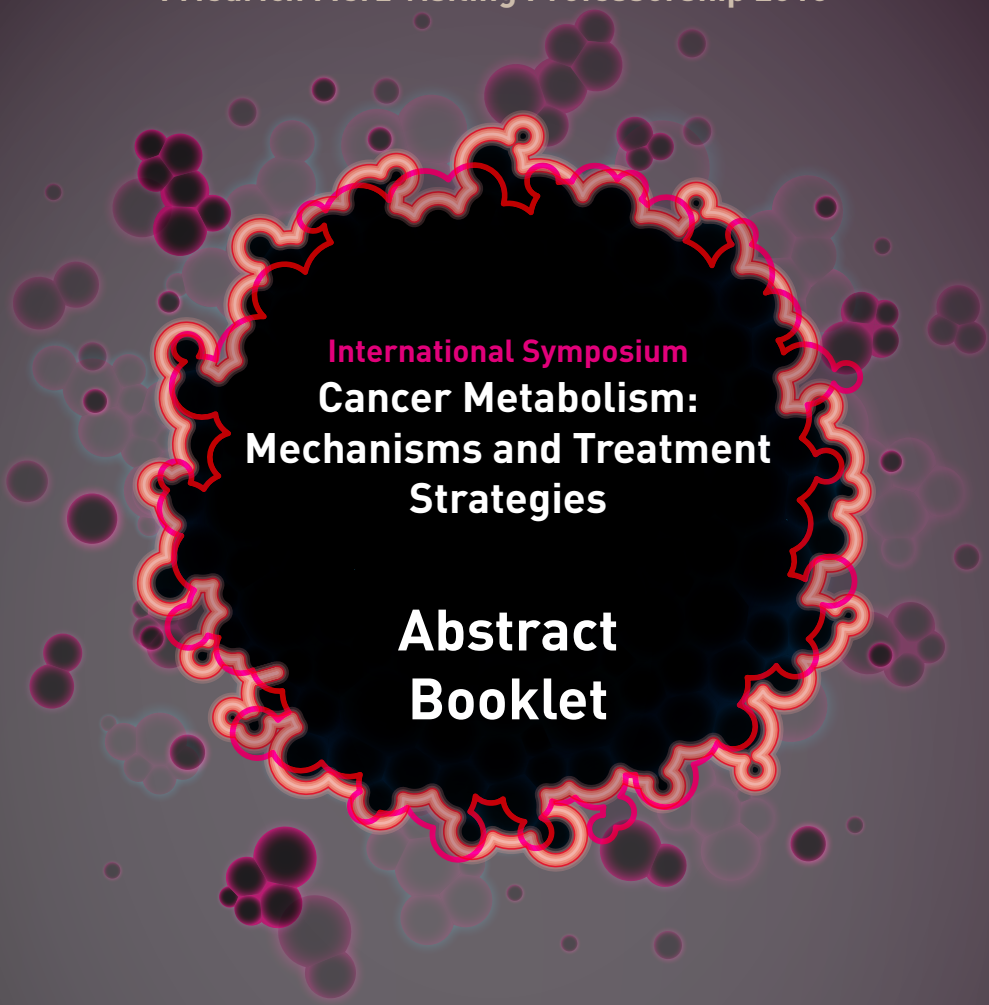
Friedrich Merz Visiting Professorship 2016



International Symposium

Cancer Metabolism: Mechanisms and Treatment Strategies

Abstract Booklet

November 23rd, 2016

9.30 am - 5.30 pm

University Hospital
Frankfurt, Germany

Foreword

Dear friends and collegues,

It is a pleasure to welcome you to the International Symposium „Cancer Metabolism: mechanisms and treatment strategies", taking place on the occasion of the stay of Prof. Valter D. Longo in Frankfurt as the recipient of the Friedrich Merz Visiting Professorship 2016.

The meeting will address recent progress in the exciting field of cancer metabolism in general, and glioma metabolism, in particular. There will be a focus on mechanisms, models and clinical applications of altered nutrition, including ketogenic diet, cyclic fasting and fasting-mimicking diets. The recently discovered impact of nutritional interventions on immune anti-tumor responses will be a special highlight.

The key note lecture will feature Valter D. Longo, who pioneered the concept of starvation-dependent differential stress resistance and sensitization in cancer treatment.

Future research directions and applications of nutritional interventions will be explored in a round-table panel discussion at the end of the conference.

We thank Merz for generously supporting this visiting professorship and the scientific meeting, which has enabled us to bring leading international researchers to Frankfurt.

We are looking forward towards a stimulating conference with interesting talks and lively discussions!

