e:Medium NEWSLETTER

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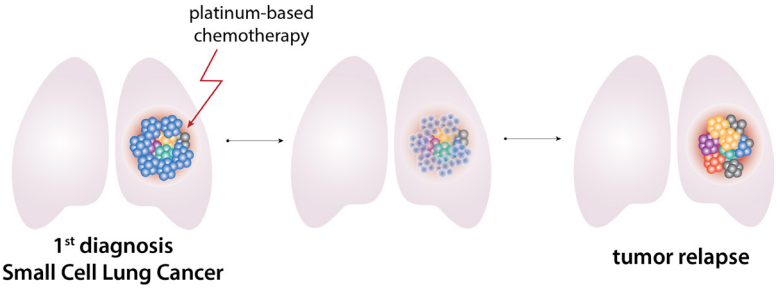
Dear Reader,

As we reach the culmination of our funding period, we reflect on the remarkable achievements of e:Med. Thus, in more than 2300 articles e:Med scientists have published their outstanding work funded by the BMBF. In this issue of e:Medium, you can read about current impressive examples from the broad spectrum of topics that make up e:Med, united by the interdisciplinary approach of systems medicine. e:Med fostered a vibrant research community by so far organizing 9 successful annual meetings, 2 outreach events, and numerous workshops and seminars. The e:Med Meeting 2024 will take place November 21 - 23 in the heart of the cosmopolitan city of Hamburg. Join, dive into this great community, find out about the state of research and find partners for future collaborations. Be part of it!

Stay curious and enjoy reading!
Your e:Med Management Office

Unveiling Chemotherapy Resistance in Lung Cancer

New Insights from Comprehensive Tumor Analysis



Small cell lung cancer (SCLC) is a particularly aggressive lung tumor mainly found in heavy smokers. Most patients are treated with chemotherapy in order to counteract the rapid proliferation of the tumor. Patients with SCLC are highly sensitive to treatment with chemotherapy; however, the tumors relapse frequently within a few months. To understand the exact development of tumors in individual patients during treatment and relapse is a great challenge and goal. In a comprehensive research endeavor supported by the German Research foundation (DFG), scientists of the e:Med alliance InCa led by Professor Dr. Roman Thomas (University of Cologne) delved into the development of tumors throughout treatment regimens. They identified distinct populations of tumor cells that respond disparately to chemotherapy in the initial stages of the illness and subsequent treatments as the disease progresses.

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UNVEILING CHEMOTHERAPY RESISTANCE IN LUNG CANCER
New Insights from Comprehensive Tumor Analysis

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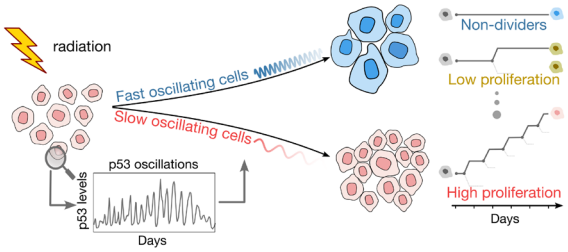
"When the tumor returned - which occurs in almost all patients - a different dominant cell population was usually found and frequently tumors at relapse harbored ancestral tumor clones. With further treatments during the course of therapy, for example with radiation, the cancer cells emerged with characteristics of the genetic damage caused by the first-line chemotherapy", summarizes Professor Dr. Julie George (University of Cologne), first author and leader of the study) the sobering but important observation. By employing multi-region sequencing of 160 tumors from 65 patients, the team traced tumor development from diagnosis through chemotherapy and immunotherapy. They discovered that the effectiveness of therapy early on is largely attributed to prevalent populations of treatment-sensitive cancer cells present at diagnosis. Additionally, they found that these dominant sensitive cell populations mask other diverse cancer cells, originating from early precursors, which are resistant to treatment and proliferate unchecked post-successful treatment. These cancer cells reveal genetic alterations reflective of the damage caused by initial chemotherapy. The researchers identified specific genetic characteristics within tumor cells associated with resistance to chemotherapy. The study's findings suggest that cancer genome alterations not only drive malignant transformation in SCLC but also influence the clinical phenotypes of chemotherapy sensitivity, tumor progression and relapse. The efficacy of future treatment developments may be hindered by the number of therapy-resistant tumor cells. Therefore, one potential therapeutic approach could involve administering intensive initial treatment to minimize the emergence of resistant cancer cells later on.

