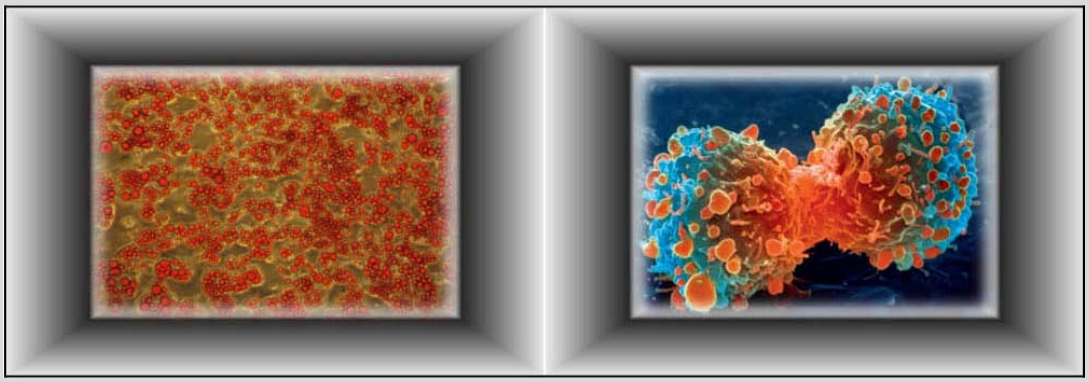
DKFZ-MOST Cooperation in Cancer Research

5th German-Israeli Cancer Research School

Hotel Pichlmayrgut, Austria

December 9-13, 2012

Metabolism and Cancer



Program and Book of Abstracts

GERMAN CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

Ministry of Science and Technology (MOST), Israel

Foreword

The German Israeli Cooperation in the field of cancer research, founded in 1976, has supported more than 150 joint research projects. The 35th Anniversary will be celebrated in Heidelberg on March 2013 during the 36th Meeting of the Joint Scientific Program Committee.

In 2006, during the 30th Anniversary of the Cooperation, the idea of a "German Israeli Cancer Research School" was conceived. Our aim was to bring together young scientists (students and post docs in particular of the program) with the senior scientists in the field of cancer research from both countries, Israel and Germany, for the exchange of knowledge and ideas in a friendly and casual atmosphere. Lectures by well-renounced scientists from both countries give the opportunity to discuss the most recent scientific methods and achievements in exciting and emerging areas of cancer research.

For this 5th School of Cancer Research, the topic "Metabolism and Cancer" was chosen. We are indebted to Prof. Ari Elson and Prof. Stephan Herzig for organizing the scientific program and to Ms Elfriede Mang, Ms Tatiana Golea and Ms Nurit Topaz for all the administrative matters.
The speakers will highlight recent advances in common signalling nodes between normal cells, discuss the recently established risk connection between metabolic dysfunction and cancer, and present novel therapeutic approaches in this area of biomedicine.

Again, as during the other schools, enough time will be reserved for social activities to enhance interactions amongst both the participating students and scientists.

We look forward to an exciting and interesting 5th German Israeli Cancer Research School in Pichl, Austria.

Wolfhard Semmler
DKFZ-Coordinator Israel-Cooperation
and of the Schools

Varda Rotter
Israeli Coordinator
of the Schools

Ahmi Ben-Yehudah
MOST Coordinator

Program

MONDAY, DECEMBER 10TH, 2012

08:30 Welcome and Introduction
Prof. Ari Elson, Weizmann Institute of Science, Rehovot;
Prof. Stephan Herzig, German Cancer Research Center, Heidelberg;
Dr. Ahmi Ben-Yehudah, Ministry of Science and Technology, Jerusalem;
Prof. Dr. Dr. Wolfhard Semmler, German Cancer Research Center (DKFZ), Heidelberg

Moderator: *Stephan Herzig*

09:00 Metabolic reprogramming in lymphoma development and therapy
Jan Doerr, MDC, Berlin

09:45 Increased risk of cancer on obesity and diabetes; is hyerinsulinemia the culprit?
Derek LeRoith, The Clinical Research Institute at Rambam, Haifa

10:30 Coffee Break

10:45 Signaling and metabolism in Neoplastic cells
Carolyn Algire, DKFZ, Heidelberg

11:30 Transcriptional and epigenetic control of the IGF-1 receptor gene: Implications in metabolism and cancer
Haim Werner, Tel Aviv University, Tel Aviv

12:15 Skiing/winter sports

16:00 Coffee and cake

16:30 Poster Session by students & general discussion
Moderator: *Ari Elson*

18:30 Dinner

19:45 Sledging

22:00 Social gathering

TUESDAY, DECEMBER 11TH, 2012

Moderator: *Haim Werner*

08:45 **Growth control by mTOR**
Ganna Panasyuk, Inserm, Paris

09:30 **Elucidation of metabolic changes in breast cancer using high resolution mass spectrometry based proteomics**
Tamar Geiger, Tel Aviv University, Tel Aviv

10:15 Coffee Break

10:30 **Promoting of metabolic health and lifespan by transiently increasing oxidative stress**
Michael Ristow, Institut für Ernährungswissenschaften, Jena

11:15 **Protein tyrosine phosphatases in cancer and metabolism**
Ari Elson, Weizmann Institute of Science, Rehovot

12:15 **Skiing/winter sports**

16:00 Coffee and cake

16:30 **Poster Session by students & general discussion**
Moderator: *Tamar Geiger*

19:00 Dinner

Moderator: *Rudolf Kaaks*

20:00 **Exploring dietary and metabolic mechanism of colorectal cancer development. Recent results from the EPIC cohort**
Mazda Jenab, IARC, Lyon

20:45 **Regulation of mammalian life-span by sirtuins**
Haim Cohen, Bar-Ilan University, Ramat Gan

WEDNESDAY, DECEMBER 12TH, 2012

Moderator: *Eyal Gottlieb*

08:45 **Nutrition, lifestyle and cancer: epidemiological evidence implicating the role of endogenous hormones and metabolism**
Rudolf Kaaks, DKFZ, Heidelberg

09:30 **Metabolic control of cancer cell's fate**
Eyal Gottlieb, The Beatson Institute for Cancer Research, Glasgow

10:15 Coffee Break

10:30 **PPARs stand at the crossroads of metabolism, tissue repair and cancer**
Walter Wahli, UNIL, Lausanne

11:15 **Typ 2 diabetes and risk of cancer**
Karsten Muessig, Deutsches Diabeteszentrum, Duesseldorf

12:00 **Skiing/winter sports**

16:00 Coffee and cake

16:30 **p53 and systemic metabolism – from regulation of atherosclerosis to chemotherapy clearance**
Ido Goldstein, Weizmann Institute of Science, Rehovot

17:15 **Poster Awards**
Moderators: *Stephan Herzig* & *Ari Elson*

17:30 **Concluding Discussions**

19:00 Dinner

Contents of the Abstract Book:

Abstracts of Lectures

(in alphabetical order)

Signaling and Metabolism in Neoplastic Cells

Carolyn Algire

German Cancer Research Center, Heidelberg, Germany

Energy balance plays a pivotal role in both the risk of developing cancer and the progression of the disease. Neoplastic cells display altered metabolic requirements that serve to maintain a state of uncontrolled cell proliferation, even in the absence of external growth signals. The intricate pathways and feedback loops that keep cancer cells in a state of proliferation are complex and not fully understood. In the past, cancer cell metabolism research has focused on increased glycolysis and repressed oxidative phosphorylation, an effect known as the “Warburg Effect”; however, recent advances have shown the “Warburg Effect” is not the result of damaged mitochondria, as originally thought. Instead, the mitochondria of neoplastic cells have been reprogrammed to accommodate the needs of a transformed cell. In addition to increased glucose uptake, neoplastic cells require increased synthesis of nucleotides, lipids, signaling molecules and reduction equivalents in order to produce viable daughter cells.

Metabolic signatures of neoplastic cells are a reflection of oncogene-directed reprogramming and the micro-environment in which the cells are growing. Mutations in metabolic pathways can help neoplastic cells adapt to increased energy demands, often in the presence of low glucose and poor oxygen supply. The tumor micro-environment can also impact the aggressivity of the tumor, as exemplified by accelerated tumor growth in animal models of diet induced obesity, inflammation and diabetes. Identification of the metabolic abnormalities associated with activation of particular oncogenes or loss of tumor suppressor genes, and improved understanding of the pathways involved can aid in the design of novel therapeutics that target and exploit these abnormalities, possibly rendering cancer cells unable to proliferate. This presentation will review the metabolic pathways involved in cancer cell metabolism, metabolic reprogramming as a consequence of cell mutations and how whole body energy balance can affect the proliferation of neoplastic cells.