With cordial greetings,
Joachim P. Steinbach, on behalf of the organizers

Program

Cancer Metabolism: Mechanisms and Treatment Strategies

9.30 am **Welcome Address from the Vice President of the Goethe University Frankfurt**
Manfred Schubert-Zsilavecz, Frankfurt

9.40 am **Welcome Address from Merz Pharma AG**
Stefan Albrecht, Frankfurt

9.45 am **Introduction from the Director of the Universitary Cancer Center Frankfurt**
C. Brandts, Frankfurt

Session 1 Metabolic Alterations in Gliomas

Chairs: Patrick Harter

10.00 am **Tryptophan Metabolism as a Target for Glioma Therapies**
Christiane Opitz, Heidelberg

10.30 am **Alterations of Glucose Metabolism in Glioma Cells**
Katrin Lamszus, Hamburg

11.15 am Coffee Break

Keynote Lecture

Friedrich Merz Guest Professorship Lecture
Chairs: Claus Rödel/Karl-Heinz Plate

11.30 am **Starvation-dependent Differential Stress Resistance and Sensitization in Cancer Treatment**
Valter Longo, Los Angeles

12.30 pm Lunch Break and Press Conference

Session 2 Molecular Mechanisms of Starvation Signaling in Cancer

Chairs: Florian Greten

1.30 pm **Fasting Plus Tyrosine Kinase Inhibitors in Cancer**
Alessio Nencioni, Genoa

2.15 pm **Starvation Signaling and Resistance Towards Kinase Inhibitors**
Michael Ronellenfitsch, Frankfurt

2.45 pm **The Anti-malarial Atovaquone Increases Radiosensitivity by Alleviating Tumour Hypoxia**
Emmanouil Fokas, Frankfurt

3.15 pm Coffee Break

Session 3 Applications for Metabolic Targeted Therapies

Chairs: Volker Seifert/Wilfried Roth

3.30 pm **Clinical Application of Dietary Concepts in Brain Tumor Patients: The ERGO Studies**
Johannes Rieger, Tuebingen/Frankfurt

4.15 pm **Altering Metabolism for the Therapy of Glioma and other Cancers**
Adrienne Scheck, Phoenix

5.00 pm **Panel Discussion: Future Strategies for metabolically targeted therapies**
(Discussants: V. Longo, A. Scheck, J. Rieger, J. Steinbach)

5.30 pm **Concluding Remarks and Adjourn**
Joachim Steinbach, Frankfurt

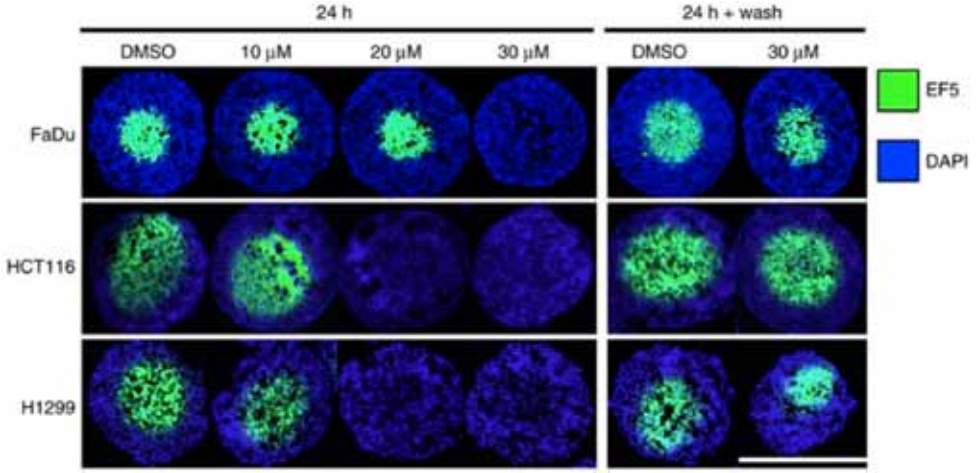
Abstract

Emmanouil Fokas, Frankfurt

Emmanouil Fokas MD DPhil is Professor of Translational Radiooncology at the University Hospital Frankfurt and deputy director of the clinic for Radiation Therapy and Oncology. His research interest is in tumor microenvironmental and immunologocial effects on therapeutic efficacy.