George, J., ... and R. K. Thomas. „Evolutionary trajectories of small cell lung cancer under therapy." Nature (March 2024)

INSIGHTS IN CELLULAR PROLIFERATION HETEROGENEITY:
Signaling Dynamics and Radiation Response Heterogeneity

The development of effective cancer treatments is hampered by the variability of tumor cell subpopulations and their different growth and resistance patterns. Although highly proliferating tumors are associated with improved therapeutic outcomes in chemotherapy and radiotherapy treatments, many patients with highly proliferative tumors still exhibit a high degree of resistance to treatment.
In order to develop new treatment strategies against tumor cells, it is important to decipher the processes that determine tumor heterogeneity.



The research team led by Dr. Adrian Granada (Charité Berlin), project leader in the DeepLTNBC junior research alliance, investigated the interplay between DNA damage, important signal transducers of the DNA damage response and the proliferation behavior of individual cells at the single cell level. The team wanted to understand how these three factors are quantitatively related and how they contribute to maintaining the heterogeneity of cell proliferation, i.e. the differences in the rate and pattern at which cells divide and multiply. Cells recognize DNA damage through a series of checkpoint mechanisms that enable DNA repair and proliferation control. The scientists realized that the variability of naturally occurring endogenous DNA damage contributes significantly to the heterogeneity of proliferation. Using a comprehensive time-series analysis of the signaling dynamics of the DNA damage-responsive transcription factor p53 and its target p21, the scientists showed that in a cell population, DNA damage levels are quantitatively encoded in the amplitude of p53 and p21, which progressively regulate proliferation. This means that the severity of DNA damage in the cells correlates with the amount of p53 and p21 in the cells. The greater the damage, the more of these molecules are present. The results suggest a model in which the p53 network is able to recognize different degrees of DNA damage and gradually optimize proliferation at the cell population level. Endogenous DNA damage may thus be an important source of proliferation heterogeneity and have implications for tissue growth and homeostasis as well as tumor formation. However, further research is needed to validate this model and understand the mechanisms driving endogenous DNA damage heterogeneity, while establishing a link to p53 dynamics and cell proliferation at the single cell level.

Gutu, N., ... AE. Granada. „p53 and p21 dynamics encode single-cell DNA damage levels, fine-tuning proliferation and shaping population heterogeneity." Commun. Biol. (Nov 2023).

GRADUALLY ZOOMING IN ON SCHIZOPHRENIA
Deciphering the schizophrenia patho-mechanism

Schizophrenia is a devastating disease for the individuals as well as an economic burden on the healthcare system. It is a neuro-developmental psychiatric disorder where individuals experience and interpret reality differently. Although it is highly heritable, little is known about its pathology.

In complex diseases such as schizophrenia, mostly, not the genes but their regulation is defective. There are thousands of genetic variants, especially Single Nucleotide Polymorphisms (SNPs) which are statistically associated with schizophrenia. However, most of them reside on non-coding parts of DNA, mostly on Gene-Regulatory-Elements (GREs). Another challenge in schizophrenia research is the inaccessibility of human neuronal cells to research. A team of e:Med scientists from the junior research group DiNGS under the supervision of Professor Dr. Michael Ziller (University of Münster) addressed the molecular mechanism behind the development and manifestation of schizophrenia by developing a roadmap to identify functional genetic variation leading to the disease state.To gradually zoom in on the molecular mechanism, firstly, scientists found out schizophrenia-associated SNPs by statistical analysis. This revealed thousands of statistically associated genetic variations. However, the actual impact of the genetic variants on the disease state was unknown. To figure out which of the variants are relevant, the scientists employed multi-stage functional assays. This enabled them to identify disease-relevant cell types, cellular states and those variants that modify the gene expression relevant to schizophrenia. Leading up to identification of disease-relevant SNPs, scientists began by building GRE libraries in various cell types. Further, they investigated epigenomic profiles of cell types and found that disease-associated SNPs are present at early developmental stages of neurons. As suitable models for neurons, they utilized induced neurons (iNeurons) and induced neuronal precursor cells (iNPCs). In a decisive step, scientists went on to discover the target genes of these variants and explored their biological meaning by CRISPR-based genome editing without removing them from their environment (endogenously). “We uncover that only 620, ~1.7% of schizophrenia variants are functional and operate in a highly condition- and cell type-specific manner,” explains Professor Dr. Ziller. “Lastly, we identify a novel mechanism modulating the electrophysiological properties of human neurons”.
In conclusion, this research provided a roadmap to identify functional genetic variants of schizophrenia. The scientists illustrated how to dissect genetic variants and discover those that are operational in specific conditions and cell types. This roadmap could also be useful in future research that aims to identify functional genetic variants in other highly heritable, complex diseases.