Regulation of lifespan by sirtuins

Haim Cohen

Bar-Ilan University, Ramat Gan, Israel

The sirtuins are highly conserved enzyme homologues of the yeast Sir2, with activities of NAD+ dependent deacetylase and/or mono ADP ribosyltransferase. A long line of evidence has implicated sirtuins in regulating the aging process of yeast, worms, flies, and rodents. Moreover, much work has been published on the important role of sirtuins in several age-related diseases such as diabetes type II, cancer, cardiovascular diseases, and dyslipidemia. Until recently, the role of the seven mammalian sirtuins, SIRT1 to SIRT7, in regulating lifespan was unclear. Here, we review the role of sirtuins in regulating lifespan, In particular by regulating metabolism and genome stability. Especially in light of a recent publications showing a direct regulation of mammalian lifespan by a sirtuin family member, SIRT6.

Metabolic reprogramming in lymphoma development and therapy

***Jan R. Dörr*[1], *Yong Yu*[2], *Christoph Loddenkemper*[3], *Katharina Schleicher*[1], *Susanne Kratzat*[4], *Stefan Walenta*[5], *Ulrich Keller*[4], *Andreas K. Buck*[6], *Harald Stein*[7], *Wolfgang Müller-Klieser*[5], *Bernd Dörken*[1,2], *and Clemens A. Schmitt*[1,2]**

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[2]Max-Delbrück-Center for Molecular Medicine, Berlin, Germany
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[4]III. Medical Department, Technical University Munich, Munich, Germany
[5]Johannes Gutenberg University, Institute of Physiology and Pathophysiology, Mainz, Germany
[6]Department of Nuclear Medicine, Technische Universität München, Munich, Germany
[7]Charité - Universitätsmedizin Berlin/Department of Pathology, Berlin, Germany

The hyperproliferation of tumor cells as a result of oncogene activation or loss of tumor suppressor function does not only require self-sufficiency in growth signals or the evasion of cellular failsafe mechanisms, such as apoptosis or senescence, but also involves changes of energy metabolism in order to fuel cell growth and division. A hallmark feature of this cancer-specific metabolic phenotype, first described by Otto Warburg in the 1930s, is aerobic glycolysis: In contrast to normal cells, cancer cells reprogram their glucose metabolism in the presence of oxygen by increasing glucose uptake, glycolysis and lactate production, while suppressing the TCA cycle. The transcription factor Myc, which is activated in many types of cancer, particularly in lymphomas and leukemias, has emerged as a key regulator of aerobic glycolysis: It directly activates the transcription of many glycolytic enzymes, including those, which catalyse rate-limiting steps, such as hexokinase 2 and lactate dehydrogenase a. In this study we analyse the metabolic phenotype of lymphomas arising in Eμ-myc transgenic mice before and after therapy-induced senescence (TIS), a terminal G1 growth arrest in response to cytotoxic drug treatment, by transcriptome, metabolome and metabolic flux analysis in vitro as well as [^{18}F]-fluoro-thymidin positron emission tomography (FLT-PET) and [^{18}F]-fluoro-deoxyglucose PET (FDG-PET) imaging in vivo. Furthermore, we present evidence that a TIS-associated increase in glucose metabolism is a cellular response to cope with SASP-related proteotoxic stress. Inhibition of glycolytic or oxidative energy production, of lysosomal ATPases, or depletion of ATP all resulted in selective toxicity to tumor cells that had entered TIS before, but not to normal cells, which lack a TIS response. This senescence-targeting metabolic co-therapy is associated with improved overall survival of lymphoma bearing mice. Therefore, TIS-associated metabolic reprogramming imposes a cancer-specific vulnerability that can be selectively exploited by conceptually novel, „synthetic lethality“-like sequential treatment strategies against senescent tumors. This not only holds true for the Eμ-myc mouse lymphoma model, but also for the human condition, where primary samples of acute myeloid leukemias and various carcinoma cell lines recapitulated the senescence-conferred susceptibility to energy-depleting therapies. Overall, pharmacological targeting of metabolic demands upon TIS induction considerably adds to the long-term efficacy of cancer therapy.

Protein Tyrosine Phosphatases in Cancer and Metabolism

Ari Elson

Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot, Israel

In this overview talk we will introduce the protein tyrosine phosphatase (PTP) superfamily and explain its physiological roles, common principles of action and regulation of its members. We will discuss functions of PTPs in regulating specific metabolic processes and in regulating cellular transformation. Particular emphasis will be placed on two PTPs, which play roles in both systems: PTP1B and PTPe. We will discuss participation of PTPs in both sides of the transformation process, as supporters of the transformation process or as anti-oncogenes. We will show that PTPe and PTP1B can support cellular transformation by activating downstream kinases. We will also discuss the roles of PTP in regulating metabolic processes. Both PTPe and PTP1B down-regulate signaling by the receptors for insulin and leptin at the cellular and whole-animal levels, inducing hypersensitivity of leptin and insulin, resistance to weight gain, and improved regulation of glucose homeostasis in mice that lack either PTP.

Elucidation of metabolic changes in breast cancer using high resolution mass spectrometry based proteomics

Yair Pozniak[1]*, Livnat Jerby[2]*, Eytan Ruppin[1,2] and Tamar Geiger[1]

[1]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [2]The Blavatnik School of Computer Science, Tel Aviv University, Israel; *equal contribution

Metabolic reprogramming is an emerging cancer hallmark. After the initial recognition of the Warburg effect, the identification of oncogenes and tumor suppressors that affect metabolism, and the discovery oncogenic mutations in metabolic enzymes have re-stimulated the interest in this connection. Global and unbiased analyses of breast cancer clinical samples can unravel the network changes that occur with cancer progression and lead to better understanding of the mechanisms of metabolic remodeling. Analysis of the protein levels reflect more accurately the cellular phenotype than mRNA levels, however due to technological challenges, till today, the majority of expression analyses of breast cancer clinical samples have been performed on the transcript level. Technological developments in the proteomic field, such as high-resolution mass spectrometry combined with accurate quantification techniques can now enable a global view of cancer proteomes. Stable Isotope Labeling with Amino Acids in Cell Culture (SILAC) is a metabolic labeling technique that enables accurate quantification of proteins in mass spectrometry-based experiments. We have extended the applicability of SILAC to tissue sample with the development of the super-SILAC technique, in which a mixture of heavy labeled cell lines serves as an internal standard for tissue quantification. In combination with a method for extraction of proteins from formalin-fixed paraffin-embedded tissues, super-SILAC can be used to quantify panels of archived breast cancer clinical samples. We further combined our results with advanced computational analysis and metabolic modeling and revealed the global changes in cell growth and metabolite utilization with cell transformation. This work is the basis for future analysis, which aims to elucidate the biological significance of these metabolic alterations.

P53 and systemic metabolism – from regulation of atherosclerosis to chemotherapy clearance

Ido Goldstein

Weizmann Institute of Science, Rehovot, Israel

p53 is a sequence-specific transcription factor which controls cell-fate decisions through regulating gene expression. In an attempt to find p53-dependent, metabolism-related gene expression patterns we employed the microarray technique thereby revealing 341 genes whose expression was induced by p53 in the liver-derived cell line HepG2. From this gene list we identified three groups of genes, each pertaining to a specific metabolic process. **The first group** consisted of 20 genes involved in many aspects of lipid homeostasis. The mode of regulation of three representative genes (*PLTP*, *ABCA12* and *CEL*) was further characterized. In addition to HepG2, the genes were induced in a p53-dependent manner in other liver-derived cell types. Furthermore, p53 was found to bind to their promoter in designated p53 responsive elements (p53REs) and to increase their transcription in a reporter gene assay. Of note, p53 induced a significant elevation in the protein level of PLTP and CEL and augmented the activity of secreted PLTP, which plays a major role in lipoprotein biology and atherosclerosis pathology. **The second group** (of 11 genes) encode cytochrome P450 enzymes which are liver-resident enzymes participating in various metabolic processes. The mode of regulation of four representative genes (*CYP3A4*, *CYP3A7*, *CYP4F2* and *CYP4F3*) was further characterized. In addition to HepG2, the genes were induced in a p53-dependent manner in other liver-derived cell types. Furthermore, p53 was found to bind to p53REs in the genes' DNA regulatory regions and to enhance their transcription in a reporter gene assay. Importantly, when p53 was activated following the administration of either of three different anti-cancer chemotherapeutic agents, it was able to induce the expression and activity CYP3As, the main factors in systemic clearance of these agents. **The third group** consists of genes involved both in gluconeogenesis (G6PC, PCK2) and in supplying glucogenic precursors (GK, AQP3, AQP9, GOT1). Accordingly, p53 augmented hepatic glucose production in both human liver cells and primary mouse hepatocytes.