The Anti-malarial Atovaquone Increases Radiosensitivity by Alleviating Tumour Hypoxia

Tumour hypoxia renders cancer cells resistant to cancer therapy, resulting in markedly worse clinical outcomes. To find clinical candidate compounds that reduce hypoxia in tumours, we conduct a high-throughput screen for oxygen consumption rate (OCR) reduction and identify a number of drugs with this property. For this study we focus on the anti-malarial, atovaquone. Atovaquone rapidly decreases the OCR by more than 80% in a wide range of cancer cell lines at pharmacological concentrations. In addition, atovaquone eradicates hypoxia in FaDu, HCT116 and H1299 spheroids. Similarly, it reduces hypoxia in FaDu and HCT116 xenografts in nude mice, and causes a significant tumour growth delay when combined with radiation. Atovaquone is a ubiquinone analogue, and decreases the OCR by inhibiting mitochondrial complex III. We are now undertaking clinical studies to assess whether atovaquone reduces tumour hypoxia in patients, thereby increasing the efficacy of radiotherapy.


24 h
24 h + wash
DMSO
10 μM
20 μM
30 μM
DMSO
30 μM
EF5
DAPI
FaDu
HCT116
H1299

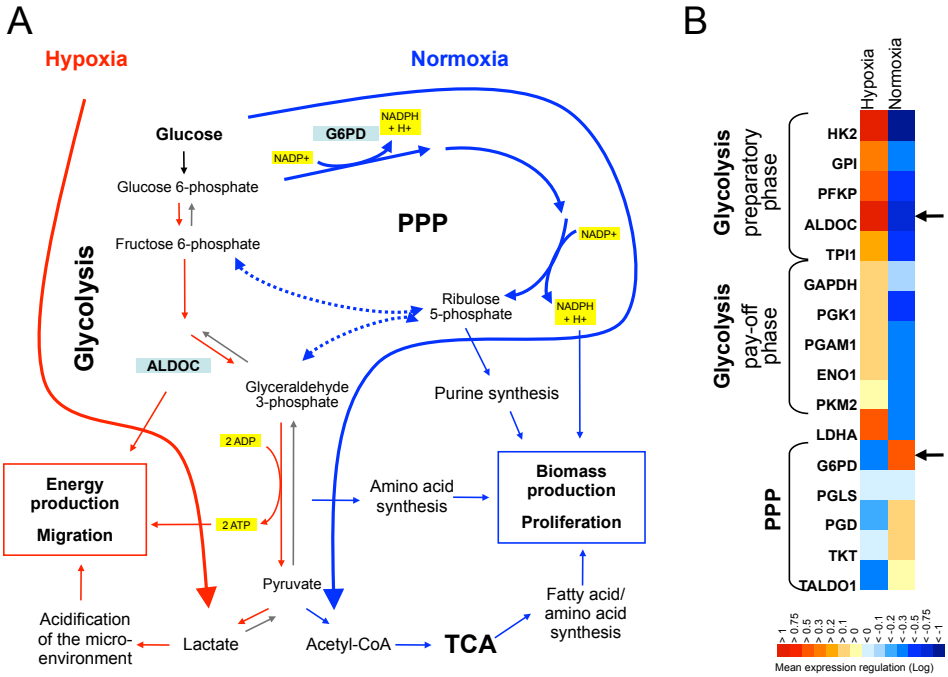
Abstract

Katrin Lamszus, Hamburg

Katrin Lamszus MD is scientific head of the Hans-Dietrich-Herrmann Laboratory for Brain Tumor Biology at the University Medical Center Hamburg-Eppendorf (UKE). Her work focuses on the basis of brain tumor development as well as the development of new treatments. Specific interest of her laboratory lies on glioma metabolism, tumor stem cells, EGFR signaling in glioblastoma, clonal analyses on intratumoral heterogeneity of glioblastomas as well as tumor immunology.

Alterations of Glucose Metabolism in Glioma Cells

The aggressive clinical phenotype of malignant gliomas is closely linked to characteristic adaptations of cellular metabolism. Activated oncogenes and inactivated tumor suppressors redirect glucose metabolism away from oxidative phosphorylation to aerobic glycolysis (Warburg effect). This allows cells to survive conditions of fluctuating oxygen tension that would be lethal to cells that rely on oxidative phosphorylation to generate ATP. High rates of glycolysis are further necessary to meet the increased anabolic requirements of the growing and dividing tumor cells. Glycolytic intermediates fuel the pentose phosphate pathway (PPP), which generates ribose-5-phosphate and NADPH for the biosynthesis of nucleic acids and fatty acids. Activation of the PPP is elevated in glioblastoma cells under normoxic conditions, whereas hypoxia causes downregulation and a flux shift towards glycolysis. This shift is further associated with reduced cell proliferation but accelerated migration, linking the metabolic switch to the "go versus grow" behaviour. Glycolysis also fuels the serine synthesis pathway, which contributes to nucleotide, protein and lipid synthesis and is closely linked with the folate and methionine cycles. Another advantage of enhanced glycolysis is high lactate production and acidification of the microenvironment, which contribute to tumor invasion and immune suppression. Finally, during evolution glycolytic enzymes have frequently acquired secondary "moonlighting" functions. For example, hexokinase 2 exerts anti-apoptotic effects and glucose 6-phosphate isomerase is identical to autocrine motility factor (AMF), a secreted cytokine that can stimulate glioma cell migration. Taken together, glucose metabolic rewiring contributes to glioma progression by diverse mechanisms, offering multiple vulnerabilities for therapeutic targeting.