Rummel C., ... and M. J. Ziller, „Massively parallel functional dissection of schizophrenia-associated noncoding genetic variants.“ Cell (Nov 2023)

TRYPTOPHAN: EARLY WARNING OF CHRONIC INFLAMMATION?
An amino acid as inflammation marker

Tryptophan (Trp) is an essential amino acid but as it cannot be created by the human body itself Trp needs to be taken from dietary resources. One of the ways Trp is broken down, by the kynurenine pathway, results in pro-inflammatory molecules. Recent studies showed that individuals affected from irritable bowel syndrome, a chronic inflammatory disease of the intestines, have elevated levels of these metabolites. However, it is not yet known if Trp usage at higher rate is a chronic inflammatory disease (CID) phenomenon.
e:Med scientists of the alliances Try-IBD, iTREAT, and GUIDE-IBD under the supervision of Professor Dr. Konrad Aden, Professor Dr. Philip Rosenstiel, and Professor Dr. Silke Szymczak,

respectively, joined their forces to address Trp involvement across CIDs.
In the CID group of diseases, the body manifests permanent or recurring inflammation. Inflammation is body’s response against harmful microbes, irritants of dead cells. But when the inflammation persists, patients suffer all throughout their lives. Although CIDs may

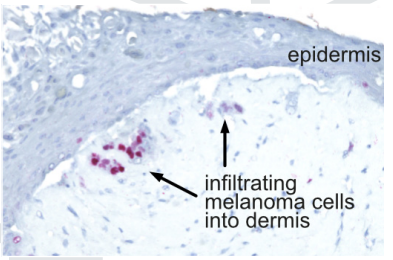
manifest in different organs such as skin, stomach and muscles, they may share common molecular mechanisms. As there is no final cure but only disease management, patients also need lifelong treatment. Despite available therapeutic options, CID patients experience treatment failure, side effects, and some disease activity remains. Therefore, it is imperative to improve diagnostics and refine therapy by dissecting the pathology of inflammation.

e:Med researchers analysed serum and stool samples from 2000 patients for Trp levels to gain an understanding of the overall distribution of Trp metabolism across 13 CIDs, including Crohn's Disease, Ulcerative colitis, Psoriasis, Systemic Lupus and various rheumatoid diseases. In 9 out of 13 chronic diseases, tryptophan levels were lower in patients with CID than in healthy people. Moreover, the scientists identified the kynurenine pathway as the main catabolic route responsible for Trp degradation across all CIDs. In an analysis of serum Trp levels against a well-established inflammation marker, CRP protein, they found that Trp levels can indicate even the subtle levels of change in the disease symptoms. In addition, patients who are receiving advanced therapy because the first line of therapy had failed, showed an increased Trp level variation in their serum. This suggests that Trp levels can point out how far the disease has progressed. In line with these results, tryptophan could serve as a complementary marker to the established laboratory tests, to determine the severity of the disease and help to predict treatment options.

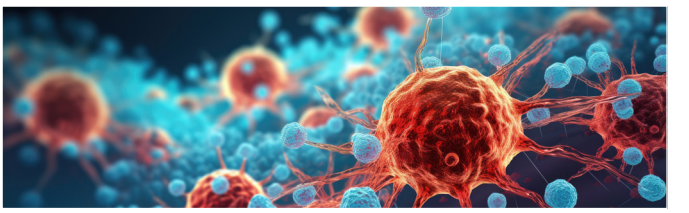
Harris, D. M.M., S. Szymczak, ... P. Rosenstiel, S. Waschin, S. Schreiber and K. Aden. „Tryptophan degradation as a systems phenomenon in inflammation – an analysis across 13 chronic inflammatory diseases." eBioMedicine (April 2024)

HOW COMBINATION THERAPY IMPROVES MELANOMA TREATMENT
Synergy of MEK/BRAF inhibitors with immunotherapy

In the quest to combat melanoma, the most dangerous type of skin cancer, e:Med scientists from the junior research alliance MelBrainSys have turned their attention to malignant melanoma with NRAS mutations, which drives aggressive tumor growth in about 25% of cases. While immune checkpoint inhibitors have shown promise, they often fail due to intrinsic resistance of the tumors, regardless of their mutation status. In addition, clinical trials focusing on targeting downstream players of the MAPK pathway, showed a moderate efficacy of MEK inhibitors (MEKi) such as binimetinib, with resistance to the MEK inhibitor remaining a hurdle. This leaves a significant portion of patients with NRAS-mutant melanoma without effective treatment options.