Collectively, these findings position p53 as a regulator of various metabolic pathways and put forward a role for p53 in maintaining systemic homeostasis.

Metabolic control of cancer cells' fate

Eyal Gottlieb

The Beatson Institute for Cancer Research, Glasgow, UK

In order to engage in fast replicative division, a cancer cell must duplicate its genome, synthesis proteins and lipids, and assemble these components to form daughter cells. These activities require increased uptake of nutrients to be used as biosynthetic precursors and an energy source. However, rapid tumour growth surpasses the required blood supply and exposes cancer cells to extreme conditions of metabolic deficit and stress. Therefore, cancer cells undergo many metabolic changes (collectively known as 'metabolic transformation') that support their growth and survival. Cancer cells metabolism is exemplified by high glucose consumption and lactate production. Specifically, they over-express the M2 isoform of the tightly regulated enzyme pyruvate kinase (PKM2), which controls the glycolytic flux. Furthermore, cancer cells are highly dependent on de novo biosynthesis of serine and glycine from glucose. Pyruvate kinase, which catalyses the last step of glycolysis, has emerged as a potential regulator of these metabolic phenotypes. However, the mechanisms by which PKM2 coordinates high energy requirements with high anabolic activities, and supports cancer cell proliferation, are still not completely understood. We identified a novel rheostat-like mechanistic relationship between PKM2 activity and serine biosynthesis. We show that serine can bind to and activate PKM2 and that following serine deprivation, PKM2 activity in cells is reduced. This reduction in PKM2 activity shifts cells to a fuel-efficient mode where more pyruvate is diverted to the mitochondria and more glucose derived carbon is channelled into serine biosynthesis to support cell proliferation.

Exploring Dietary and Metabolic Mechanisms of Colorectal Cancer Development

Recent results from the EPIC cohort

Mazda Jenab

Section of Nutrition and Metabolism, International Agency for Research on Cancer (IARC-WHO), The World Health Organization, Lyon, France

Worldwide, colorectal cancer (CRC) ranks fourth in men and third in women in incidence with over 1 million new cases occurring every year. There is wide global variation in incidence rates, which change over time and vary with differences in diet and lifestyle, as evidenced historically by migrant studies and recently by a large body of epidemiologic evidence. For these reasons, CRC has been identified as a cancer that is potentially preventable by changes in diet and lifestyle, such as reduction of obesity (particularly visceral adiposity), physical inactivity, consumption of red/processed meats and alcohol; increase intake of calcium, milk/dairy products, and foods containing dietary fiber, as recommended in the recent 2007 WCRF report.

The study of CRC etiology is very complex since the colorectum is constantly exposed to various dietary, environmental, metabolic and hormonal factors from both the systemic and luminal sides. The underlying biologic mechanisms relating diet and lifestyle to CRC are not well established and are the subject of intense current research in the EPIC cohort. The main drivers of these associations are thought to be the metabolic abnormalities of obesity and energy excess, as well as chronic inflammation, oxidative stress and modulation of cell cycle kinetics. The key metabolic consequences of obesity and energy excess include the development of type 2 diabetes, dyslipidemia, insulin resistance and hyperinsulinemia. Insulin is central to energy regulation and may directly influence CRC risk via mitogenic/antiapoptotic effects through the insulin receptor or by increasing energy provision to CRC cells with growth-promoting consequences. Many of these factors are related to the metabolic syndrome, a heterogeneous condition clustering various metabolic abnormalities. It has been shown to play a major role in the development cardiovascular diseases and diabetes mellitus, and is also thought to be closely associated with CRC risk.

Similarly, chronic inflammation and increased oxidative stress are being explored as inter-related mechanistic pathways towards CRC promotion. The latter can be exacerbated by diets poor in antioxidant nutrients, which lead to an oxidant/antioxidant imbalance. Both dietary depletion of antioxidant nutrients, such as vitamin E and increased intake of pro-oxidant nutrients, such as iron (e.g. from high intake of red meats) have been shown to increase levels of oxidative stress in the colorectum.

A compound of major interest in CRC prevention is vitamin D. It has been shown to have roles in cell cycle regulation, growth factor signaling, and modulation of immune and inflammatory responses. Many epidemiological studies worldwide, including results from the EPIC cohort, show strong inverse CRC risk associations with this compound. Yet to date, randomised trials of vitamin D supplementation and cancer risk, regarded as the gold standard of showing a cause and effect relationship, have been largely inconclusive.

Despite advances in screening and treatment, CRC mortality has declined only modestly in recent years in most European or other Western countries. Identification of the key modifiable dietary and lifestyle determinants of CRC risk and their underlying mechanisms of action can contribute greatly to the formulation of effective CRC preventive strategies.

Excess body weight, diabetes and cancer: epidemiologic evidence implicating hormonal and metabolic mechanisms.

Rudolf Kaaks

Division of Cancer Epidemiology; German Cancer Research Center (DKFZ), Heidelberg, Germany

Epidemiological observations increasingly implicate nutritional energy balance as a key risk factor for cancer development. Excess body weight is associated with increased risks of cancers of the endometrium, breast (postmenopausal women), kidney (renal cell tumours), colon, pancreas and oesophagus (adenocarcinomas), and is also a well-documented risk factor for high-grade prostate cancer. By contrast, regular physical activity reduces the risks of breast and colorectal cancers and potentially other tumour types, and overall, excess weight and lack of physical activity have been estimated to potentially account for one quarter to half of the occurrence of the most frequent tumour types in affluent, industrialized societies. Animal experiments have shown uniformly protective effects of dietary energy restriction against tumor development.

Physiologic mechanisms that are thought to account for these effects of nutritional energy balance on cancer risks include changes in the metabolism of endogenous hormones, growth factors and inflammation factors, as well as in energy and nutrient status at the level of single cells. Together, these physiologic changes may stimulate cell growth and proliferation, inhibit apoptosis, and favour the occurrence of genetic mutations through increased oxidative stress. The key mechanisms that underlie these relationships of nutritional energy balance with cancer development may strongly depend, however, on tumour type.

Prospective cohort studies have shown relationships of risks of various cancer types with blood levels of glucose and insulin, and insulin-like growth factor-I. Furthermore, increased levels of circulating androgens and estrogens and reduced levels of progesterone are strongly implicated especially in the development of cancers of the endometrium and breast, among women with excess weight. The implication of specific hormonal or metabolic factors in cancer development is further increased by a growing body of evidence from human intervention studies – e.g. using selective estrogen receptor modulators [SERMS] and aromatase inhibitors – and epidemiological studies on the effects of specific hormonal medications (e.g., oral contraceptives and postmenopausal hormone replacement therapy; specific anti-diabetic drugs). Finally, several studies have shown increased risks of cancer, e.g. of the colorectum and endometrium, among subjects with higher than average serum levels of inflammation factors such as C-reactive protein, TNF-alpha or various interleukins. Knowledge gained about the hormonal and other physiologic mechanisms that link nutritional energy balance to cancer increasingly is also informing translational research into cancer preventive and curative treatments.

Increased risk of cancer on obesity and diabetes; is hyperinsulinemia the culprit?

Derek LeRoith

Diabetes and Metabolism Clinical Research Center of Excellence, Clinical Research Institute at Rambam, Rambam- Health Care Campus
The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel

There is strong epidemiological evidence that the metabolic syndrome, obesity and Type 2 diabetes predispose the individual to an increased cancer risk and cancer-related mortality, including breast cancer. We used a genetically engineered mouse model of hyperinsulinemia (MKR) to study these effects on transgenic-induced or orthotopically-introduced mammary tumors.

The MKR male mice are diabetic with severe insulin resistance, hyperinsulinemia, hyperglycemia and hyperlipidemia; female MKR mice demonstrate only hyperinsulinemia in the absence of hyperglycemia and hyperlipidemia and therefore are extremely useful to study hyperinsulinemia in isolation on cancer development.

In the hyperinsulinemic female mouse, mammary tumors that developed from MVT1 (c-myc/vegf oncogenic) cells grew faster and resulted in more lung metastases than in wild type mice with normal insulin levels. Blocking the action of the insulin/IGF-1 receptors using a tyrosine kinase inhibitor reduced the tumor size and extent of metastases. Reducing the hyperinsulinemia demonstrated a similar inhibition. Thus, hyperinsulinemia alone may enhance tumor growth and metastases.

A similar result was obtained using the inducible Neu oncogenic transgenic mouse on the MKR background (rtTA-Neu/MKR), where doxycycline-induced mammary tumors and metastases were affected by the hyperinsulinemia.