A
Hypoxia
Normoxia
Glucose
G6PD
NADPH + H+
NADP+
Glucose 6-phosphate
PPP
Fructose 6-phosphate
Glycolysis
NADP+
Ribulose 5-phosphate
NADPH + H+
ALDOC
Glyceraldehyde 3-phosphate
Purine synthesis
2 ADP
Energy production
Migration
2 ATP
Amino acid synthesis
Biomass production
Proliferation
Pyruvate
Fatty acid/ amino acid synthesis
Acidification of the micro-environment
Lactate
Acetyl-CoA
TCA
B
Hypoxia
Normoxia
Glycolysis preparatory phase
HK2
GPI
PFKP
ALDOC
TPI1
Glycolysis pay-off phase
GAPDH
PGK1
PGAM1
ENO1
PKM2
PPP
LDHA
G6PD
PGLS
PGD
TKT
TALDO1
> 1
> 0.75
> 0.5
> 0.3
> 0.2
> 0.1
> 0
< 0
< -0.1
< -0.2
< -0.3
< -0.5
< -0.75
< -1
Mean expression regulation (Log)

Abstract

Valter D. Longo, Los Angeles

Valter D. Longo PhD is the Edna Jones Professor in Gerontology and Professor in Biological Science at the University of Southern California (USC), Los Angeles. He is also the Director of the USC Longevity Institute. He is interested in understanding the fundamental mechanisms of aging in yeast, mice and humans by using genetics and biochemistry techniques. He is also interested in identifying the molecular pathways conserved from simple organisms to humans that can be modulated to protect against multiple stresses and treat or prevent cancer, Alzheimer's Disease and other diseases of aging. The focus is on the signal transduction pathways that regulate resistance to oxidative damage in yeast and mice.

Starvation-dependent Differential Stress Resistance and Sensitization in Cancer Treatment

Working in S. cerevisiae, we described the effect of glucose in activating the Ras-adenylate cyclase-PKA pathway and inactivating zinc finger transcription factors Msn2/4, leading to reduced stress resistance and accelerated aging. We later discovered that the Tor-S6k/Sch9 pathway, activated by amino acids and particularly by threonine and valine, promotes growth, aging and cellular sensitization via the inactivation of transcription factor Gis1. Based on our discoveries in yeast, we showed how the removal of all nutrients (starvation/fasting) can reduce both glucose and IGF-1 and cause protection from chemotherapy in normal mammalian cells and mice while sensitizing a variety of cancer cells to chemotherapy but also to new generation cancer drugs like tyrosine kinase inhibitors. I will present evidence on the molecular mechanisms responsible for both the protective effects of starvation in normal cells and its sensitizing effects in different cancer cell types.