Recognizing the need for more effective second-line therapies, scientists explored combination strategies, notably pairing the MEKi with BRAF inhibitors (BRAFi), which is currently used successfully to treat BRAF-mutant melanoma. This approach proved fruitful, significantly enhancing antitumor effects without activating problematic pathways associated with skin cancer development. Additionally, these combinations demonstrated immunomodulatory effects, suggesting a potential synergy with immunotherapy. e:Med scientists under the supervision of Dr. Dana Westphal and Professor Dr. Friedegund Meier (TU Dresden) aimed to systematically investigate three different BRAFi/MEKi combinations in NRAS-mutant melanoma cells, shedding light on their impact on cell growth, cell death and immunogenicity. The findings in fact unveiled promising insights: combined BRAF/MEK inhibition not only inhibited tumor growth but also modulated the immune microenvironment, potentially enhancing immune recognition and response against the tumor. This work lays the foundation for a new treatment strategy in NRAS-mutant melanoma, emphasizing the importance of combination therapies and integration with immunotherapy. By understanding and addressing resistance mechanisms, researchers aim to develop more efficient and durable treatment strategies for patients with NRAS-mutant melanoma. However, in translating these findings into clinical practice, challenges remain, particularly in managing resistance mechanisms that develop against BRAF/MEK inhibition and in minimizing toxicities.



Overall, these findings offer hope for improved outcomes in melanoma treatment, underscoring the potential of combination therapies and the importance of continued research in advancing precision medicine approaches to combat this deadly disease.

Dinter, L., ... F. Meier, B. Seliger and D. Westphal „BRAF and MEK inhibitor combinations induce potent molecular and immunological effects in NRAS-mutant melanoma cells: Insights into mode of action and resistance mechanisms." Int. J. Cancer (Nov 2023).

Networking - BMBF-Funded Networks

The e:Med community is excellent. In order to further strengthen networking, we are introducing thematically relevant networks

Modeling Network for Severe Infectious Diseases (MONID): Founded in 2022, MONID's focus is on sustainable strengthening of modeling competence in Germany to enhance pandemic resilience and improve the effectiveness and efficiency of health measures. Key subjects are research, its infrastructure and capacities as well as method development.
https://monid.net

Liver Systems Medicine against Cancer (LiSyM-Cancer): Established in 2021 with three consortia, LiSyM-Cancer takes on the integrative systems medicine approach to tackle liver cancer within the framework *National Decade Against Cancer*. Main focus is the identification of relevant biomarkers for the early diagnosis and prevention of hepatocellular-carcinoma (HCC), and moreover, data sharing and management in research networks. www.lisym-cancer.org

Medical Informatics Initiative Germany (MII): Founded in 2016, the aim of the MII is to digitally network routine data from patient care throughout Germany and make it available for medical research in order to treat diseases faster and more effectively in the future. In MII, all institutions of university medicine in Germany are working together with non-university clinics, research institutions, companies, health insurance companies and patient representatives. The German Portal for Medical Research Data (FDPG) is central to this infrastructure as are the Data Integration Centres (DIC). www.medizininformatik-initiative.de

EXPLORE Precision Medicine e:Med Event at Futurium Berlin

Monday morning in Berlin. School classes and MINT courses (MINT: Mathematics, computer science, natural science and technology) of 400 students and teachers stream toward the Futurium. A futuristic building between Berlin central station and the Spree river, ideal for topics of the future. "EXPLORE Precision Medicine" is the topic of the future today. The special feature: no static exhibition, but the scientists themselves are here and explain their research. A great all-round experience awaits the students: from the offer to try one's hand as a doctor, simulation of the brain, observing cancer cells under the microscope, and VR applications to extraction of one's own genetic material DNA to take away and immersion in the complex world of molecular interaction via VR headsets - one can try it all. A versatile exhibition with 19 interactive stands, workshops ranging from learning AI to valuing genetic data, lectures from a

vivid introduction to systems medicine through to career examples, everything at first hand. 60 scientists from all over Germany gathered to give the next generation a spark about this exciting new interdisciplinary field of medicine. A pioneering day. Forward-looking. The right time to find out about the future.

In addition, there is a 50 page booklet nicely illustrated and with easy to understand texts for further study at home and at school. This booklet can be ordered online via the e:Med Managing office. EXPLORE Precision Medicine was organized by the BMBF-funded research network e:Med Systems Medicine on October 9, 2023. www.sys-med.de/de/explore-precision-medicine

e:Med News

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Here you find information about:
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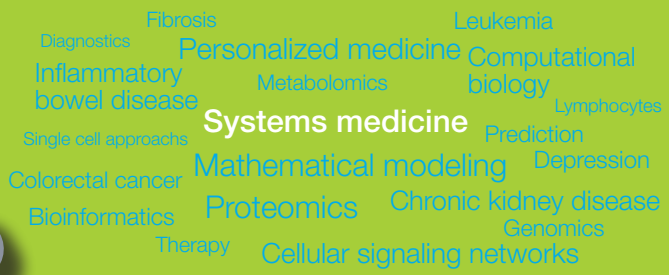
- project groups and networking
- links to funding info, calendar, events, systems medicine news
- latest scientific results of the e:Med community

www.sys-med.de/en



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