We propose that elements of the metabolic syndrome, found in obese individuals and patients with type 2 diabetes, and this case the hyperinsulinemia enhance cancer growth and metastases. We are examining how hyperinsulinemia alters primary tumor phenotype, increase primary tumor growth and metastases. These studies have demonstrated evidence of epithelial-mesenchymal transition, such as increased vimentin expression and alterations in microRNAs such as miR-9 that could explain the more aggressive phenotype and tendency to metastasize.

Type 2 diabetes and risk of cancer

Karsten Muessig

Deutsches Diabeteszentrum, Duesseldorf, Germany

Patients with type 2 diabetes mellitus and subjects with glucose intolerance are at a moderately increased risk for cancer. Insulin resistance together with hyperinsulinemia appears to play an important role in linking cancer and metabolic disorders through activated cell proliferation. While antidiabetic agents, which increase plasma insulin levels, seem to enhance cancer risk, insulin sensitizing drugs diminish the risk. Very recent clinical studies do not allow the conclusion that treatment with certain insulins, comprising the long-acting analogue insulin glargine, is associated with increased cancer risk. The present talk aims to give a comprehensive overview on the association between diabetes mellitus, its treatment, and cancer.

Cell growth control by mTOR

Ganna Panasyuk*, *Mario Pende

Inserm, Paris, France

Mammalian Target of Rapamycin (mTOR) plays an evolutionary conserved role in the control of organismal growth depending on nutrient availability. In the last few years our laboratory has investigated the functions of the mTOR substrates, Akt and S6 kinases. I will present evidence that Akt2 and S6K1 have complementary roles in the control of nutrient homeostasis.

S6K1 is a nutrient-sensitive kinase controlling cell size. One of the most common hypotheses is that S6K1 may act on cell growth by up-regulating protein synthesis. However by a number of techniques including microarray analysis on polysomal fractions, we fail to uncover a translational control by S6 kinases. Importantly S6 kinases regulate the expression of nucleolar proteins involved in rRNA processing and ribosome assembly. Since genetic screening for cell size regulators in yeast and Drosophila are enriched in nucleolar factors, our data reveal an evolutionary conserved signal transduction pathway that functionally links ribosome biogenesis and cell size. I will also present the involvement of mTOR and S6 kinase in Tuberous Sclerosis disease.

Akt2 is involved in the metabolic action of insulin, as underlined by the insulin resistance of the Akt2 knockout mice for their glycemic control. By using liver specific deletion of the tumour suppressor PTEN, we identify Akt2 are an essential factor promoting steatosis-associated tumorigenesis through the transcription factor PPARg and metabolic gene program.

PROMOTION OF METABOLIC HEALTH AND LIFESPAN BY TRANSIENTLY INCREASING OXIDATIVE STRESS

Michael Ristow

Until Dec 2012: Dept. Human Nutrition, Inst. of Nutrition, Univ. Jena, Germany
From Jan 2013: Energy Metabolism Lab, D-HEST, ETH Zürich, Switzerland

Recent evidence suggests that calorie restriction and specifically reduced glucose metabolism induces mitochondrial metabolism to reduce cancer growth, and to extend life span in various model organisms, including S. cerevisiae, D. melanogaster, C. elegans and possibly mice. In conflict with Harman's free radical theory of aging (FRTA), these effects may be due to increased formation of reactive oxygen species (ROS) within the mitochondria causing an adaptive response that culminates in subsequently increased stress resistance assumed to ultimately cause a long-term reduction of oxidative stress. This type of retrograde response has been named mitochondrial hormesis or mitohormesis, and may in addition be applicable to the health-promoting effects of physical exercise in humans and impaired insulin/IGF1-signaling in model organisms. Consistently, abrogation of this mitochondrial ROS signal by antioxidant supplements impairs the lifespan-extending and health-promoting capabilities of glucose restriction and physical exercise, respectively. In summary, the findings discussed indicate that ROS are essential signaling molecules which are required to promote health and longevity. Hence, the concept of mitohormesis provides a common mechanistic denominator for the physiological effects of physical exercise, reduced calorie uptake, glucose restriction, and possibly beyond.

PPARs stand at the crossroads of metabolism, tissue repair and cancer

Walter Wahli

Center for Integrative Genomics, National Research Center Frontiers in Genetics, University of Lausanne, Lausanne, Switzerland

The three isotypes of peroxisome proliferator-activated receptors (PPARs), PPARα, β/δ and γ, are ligand-inducible transcription factors that belong to the nuclear hormone receptor family. While they are best known as transcriptional regulators of lipid and glucose metabolism, PPARs are also implicated in additional important functions.

PPARα is involved in sexual dimorphism especially by down-regulating gene expression. Using the steroid hydroxylase Cyp7b1 gene as a model, the molecular mechanism of this PPARα-dependent repression was elucidated. Physiologically, this repression confers protection against estrogen-induced intrahepatic cholestasis.

The activation of PPARβ/δ induces a protection against diabetes and obesity. Ablation of Pparβ/δ in the pancreas leads to hyperinsulinemia due to an increase of pancreatic β-cell mass and insulin secretion. The results obtained provide evidence for a repressive role for PPARβ/δ in β-cell mass and insulin exocytosis. Furthermore, we have described a number of roles for PPARβ/δ in skin homeostasis. We showed that the activation of PPARβ/δ triggers keratinocyte survival. PPARβ/δ also stimulates cellular cascades required for keratinocyte directional sensing and migration. In addition, we demonstrated that the regulation of PPARβ/δ activity in fibroblasts contributes to the homeostatic control of keratinocyte proliferation. IL-1 produced by the keratinocytes activates PPARβ/δ expression in the underlying fibroblasts. In turn, PPARβ/δ inhibits the mitotic activity of keratinocytes, via inhibition of the IL-1 signaling pathway and reduction of mitogenic factors production by the fibroblasts. Our ongoing work demonstrates that PPARβ/δ is involved in skin tumor development after UV irradiation through the control of c-Src expression and downstream signaling pathways. In conclusion, PPARs are implicated in important processes controlling cellular fate as well as in major metabolic and inflammatory regulations with obvious medical implications, especially related to metabolic diseases, tissue repair and cancer.

Transcriptional and epigenetic control of the IGF-1 receptor gene: implications in metabolism and cancer

Haim Werner

Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

The insulin-like growth factors (IGFs) are important players in a network of biochemical events linking metabolic and mitogenic pathways. The bioactivity of IGF-1 depend on the concerted actions of a number of factors, including nutritional status, developmental stage, ligand biosynthesis, interactions with other hormonal systems, regulation of ligand bioavailability by IGF binding proteins, etc. Deregulation of the insulin/IGF axis has major pathological implications, ranging from nutritional-hormonal-metabolic conditions to disorders of proliferation.

Activation of the IGF-1 receptor (IGF-1R) signaling pathway is a fundamental requirement for acquisition of a neoplastic phenotype. IGF-1R gene expression is determined, to a large extent, at the transcriptional level. The IGF-1R promoter has been identified as a molecular target to a number of stimulatory transcription factors as well as nuclear proteins with tumor suppressor activity, including p53/p63/p73, BRCA1, Wilm's tumor-1, E2F1, HMGA1, etc. The etiology of cancers associated with loss-of-function mutation of tumor suppressors has been correlated with the inability of mutant tumor suppressors to suppress transcription of downstream targets, including the IGF-1R gene. Likewise, gain-of-function mutations of oncogenes have been associated with increased transactivation of the IGF-1R promoter.

In addition to transcriptional regulatory mechanisms, epigenetic events have been recently explored as an additional control level of IGF-1 action. Global methylation analyses have identified genes whose hypermethylation at specific cancer stages may lead to silencing or activation of the IGF-1R signaling pathway. Elucidation of the transcriptional and epigenetic mechanisms involved in IGF-1R regulation will improve our ability to deliver IGF-1R targeted therapies in a more effective manner.

Abstracts of Posters

The lymphatic vessel-adipose tissue interface: Implications on metabolic disorders and cancer

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Adipose tissue growth plays a pivotal role in the development of metabolic abnormalities such as insulin resistance. Besides the obvious effects on metabolism, there are many processes during adipose tissue expansion, which are not directly related to metabolism. Adipose tissue expansion may lead to hypoxia which is similarly observed during pathological tissue growth, e.g., as it occurs in tumors. As such, adipose tissue growth and tumor growth may – at least in part – follow similar growth factor and signaling networks. In line with this concept, adipose tissue has been described as a rich source of angiogenic cytokines, which mediate blood vessel angiogenesis but also of lymphangiogenesis. Lymphatic vessels maintain fluid balance, immune surveillance and transport of lipids in the body. During tumor progression, they actively facilitate metastasis. Failure in lymphatic transport and leakage from lymphatic vessels may result in lipid accumulation, which in turn may drive adipogenesis. Moreover, a high lipid content in the body can disrupt lymphatic transport and may alter the structure of collecting lymphatics, e.g. as observed in ApoE-deficient mice. Clearly, all of these circumstantial findings suggest an intricate crosstalk between adipose tissue and the lymphatic system. Our lab has recently identified CD36 to be present in human lymphatic endothelial cells (LECs). Both, differentiating adipocytes and macrophages strongly express the scavenger receptor CD36. As such, ongoing experiments are aimed at studying the role of CD36 in the context of lymphatic function and adipogenesis. The results of these studies will contribute to establishing a causal molecular basis for the surprising functional link between lymphatic function and adipogenesis.

