in peripheral than in tumor-infiltrating T cells. Further characterization of the tumor cells revealed expression of granzyme B and proteinase inhibitor 9 (PI-9), granzyme B's specific inhibitor. However, in a final cytotoxicity assay, tumor cell elimination was significantly higher in peptide-stimulated than control T cells and neither ICI nor PI-9 inhibitor further improved the outcome significantly.
Discussion: These results prove the complexity of immune evasion and suppression mechanisms active in tumor cells. They further underline the importance of more personalized approaches in future immunotherapies and they also demonstrate the superiority of tumor-naïve peripheral blood T cells compared to highly exhausted tumor-infiltrating T cells.
Conclusion: Tumor cells use a complex network of immunosuppressive strategies and multimodal immunotherapeutic approaches are needed to overcome these barriers.

Disclosure Statement: The authors declare that there are conflicts of interest. The conflicts were submitted to the congress organizer KUKM GmbH and KUKM can disclose them if needed.