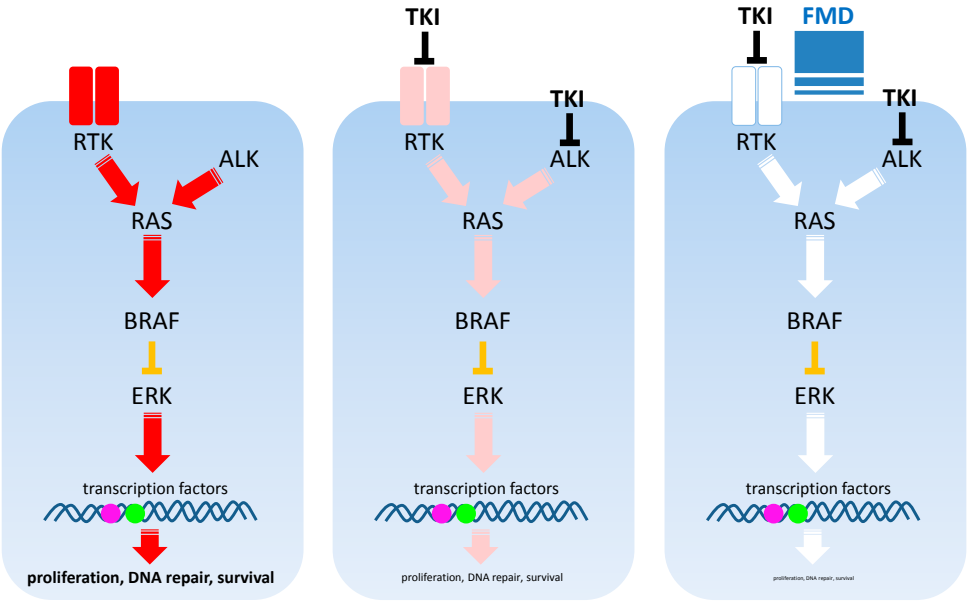
Abstract

Alessio Nencioni, Genoa

Alessio Nencioni MD is Professor at the Department of Internal Medicine at the Università degli Studi di Genova. One of his research interests lies on the effects of signal transduction inhibitors in the context of dietary interventions such as short term starvation to treat cancer.

Fasting Plus Tyrosine Kinase Inhibitors in Cancer

Tyrosine kinase inhibitors (TKIs) are the mainstay of treatment in many types of cancer, including lung and renal cancer. However, their benefit is frequently short-lived, mandating the search for safe potentiation strategies. Cycles of fasting enhance the activity and reduce the toxicity of chemo-radiotherapy in preclinical cancer models and dietary approaches based on fasting are currently explored in clinical trials at American and European institutions. We conducted a preclincial study to determine whether combining fasting with TKIs could be potentially beneficial. Culture conditions that recreate the metabolic consequences of fasting were found to increase the ability of commonly administered TKIs, including erlotinib, gefitinib, lapatinib, crizotinib and regorafenib, to block cancer cell growth, to inhibit the mitogen-activated protein kinase (MAPK) signaling pathway and to reduce E2F-mediated transcription. In lung and colorectal cancer xenografts, both TKIs (crizotinib and regorafenib) and cycles of fasting were found to slow tumor growth (to a similar extent), but, when combined, these interventions were significantly more effective than either type of treatment alone. Therefore, cycles of fasting or of specifically designed fasting-mimicking diets could be a safe and effective approach to potentiate the activity of TKIs in the clinic.



Potentiation of TKI activity by a FMD. TKIs in clinical use block the activity of receptor tyrosine kinases (RTK) and oncogenic TKs achieving remarkable clinical responses. Nevertheless, due to adaptation/resistance mechanisms in cancer cells the ability of these drugs to control tumour growth is partial and, frequently, short lived. However, when administered in concomitance with short term starvation regimens, such as a FMD, TKIs achieve a more thorough inhibition of the oncogenic signaling pathways leading to a more effective tumour growth inhibition.