The link between the metabolic syndrome and Cancer

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The metabolic syndrome, including patients with either obesity or Type 2 diabetes, is associated with an increased risk of cancer and cancer-related mortality. We chose two animals model to investigate these epidemiological studies.

The first: Cancer and Type 2 diabetes:

The goal of my work is to determine the factors involved in enhanced breast cancer development and progression in Type 2 diabetes. Epidemiological studies have shown that the risk of developing breast cancer is significantly increased in patients with Type 2 diabetes, and also that prognosis is worsened in diabetic individuals. While adiposity is also related to increased risk of cancer development and mortality, it is now clear that breast cancer risk in diabetic individuals is independent of adiposity. The mechanisms involved in the effect of diabetes on breast cancer risk and mortality have not been established. Type 2 diabetes is defined by insulin resistance, hyperinsulinemia, and hyperglycemia; a constellation of factors that are known to affect cellular metabolism. We developed a mouse model of Type 2 diabetes (called MKR) by inducing severe insulin resistance in the skeletal muscle through transgenic expression of a dominant-negative IGF type 1 receptor (IGF-1R). The resultant phenotype displays all of the classic components of Type 2 diabetes, except for increased adiposity. In preliminary data, we show that the MKR mouse develops mammary tumors at increased rates and with more aggressive features than control animals. Therefore the MKR mouse can be used to study the role of factors such as hyperinsulinemia in breast cancer risk in the absence of the confounding factors associated with adiposity. We hypothesize that the enhanced cancer growth and metastases in Type 2 diabetes is related to hyperinsulinemia that leads to activation of the insulin receptors (IRs) and IGF-1Rs (probably through hybrid receptors) and propose the next aim. Aim: Determine whether the enhanced incidence, growth and metastases of mammary tumors in mice with Type 2 diabetes is due to a cell-autonomous action on the mammary epithelium mediated by hyperinsulinemia or hyperglycemia. In order to determine the relative contribution of hyperinsulinemia and hyperglycemia as the main etiological factor in the increased tumor development we treated the MKR mice with Leptin. Leptin is an adipocyte-derived hormone that plays a key role in the regulation of food intake and energy expenditure. Our previews data shown that leptin improves insulin resistance and hyperglycemia in MKR mice (mouse model of Type 2 Diabetes), Our data suggest that leptin could be a potent antidiabetic drug in cases of type 2 diabetes that are not leptin resistant. Results: we used the syngeneic Met-1 and Mvt-1orthotopic model for breast cancer. 9 weeks old females or males MKR mice were injected with Met-1 or with Mvt-1 cancer cells (into mammary fat pad #4 in females or subcutaneous in males). One week after cell injection Alzet pumps with Leptin were implemented in these mice for 14 days. This experimental design allows us to see the leptin effects on Breast cancer progression and metastasis (only with Mvt-1 cells). During the 14 days the mice were weighed, tumor volume was measured and fat was measured with NMR. At the end point of the experiments the mice were sacrificed; blood samples were rapidly taken from the heart of anesthetized mice in order to determine insulin levels at the serum. Tumors and other organs were excised and weighed, parts of them were fixed for histological analysis and the remaining tissues were quickly frozen for biochemical and molecular biology analysis. The results obtained

from several experiments show a trend of decrease in the tumor parameters (weight and volume) in mice treated with Leptin compared to the control groups (treated with PBS). Our ongoing experiments will try to prove that leptin has effects on serum insulin, glucose and FFA levels as wells as on the tumor progression.

The second: The role of hyperlipidemia in the growth and metastases of colon tumors.

Metabolic syndrome comprises abdominal obesity, hyperlipidemia, hypertension and glucose elevations. Even though the elevation of circulating cholesterol and triglyceride levels has been associated with cardiovascular diseases, increasing data are pointing towards a link between elevation of circulating levels of cholesterol and triglycerides and certain malignancies, such as prostate and breast. Other studies suggest that hypertriglyceridemia maybe the causative agent in certain malignancies such as colon cancer [7].

We hypothesize that hyperlipidemia, particularly the hypercholesterolemia in the ApoE-/- mice will cause enhanced growth of mouse colon carcinomas. Furthermore, that the hypcholesterolemia will enhance liver metastases.

Aim: To determine whether the tumor growth of MC38 colon carcinoma cells will be enhanced by the hyperlipidemic state of the ApoE-/- mice compared with control mice.

We will study whether the hyperlipidemia in the ApoE-/- affects the growth of primary mc38 colon carcinoma growth. Preliminary results show that the tumors develop subcutaneously in B6 male and female mice. mc38 cells will also be implanted onto the caecum of hypercholesterolemic apolipoprotein knockout(ApoE-/-) mice and B6 wild-type controls (WT) after 10 weeks of a high fat diet (as previously described by my laboratory, Wu et al 2002). After 6 weeks mice will be euthanized and caecal tumors will investigate.

Expected result: Our recent work on ApoE-/- in breast cancer, demonstrated an increased growth in ApoE-/- mice (unpublished data). We therefore anticipate that we will show similar results with colon cancer, and this will allow us to extend the concept to cancer risk and growth in general.

Thyroid hormones and their analogs: growth factors vs. therapeutic agents in cancer

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Introduction: Thyroid hormones (T3 and T4) are essential for normal cell metabolism, growth, and development. Besides these well established genomic actions, T3/T4 enhance cancer cell proliferation, invasion and angiogenesis via a discrete binding site on the αvβ3 integrin. This integrin is generously expressed on dividing blood vessels and cancer cells. Binding of T3 and, with higher affinity, T4 to αvβ3 activates MAPK/cell proliferation and Pi3K/ Hif1α pathways and can defeat pro-apoptotic activity of drugs by anti apoptotic actions. The binding site for the thyroid hormones is near the RGD recognition site, through which binding of extra cellular matrix (ECM) proteins occur. The fact that αvβ3 is over expressed in a variety of cancer types led to the development of several RGD-based and integrin-specific antibodies, however, only modest clinical success were achieved so far. It was recently suggested that such integrin inhibitors may paradoxically enhance angiogenesis and tumor growth, implying that these agents should be redesigned in order to improve their efficacy to treat human cancers. We propose to distinguish between the classical RGD and the novel thyroid binding sites on αvβ3 integrin.

A deaminated T4 analog, Tetraiodothyroacetic acid (tetrac) and the newly developed tetrac-nanoparticle (tetrac NP), lack traditional agonist T4 functions and were found to selectively block T3/T4 binding to αvβ3 and reduce cancer cell proliferation, migration, angiogenesis and induce apoptosis and double strand breaks. Additionally, tetrac has been pre-clinically shown to chemosensitize commonly used cancer drugs in several tumor models and to enhance response rates to radiation therapy.

Interestingly, cells from multiple myeloma (MM) and ovarian cancer, two highly refractory malignancies, interact with αvβ3 integrin for their invasion and growth and thyroid diseases were associated with increased MM and ovarian cancer risk. The thyroid-integrin interaction was never studied in these models.

Results: Results from MM (CAG, RPMI-8226, ARK, ARP-1 and U266) and ovarian cancer cells (OVCAR-3, SKOV-3 and A2780) indicate an increase in cell proliferation/survival (WST-1,CyQuant, PCNA), αvβ3 abundance (Flow cytometry, IF) and a rapid and long lasting MAPK activation (Westerns and IF) in response to T3 and T4 (1nM and 100nM respectively). This MAPK activation was accompanied by an increased cell proliferation. Tetrac blocked T3/T4 binding to the αvβ3 integrin and consequently their proliferative actions and induced apoptosis (Annexin/PI).

Conclusions: Thyroid hormones act as growth factors in MM and ovarian cancer cells, and these effects can be efficiently and selectively blocked by tetrac. We therefore suggest a basis for a novel cancer therapy approach, based on selectively targeting the thyroid-αvβ3 axis, using tetrac and tetrac-NP, for achieving control on myeloma and ovarian cancer cells. We believe that the understanding gained from this work will be relevant to several types of cancer models.

RAGE signaling in oval cell activation during liver damage.