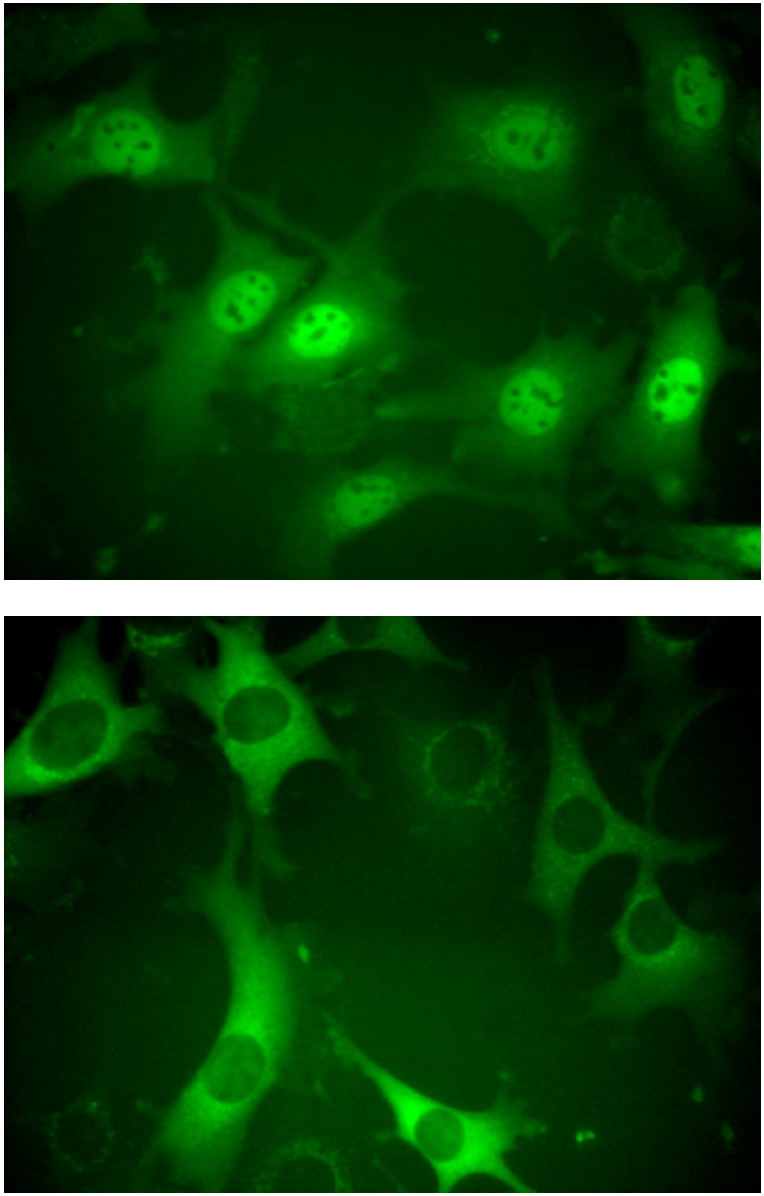
Abstract

Christiane Opitz, Heidelberg

Christiane Opitz MD is head of the DKFZ Junior Group Brain Cancer Metabolism. She has a special interest in tryptophan metabolism in brain cancer cells and pioneered work that identified tryptophan metabolites as activators of the dioxin receptor resulting in enhanced invasiveness and clonogenicity of brain tumor cells and increased formation of brain tumors.

Tryptophan Metabolism as a Target for Glioma Therapies

The definition of "evading immune destruction" as an emerging hallmark of cancer reflects the increasing recognition of immune suppression and escape as critical traits of malignancy. The degradation of tryptophan is a potent immunosuppressive mechanism involved in the suppression of anti-tumor immunity. The expression and activity of tryptophan degrading enzymes such as indoleamine-2,3-dioxygenase (IDO) or tryptophan-2,3-dioxygenase (TDO) are upregulated in tumors or in the tumor microenvironment. This talk will give an overview of the regulation of tryptophan degradation in gliomas, introduce novel assays to monitor tryptophan metabolism and outline the development of drugs that modulate this pathway.



Translocation of GFP-tagged aryl hydrocarbon receptor (AHR) into the nucleus after treatment of the cells with tryptophan metabolites.

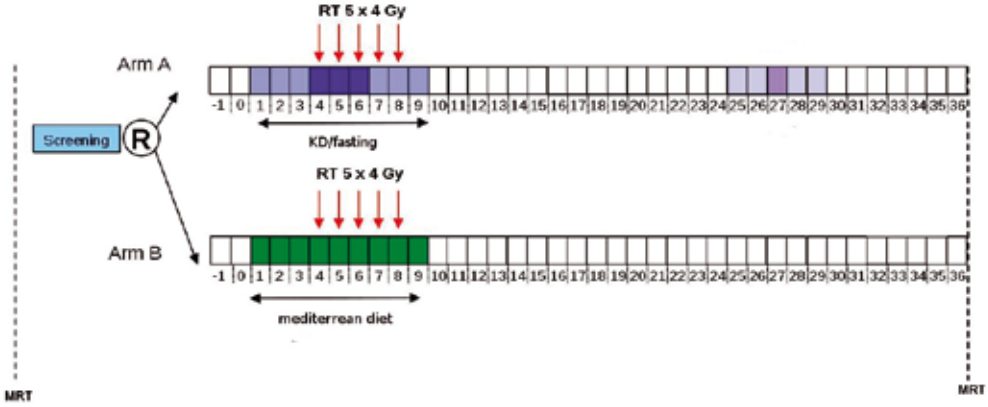
Abstract

Johannes Rieger, Tuebingen/Frankfurt

Johannes Rieger MD is the former deputy director of the Senckenberg Institute of Neurooncology and currently senior physician at the Interdisciplinary Section of Neurooncology at the University Hospital Tuebingen. His research interest focuses on tumor metabolism with a special focus on tumor mitochondrial functions as well as potential of dietary interventions for brain tumor patients. He pioneered work on ketogenic and fasting interventions at the University Hospital Frankfurt.

Clinical Application of Dietary Concepts in Brain Tumor Patients: the ERGO Studies

In recent years, it has been increasingly recognized that calorie- and/or carbohydrate restriction might have potential as a new treatment strategy against tumors. This assumption is based on a number of preclinical studies which demonstrated efficacy of restrictive diets in different animal tumor models. In 2007, we therefore set up the ERGO trial as a prospective pilot study where 20 patients suffering from recurrent malignant glioma were treated with an unrestricted ketogenic diet. We showed that the ketogenic diet (KD) could safely be applied to the patients, and that ketosis was reached in the majority of the patients. Median progression free survival (PFS) of these patients was 5 (range,3-13) weeks, and the median survival from enrollment was 32 weeks. Together, these results indicated that a dietary approach is feasible in glioma patient, but that the unrestricted diet seems to have no clear clinical efficacy against recurrent malignant glioma. Because in the majority of animal models, calorie-restriction is necessary for antitumor effects of KD, the ERGO2 study was designed. In this prospective randomized study, 50 patients with recurrent malignant glioma who are eligible for reirradiation are to be randomized to either a non-calorie-restricted mediterrean diet or a calorie-restricted KD and transient fasting during radiotherapy. The primary study end point is the progression free survival rate at 6 months, secondary end points include metabolic parameters and MRI measures of energy metabolism. Randomizsation started in 2013, and 35 patients were randomized until October 2016. As it is still unclear, which metabolic effects in tumors are achieved by KD and short-term fasting, we are now planning the ERGO3 trial where it is planned to examine the extracellular fluid of glioma tissue by microdialysis in patients before and during calorie-restriction. Together, the results of ERGO2 and ERGO3 will help us to understand whether restrictive dietary approaches can alter the metabolism and inhibit the growth of glioma in patients.



Layout of the ERGO-2 Trial

Abstract

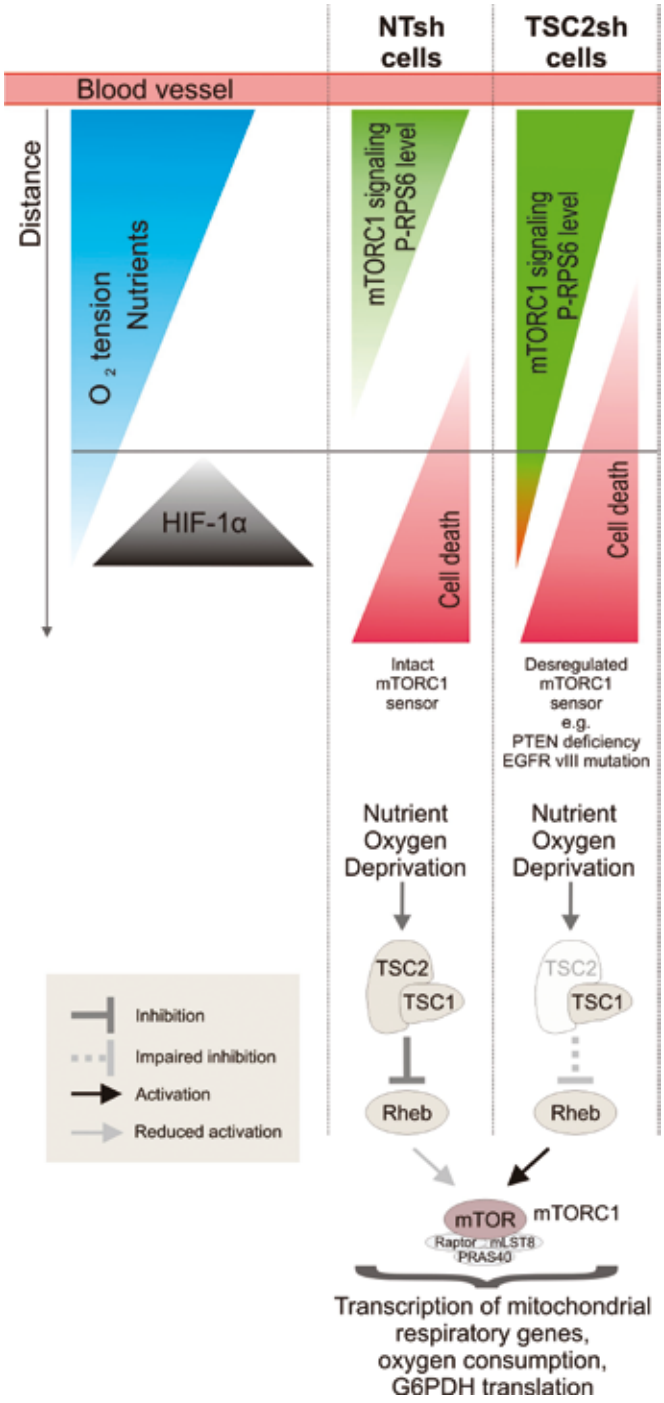
Michael Ronellenfitsch, Frankfurt

Michael Ronellenfitsch MD is head of the laboratory of the Dr. Senckenberg Institute of Neurocooncology at the University Hospital Frankfurt. His research interest focuses on cellular signaling in the tumor microenvironment including conditions of glucose and oxygen restriction and resulting effects on therapeutic resistance. In this context a special focus lies on EGFR and mTOR signaling.