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The receptor for advanced glycation end-products (RAGE) is a multiligand receptor belonging to the immunoglobulin-like superfamily. RAGE is nowadays considered as a pattern-recognition receptor, able to bind Damage Associated Molecular Patterns (DAMPs), different classes of molecules released during tissue damage and inflammation (such as HMGB1 and several calcium-binding S100 proteins). Rage engagement in inflammatory conditions and in cancer upregulates the receptor itself and activates different pro-inflammatory responses and promotes tumor development. In the liver, Rage has been shown to play an important role in chronic inflammation and damage. We previously demonstrated that in the Mdr2 knock out mouse, a model of inflammation-associated HCC development, Rage ablation impairs tumor development and causes a delay in the onset of liver damage and fibrosis. This phenotype is associated with a reduced activation of oval cells, the hepatic progenitor cells involved in liver regeneration. We found that primary oval cells and BMOL cells (an oval cell line) express high levels of Rage. In BMOL cells stimulation by HMGB1 promotes an ERK1/2-cyclin D1 dependent cell proliferation. In accordance, Rage knock-down reduces BMOL cell proliferation, and in vivo blockade of the receptor signaling by means of injection of the decoy receptor sRAGE reduces oval cell activation.

In order to analyse the role played by RAGE in oval cell activation, we are feeding Rageflx mice, a conditional knock-out mouse line, with a Choline Deficient Ethionine-supplemented diet (CDE), a dietary regime, which induces extensive oval cell activation. Oval cells isolated from CDE-fed $Rage^{flx}$ mice will be recombined in vitro by means of transduction with a lentiviral vector carrying a Cre recombinase. On parallel, another vector carrying an shRNA will be used to knock-down Rage in BMOL cell line. In Rage-positive and Rage-deleted cells, we will then characterize cellular responses (proliferation, migration, apoptosis, differentiation and cytokines release) and signalling pathways promoted by RAGE ligands.

IGF-1R regulation by microRNA-515-5p modifies breast cancer risk among BRCA1 carriers

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Ten percent of all breast cancer cases are genetic. Of these, 20-30% is caused by known mutations in the BRCA1/2 genes, tumor suppressor genes involved in maintaining genome integrity. BRCA1/2 penetrance is incomplete and is known to be affected by environmental-behavioral, epigenetic and genetic factors.

Accumulating evidence implicates a critical role of insulin-like growth factor 1 receptor (IGF-1R) in the development and progression of cancer, and particularly in breast cancer. IGF-1R is crucial for tumor transformation and for malignant cells survival. Interestingly, studies have shown that IGF-1R is negatively regulated by BRCA1 during transcription.

Lately we have observed a significant association between a single nucleotide polymorphism (SNP, rs28674628) in the 3'UTR of the IGF-1R gene and age at diagnosis of breast cancer patients (all carriers of BRCA1 mutations). This finding suggests that IGF-1R influences BRCA1 penetrance. Thus, in order to address this penetrance we tested IGF-1R regulation.

Using computational methods we demonstrated that this SNP is located within a target binding site for microRNA-515-5p. Thus far, microRNA-515-5p function was not investigated. Subsequently, we showed an inverse correlation between igf-1r mRNA and microRNA-515-5p expression levels in various human breast cancer cell lines. IGF-1R expression levels were significantly downregulated (29%) when microRNA-515-5p was constitutively expressed in cell line. Moreover, using Luciferase reported assay we demonstrated a direct functional regulation of IGF-1R by microRNA-515-5p. In addition, we identified that disrupting microRNA-515-5p and igf-1r 3'UTR binding by a single nucleotide substitution leads to de-repression and a significant increase in IGF-1R protein levels. Interestingly, we found microRNA-515-5p to be down-regulated in tumor tissue from BRCA1 mutation carriers compared to its non-neoplastic surrounding tissue, while IGF-1R levels were elevated.

Taken together, these findings support the hypothesis that a SNP located in igf-1r gene may alter microRNA regulation of IGF-1R, with a putative effect on BRCA1 penetrance and breast cancer risk. In addition, negative regulation of IGF-1R by microRNA-515-5p might be an attractive approach for cancer therapy in BRCA1 mutation carriers.

Interactions between cancer-associated fibroblasts (CAFs) and myeloid-derived inflammatory cells in the dynamic phenotype of the microenvironment during tumor progression; basic mechanisms and preclinical application of novel intervention strategies.

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Tumor development and growth is a complex process that is governed by the interaction of the malignant cells with their environment. This tumor (micro)environment that plays an essential role in controlling tumor malignancy consists of a tumor specific extracellular matrix and of cellular components such as fibroblasts, vascular cells and inflammatory cells. Our lab has previously shown that tumor cells activate the inflammatory and fibroblastic cells in the tumor microenvironment by the secretion of specific growth factors like IL-6, G-CSF, GM-CSF and PDGF. These cells then in turn express tumor promoting cytokines like HGF and VEGF and proteases (e.g. MMP-9 and MMP-13) thereby enhancing tumor growth. There is in the meantime quite a bit of information of the role of the inflammatory infiltrate and specifically of macrophages in promoting tumor growth and progression as well as on the activity of tumor activated fibroblasts. However little is known about the dynamic interaction of these stromal cell types and their reciprocal influence on each other and on the tumor cells. Therefore my project focuses on analyzing the interaction of macrophages as well as granulocytes and fibroblasts in the tumor microenvironment. Using a novel 3D in vitro co-culture models we could demonstrate that the interaction between macrophages and fibroblasts markedly influences fibroblast invasion. A further addition of neutrophils to the system leads to a strikingly enhanced tumor invasion. Thus our new model that provides a tissue like context in vitro represents an excellent possibility for a targeted interference in the respective interaction processes.

Metabolic Associations of Reduced Proliferation and Oxidative Stress in Advanced Breast Cancer

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Aberrant metabolism is a hallmark of cancer but whole metabolomic flux measurements remain scarce. To bridge this gap, we developed a novel metabolic phenotypic analysis (MPA) method that infers metabolic phenotypes based on the integration of transcriptomics or proteomics data within a human genome-scale metabolic model. MPA was applied to conduct the first genome-scale study of breast cancer metabolism based on the gene expression of a large cohort of clinical samples. The modeling correctly predicted cell lines' growth rates, tumor lipid levels, and amino acid biomarkers, outperforming extant metabolic modeling methods. Experimental validation was obtained in vitro. The analysis revealed a subtype-independent "go or grow" dichotomy in breast cancer, where proliferation rates decrease as tumors evolve metastatic capability. MPA also identified a stoichiometric tradeoff that links the observed reduction in proliferation rates to the growing need to counteract oxidative stress. Finally, a fundamental stoichiometric tradeoff between serine and glutamine metabolism was found, presenting a novel hallmark of estrogen receptor $(ER)^+$ versus ER^- tumor metabolism. Together, our findings greatly extend insights into core metabolic aberrations and their impact in breast cancer.

Role of methylglyoxal detoxification in diabetes

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Methylglyoxal (MG) is a side product in many metabolic pathways, mainly forming during glycolysis. It is highly toxic for the organism due to its property to chemically modify proteins at arginine and lysine residues to form advanced glycation end-products. This glycation is damaging to the cell when the modification is directed to amino acids located in sites of protein-protein interaction, enzyme-substrate interaction or protein-DNA interaction. MG is detoxified mainly by the glyoxalase system, which consists of two enzymes: glyoxalase I (GloI) and glyoxalase II (GloII). In my thesis I investigate the consequences of high MG accumulation in the organism, in particular to animal metabolism and insulin sensitivity. I work with fruit flies mutant for GloI, mutation that leads to physiologically high levels of MG. The results so far suggest that elevated levels of MG in fruit flies contribute towards metabolic defects that develop with time and lead to insulin resistance. Firstly, I found that GloI flies have increased lifespan and delayed development from larva to adult fly. Secondly, looking more closely to changes in metabolism, I found that GloI mutant flies have increased levels of lipids and glycogen. And lastly, these flies have a strong misregulation in the expression of insulin-like peptides: low Dilp1 expression and high Dilp3, while the activation of insulin signaling pathway is reduced. It remains to be elucidated the molecular mechanisms that connect high MG levels with these defects.