Starvation Signaling and Resistance towards Kinase Inhibitors

Glioblastomas (GBs) are characterized by a fast uncontrolled growth leading to hypoxic areas and necrosis. Signaling from epidermal growth factor receptor (EGFR) via mammalian target of rapamycin complex 1 (mTORC1) is one of the most commonly altered signaling pathways in GBs. Therefore, EGFR and mTORC1 signaling are plausible targets for GB therapy and clinical trials with inhibitors are in progress. However, EGFR and mTORC1 inhibition triggers metabolic changes leading to adverse effects under the conditions of the tumor microenvironment by protecting tumor cells from hypoxia-induced cell death. Conversely mTORC1 activation sensitizes glioma cells towards hypoxia-induced cell death.

As a model for mTOR inhibition we used pharmacological inhibitors as well as shRNA-mediated gene suppression. As a model for mTORC1 activation we used TSC2 gene suppression (TSC2sh). TSC2sh glioma cells showed increased sensitivity towards hypoxia-induced cell death that was accompanied by an earlier ATP depletion and an increase in reactive oxygen species. There was no difference in extracellular glucose consumption but an altered intracellular metabolic profile with an increase of intermediates of the pentose phosphate pathway (PPP). Mechanistically, mTORC1 upregulates the first and rate limiting enzyme of the PPP, glucose 6-phosphate dehydrogenase (G6PD), in a post-transcriptional manner. Furthermore an increase in O2 consumption in TSC2sh cells was detected. This appeared to be due to higher transcription rates of genes involved in mitochondrial respiratory function including PGC-1-α and -β. In a translational approach, the finding that mTORC1 activation causes an increase in O2 consumption and renders malignant glioma cells susceptible to hypoxia and nutrient deprivation could help identify GB patient cohorts more likely to benefit from hypoxia-inducing therapies such as the VEGF-A-targeting antibody bevacizumab.



Model of deregulated mTORC1 signalling and vulnerability to starvation conditions in glioblastoma.

Abstract

Adrienne Scheck, Phoenix

Adrienne Scheck, PhD, is Associate Professor at the Barrow Neurological Institute in Phoenix Arizona. She is also Adjunct Professor in the School of Life Sciences at Arizona State University and an Associate Investigator in the Cancer Biology Program at the Arizona Cancer Center of the University of Arizona. Her work focuses on translational research to develop novel adjuvant therapies for the treatment of brain tumors and also includes various molecular and molecular genetic techniques to investigate why current therapies sometimes fail.

Altering Metabolism for the Therapy of Glioma and other Cancers

The renewed interest in targeting metabolism as a therapy for cancer has spurred investigations on the use of a therapeutic ketogenic diet (KD) for the treatment of malignant glioma. This high fat, low carbohydrate and adequate protein diet causes a reduction in blood glucose which is thought to reduce tumor growth, while providing increased blood ketones to support the energy needs of normal tissues. Preclinical work has shown that the KD reduces tumor growth in a variety of glioma models; however, its anti-tumor activity goes far beyond the effects of reduced energy in tumor cells. Indeed, the KD has pluripotent effects on a variety of tumor processes including angiogenesis, inflammation and peri-tumoral edema, migration and invasion, the expression of pro-tumor transcriptional activators and the anti-tumor immune response. In addition to the effects of the KD when used alone, it has been shown to enhance the activity of radiation and chemotherapy in a mouse model of glioma, thus increasing survival. The data from animal models is supported by retrospective human studies showing that hyperglycemia during radiation therapy is a negative prognostic factor. Additional studies in vitro are demonstrating that increasing ketones without altering glucose levels can inhibit cell growth and potentiate the effects of radiation. Mechanistic analyses are suggesting that this may be due, in part, to epigenetic changes. Thus, while we are only beginning to understand the mechanisms through which the KD affects tumor growth and response to therapy, these data provide strong support for the use of a KD in the treatment of malignant gliomas.

Notes

Notes

Venue
Lecture Room 22-2
University Hospital Frankfurt
Theodor-Stern-Kai 7
60590 Frankfurt/Main

Details und Updates
www.kgu.de/neuroonkologie

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Local OK
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UNIVERSITY HOSPITAL FRANKFURT
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University Cancer Center

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Deutsches Konsortium für Translationale Krebsforschung