MicroRNA-125a-3p inhibits Fyn-mediated oncogenic pathways in prostate cells

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Fyn, a member of the Src family kinases (SFKs) has a pivotal role in cell adhesion, proliferation, migration and survival; its overexpression is associated with several types of cancer. MicroRNAs (miRNAs) play a major role in post-transcriptional repression of proteins expression. We reported that Fyn mRNA and protein as well as its level of activity are regulated by miR-125a-3p through interaction with Fyn's 3'UTR. Elevated levels of miR-125a-3p resulted in an arrest of the cell cycle at the G2/M stage and in a reduced cells proliferation and motility. Furthermore, the activity of focal adhesion kinase (FAK), paxillin and Akt, proteins located downstream to Fyn and known to be overexpressed in various tumors, was reduced. In contrast, inhibiting miR-125a-3p induced both proliferation and motility of cells as well as activation of the abovementioned proteins. Next, by using RNA interference of Fyn, we validated that the cellular effects of miR-125a-3p were mediated through a Fyn-directed pathway. We then confirmed the model in a prostate cancer cell-line (PC3 cells), known to overexpress Fyn, and found the same effects on the cellular functions. We are now in the process of applying the in-vitro model to an in vivo model of mice with prostate cancer, and to another in-vitro model of breast cancer cell-lines. We conclude that miR-125a-3p plays an important role in the regulation of Fyn expression and signaling pathway, implying it has a therapeutic potential.

Prediction of Anti-cancer Drug Targets that Selectively Increase ROS Production

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Enhancing therapeutic impact, by selectively targeting modifications that primarily occur in malignant cells and not in healthy cells, is of major importance and challenge in the development of anticancer agents. Modification of reactive oxygen species (ROS) levels represents such a potential. This is because ROS levels are tightly regulated at different levels in healthy and cancerous cells, through ROS generating and scavenging systems. In normal cells, maintaining and regulating moderate ROS levels is important for various cell functions, and can be deleterious when an imbalance occurs. In contrast, cancer cells that show increased aerobic glycolysis (the Warburg effect), which leads to high basal ROS levels, possibly avoid further toxic ROS accumulation by repressing respiration as well as by up-regulating the antioxidant system. Here, we study the potential of further increasing ROS levels selectively in cancer cells, in order to induce apoptosis and kill cancer cells without damaging normal cells. We identify single- and double- gene knockouts that couple the cancer cell's growth with ROS production, in in silico metabolic models of 60 different cancer cell-lines.

PathWave 2.1: a user-friendly R package for detecting differential regulation and switches in metabolic and signaling pathways

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Gene expression profiling by microarrays or transcript sequencing (RNA-Seq) enables observing the pathogenic function of cells on a mesoscopic level. We present a new version of PathWave, a tool that explicitly takes the topology of metabolic networks into account to identify both global and localized (switch-like) regulatory shifts in metabolic pathways. For this purpose, PathWave applies adjusted wavelet transforms on gene expression data after mapping it to optimized 2D grid representations of curated pathways from KEGG or BiGG. In addition, the method can also be applied to signaling pathways.

PathWave 2.1 has several important improvements including an improved construction of 2D pathway grids for the application of wavelet transforms, a more flexible and user-friendly interface and pre-arranged 2D grid representations for H. sapiens, M. musculus, D. melanogaster, D. rerio, C. elegans, and E. coli. Here, we present PathWave's basic workflow and briefly discuss the improvements and current applications.

Proteomic profiling of lymph-node positive and negative breast tumors

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Breast cancer is the second leading cause of cancer death in women in the United States. Nearly all breast cancer- related deaths occur as a result of metastasis, mainly to the liver, lungs and bones. Early detection of metastasis-prone breast cancer has important implications on the selection and aggressiveness of treatment. Although the invasion and metastasis process is well described and extensively studied, its underlying molecular mechanisms and regulation remain largely unclear. Here we use large-scale proteomic approach to elucidate changes in protein expression profiles between breast tumors, which are still confined to their original surrounding, to those that have already metastasized to lymph nodes. The recently developed super-SILAC mix for quantification of human tissue has allowed us to analyze an array of clinical human samples, rather than cancer cell lines. We focused on high-grade, Estrogen receptor positive (ER^+) invasive ductal carcinomas. While this subtype is considered to have better prognosis, the patient's lymph node status has major implications on the course and aggressiveness of treatment. Using the super-SILAC mix, combined with high-resolution mass spectrometry, we were able to quantify thousands of proteins with high confidence, both from primary tumors and metastatic lymph nodes. Identifying a protein signature that distinguishes between pre-metastatic and metastatic cancer could lead to better management of the disease and the development of novel diagnostic and therapeutic agents.

miRNAs in the regulation of EGFR-driven cell-cycle proteins in breast cancer

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The EGFR-driven cell-cycle pathway has been extensively studied due to its pivotal role in breast cancer proliferation and pathogenesis. Although several studies reported regulation of individual pathway components by microRNAs (miRNAs), little is known about how miRNAs coordinate the EGFR protein network on a global miRNA (miRNome) level. Here, we combined a large-scale miRNA screening approach with a high-throughput proteomic readout and network-based data analysis to identify which miRNAs are involved, and to uncover potential regulatory patterns. Our results indicated that the regulation of proteins by miRNAs is dominated by the nucleotide matching mechanism between seed sequences of the miRNAs and 3'-UTR of target genes. Furthermore, the novel network-analysis methodology we developed implied the existence of consistent intrinsic regulatory patterns where miRNAs simultaneously co-regulate several proteins acting in the same functional module. Finally, our approach led us to identify and validate three miRNAs (miR-124, miR-147 and miR-193a-3p) as novel tumor suppressors that co-target EGFR-driven cell-cycle network proteins and inhibit cell-cycle progression and proliferation in breast cancer.

The mechanisms involved in the enhanced risk for breast cancer associated with hyperinsulinemia

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Breast cancer is currently the most common cancer among women in industrialized countries. Recent epidemiologic studies demonstrate a positive correlation between circulating insulin levels and breast cancer risk and mortality. MKR mouse serve as a model for type 2 diabetes (T2D). The female MKR mice develop a mild diabetic phenotype, which recapitulates early stages of T2D (pre-diabetes) in humans; this phenotype makes them ideal for exploring the link between high circulating insulin levels and breast cancer initiation and progression. Recent studies, with MKR female mice demonstrated accelerated mammary gland development and breast cancer progression. The signaling axis which mediates this effect includes insulin, insulin receptor (IR)/IGF-IR, and the PI3K/Akt pathways. The role of IR in mediating insulin's mitogenic effects is vague and remained to be clarified. To this end, we took advantage over a newly characterized IR antagonist (S961).

In the present study we show that the highly metastatic mouse mammary tumor cell line MVT-1 are sensitive to insulin activation, as demonstrated by significant AKT phosphorylation following a 10 nM insulin stimulation, this effect was completely abolished by pre-treatment with the S961 inhibitor. We also demonstrated that S961 specifically inhibits the IR and has no effect on the IGF-1R. In addition, we show that insulin stimulated proliferation of MVT-1 cells through the PI3K/AKT pathway, whereas IR specific inhibition by S961 abrogated this effect. We inoculated MKR female with MVT-1 cells into the inguinal mammary fat pad to create mammary tumors. Our results demonstrate that female MKR mice had a trend of moderate tumor growth following S961 treatment, despite an impairment of glucose homeostasis.

Overall, our data suggests that the inhibition of IR could serve as a valuable therapeutic strategy in the management of diabetes-associated cancer.

WD-repeat containing transcriptional co-factors as molecular links between diabetes, obesity and pancreatic cancer

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Diabetes and the Metabolic Syndrome are common disorders associated with an increased risk for pancreatic ductal adenocarcinoma (PDAC). Here, we examine if transcriptional co-factors may link the metabolic syndrome to accelerated pancreatic carcinogenesis.

We observed that high-fat diet feeding promoted pancreatic cell proliferation in wild type and p48-Kras mice as compared to animals on low-fat diet, and that in diabetic db/db mice tumor growth was enhanced after subcutaneous injection of Panc02 cells compared to wild-type animals.

The two WD-repeat containing transcriptional co-factors, WDP1 and WDP2, were found to be significantly up-regulated in tumors of human and mouse. Immunohistochemistry in both species revealed a high expression of WDP1/2 in PanIN lesions and invasive carcinoma. Knockdown of WDP1/2 via siRNA reduced proliferation of Capan-1 and Panc02 cells. Microarray profiling showed that cell proliferation and cell cycle control pathways are significantly regulated by WDP1/2.

Our data suggest that the aberrant regulation of WDP1/2 in metabolic dysfunction may play a role in diabetes- and/or obesity-mediated PDAC development and tumor progression through their regulation of cellular proliferation pathways.

BCAT1 promotes cell proliferation via amino acid catabolism in IDH1 wildtype gliomas

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Branched chain amino-acid transaminase 1 (BCAT1) is a cytosolic enzyme that catalyzes the transamination of branched-chain amino acids (BCAAs) and α-ketoglutarate (α-KG) to branched-chain keto acids and glutamate. We found BCAT1 to be overexpressed in glioblastoma with wildtype isocitrate dehydrogenase (IDHwt) genes, whereas in IDH-mutant tumors BCAT1 expression was essentially absent.

To investigate the functional role of BCAT1 in glioblastoma we manipulated BCAT1 expression in glioma cell lines. With increasing concentrations of cell-permeable dimethyl-α-KG-substrate in the culture medium, expression of BCAT1 was upregulated. Conversely, shRNA-mediated knockdown of IDH1, a major source of α-KG in the cytoplasm, led to strong downregulation of BCAT1 expression. Inhibition of BCAT1 in glioma cells blocked glutamate excretion, which is known to cause neurotoxicity and epilepsy in brain tumor patients. BCAT1 knockdown also led to reduced proliferation and invasiveness in vitro, as well as significantly decreased tumor growth in a xenograft model. Our data demonstrate that BCAT1 overexpression is a highly specific feature of IDHwt glioblastomas making it a potential marker for diagnostic and prognostic assessment of gliomas. Furthermore, we showed that BCAA catabolism is essential for tumor growth indicating BCAT1 and BCAA metabolism as promising targets for the development of personalized glioma therapy.

Regulation of metabolic processes by global oxidation of tyrosine phosphatases

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Protein tyrosine phosphorylation is a ubiquitous control mechanism for various physiological processes such as metabolism, transformation, growth and differentiation. Regulation of tyrosine phosphorylation of proteins is maintained by a delicate balance between two families of enzymes: the protein tyrosine kinases (PTKs) and phosphotyrosine phosphatases (PTPs). Since both families have a cardinal role in cell signaling, they are well-regulated.

PTPs are inhibited by oxidation of a cysteine residue within their catalytic site. This oxidation is reversible and is a physiologically-relevant mechanism for regulating PTP activity in vivo. In particular, reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2) and superoxide radicals, were shown to play a role in this process. The concentrations of both molecules can be regulated by the enzyme Copper-Zinc Superoxide Dismutase (SOD1). We hypothesize that modulation of SOD1 expression levels will affect global PTP activity in cells and as a result disrupt insulin signal transduction on a cellular scale. We intend to challenge this hypothesis by using mouse models that either overexpress SOD1 or do not express it at all. Our initial results demonstrate that SOD1 knock-out (KO) mice exhibit impaired blood glucose regulation by glucose-tolerance test. In addition, liver AKT phosphorylation was decreased in KO mice injected intraperitoneally with insulin, which might indicate an increase of PTPs' activity due to lower levels of H2O2 in SOD1 KO mice. Further studies will be conducted to understand the role of SOD1 regulation of PTPs in metabolism and cancer.

Inhibition of Stat5 DNA-binding activity in leukemia by the use of a specifically interfering peptide aptamer construct

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Targeted approaches to cancer therapy are increasingly exploiting signaling molecules, which confer an “addiction” phenotype to tumor cells. Members of the signal transducers and activators of transcription (STAT) protein family have been found to be constitutively activated in a wide range of human tumors. Especially in case of the various types of human blood tumors STAT5 is reported to have a strong impact on tumor formation, unravelling STAT5 as a promising target structure for leukemia therapy.

We used yeast-two-hybrid screens of random peptide libraries to isolate short peptide aptamer sequences inserted into a scaffold molecule, human thioredoxin (hTRX), which specifically bind to Stat5. The scaffold forces a constrained conformation on the peptide aptamer sequence, and therefore enhances the binding specificity and the stability of the aptamer. We found a peptide aptamer sequence of 12 amino acids in length (S5-DBD-PA), able to bind with high affinity to the DNA-binding domain of STAT5. We express the peptide aptamer construct as a recombinant protein with a protein transduction domain for cellular uptake and purify it by affinity chromatography.

The uptake of S5-DBD-PA from cell culture media in concentrations of 1µM and above as well as the endogenous expression of the construct achieved by lentiviral gene transfer revealed that S5-DBD-PA is able to impair the expression of STAT5 target genes and to inhibit the growth of leukemic and solid human tumor cell lines in vitro, dependent on the transcriptional activity of Stat5 in these cells. The S5-DBD-PA mediated inhibition of the interaction between STAT5 and its cognate DNA-binding sites has been shown by luciferase reporter & gel-shift assays.

In a next step the interaction between the peptide ligand and Stat5 will be used as a template for the identification of functionally equivalent low molecular weight, drug like compounds, able to replace S5-DBD-PA at its binding site. Therefore complex compound libraries will be screened using Alpha Screen and FRET based technologies. These experiments will yield a new inhibitor, which target STAT5 protein activity and which possibly can be developed into an effective molecularly targeted drug for clinical applications.

Transcriptional regulation of BCAT1 in glioblastoma

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Branched chain amino acid transaminase 1 (BCAT1) catalyzes the first step in the catabolism of the branched chain amino acids valine, leucine and isoleucine. We previously found BCAT1 overexpression to be a highly specific marker for glioblastoma that carry wildtype IDH genes (IDHwt); in contrast, BCAT1 expression was almost absent in IDH-mutated (IDHmut) astrocytoma. We further could show that BCAT1 is essential for tumor cell proliferation and migration as well as reduced tumor growth in xenografts (Tönjes and Barbus et al.; see poster). The underlying mechanisms controling BCAT1 expression and its upregulation in glioblastoma are largely unknown. Here we show that in normal and malignant brain tissues three BCAT1 isoforms are expressed from two alternative promoters. DNA-methylation analysis by MASSarray revealed differential methylation of both promoters that correlated with BCAT1 expression in IDHwt and IDHmut astrocytomas, suggesting epigenetic control of BCAT1 expression. Further, both promoter regions were analyzed for transcription factor binding sites by in silico analyses. To continue unraveling the transcriptional regulation of the BCAT1 isoforms, we are planning to perform an isoform specific siRNA screen for kinases, phosphatases and selected transcription factors predicted by the in silico analysis.

Using this approach, we are hoping to elucidate the upstream signaling pathways that control branched chain amino acid metabolism in normal and malignant tissues, and to identify possible therapy targets in addition to BCAT1.

Mechanisms linking and altered metabolism to obesity- related colon cancer

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Obesity is linked to increased risk of colon cancer, the third most common cancer. Adipose tissue (AT) from obese differs from AT of lean in their immunogenic profile, body fat distribution and metabolic profile. AT from obese release free fatty acids (FFAs), and many pro-inflammatory chemokines, factors known to play a key role in regulating malignant transformation or cancer progression.

Energy metabolism of tumor cells results from the interplay of the two main bioenergetic pathways, oxidative phosphorylation and glycolysis. Mitochondria are important organelles in cellular processes, including cellular respiration and energy expenditure, and programmed cell death (apoptosis). The metabolic networks that confer tumor cells oncogenic and metastatic properties, such as increased proliferation and the ability to avoid apoptosis, are still not well understood. Our goal in this study is to identify key molecular signals and interactions between adipocytes and colon cancer cells that may foster the genesis and growth of the latter.

We tested the effect of 24 hours exposure of conditioned media (CM) isolated from AT of obese vs. non obese subjects on the metabolic profile of several stages of colon cancer cell lines. We found that compared to non obese, CM from obese subjects led to a reduction of basal and maximal oxygen consumption rates and to changes in the gene expression of mitochondrial proteins, with no effect on glycolytic proteins (cell viability was similar). When searching for specific molecules that can mediate the crosstalk between the obese AT and colon cells, we observed similar metabolic changes of cells that were exposed to leptin and/or insulin. Linking both approaches may lead to a more complete picture relating obesity to colon cancer.

Understanding the molecular mechanisms whereby obesity increases colon cancer risk will help in designing more relevant strategies to prevent the increasing trend in obesity-related colon cancer.

Personalized metabolic modeling successfully predicts central metabolic traits of individual normal and cancerous human cells

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The emerging field of personalized medicine encompasses the use of marker-assisted diagnosis to improve health care. However, computational models describing human physiology on an individual level have yet to be developed. Here we present a novel algorithm termed PRIME (Personalized ReconstructIon of MEtabolic models), which generates individualized genome scale metabolic models based on molecular and phenotypic data. The PRIME-derived models are first shown to successfully predict a range of metabolically-related phenotypes, including proliferation rates, gene essentiality, drug responses and metabolic biomarkers measured across an array of individual normal and cancer cell-lines. Second, PRIME-derived models identify known selective drug treatments in cancer and suggest novel ones. Finally, when applied to clinical samples' data, PRIME-derived models of breast cancer patients can be successfully used to predict their prognosis independently of known clinical/pathological predictors (such as tumor's stage, histological grade and estrogen receptor status). PRIME thus captures the phenotypic effects of transcriptomic differences between human cells, and lays a foundation for future personalized metabolic modeling applications.

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