Ion Channels & Cancer Meeting

Calcium Signaling in Cancer Workshop

December 6th-8th, 2022

Couvent des Minimes, Lille, France

ABSTRACT BOOK

CONTENTS

FOREWORD

Dear colleagues and friends,

We are delighted to meet finally in Lille for the ***Ion Channel & Cancer Meeting and Calcium Signaling in Cancer ECS session,*** *after postponing the congress for two years because of the Covid-19 pandemic.*

We are thankful we reached almost 100 participants from all over the world that will cover numerous aspects of ion channel regulation from molecular biophysics, to physiology and clinical applications in cancer biology. Indeed, the program includes remarkable speakers presenting the latest ion channel research on tumor initiation and involvement of the microenvironment in its growth and metastasis as well as on metabolism, therapy resistance and pharmacological targeting.

This meeting wouldn't be possible without the support of our sponsors, as well as the resilience and hard work of the members of the organizing committee, Valerio Farfariello, Loic Lemonnier, and the administrative support of Sandy Despeghel. We hope that the flamboyant Flemish "Couvent des Minimes" and the Christmas decorated city of Lille will be the perfect place for exciting scientific exchanges and fruitful collaborations.

Enjoy the meeting!

Dimitra and Natacha

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We thank them for their financial and material support.

PROGRAM

TUESDAY, DECEMBER 6th

12h00-14h00 Registration

12h45 Welcome

12h50-14h30 Symposium 1: "Tumor initiation"

Chaired by Natalia PREVARSKAYA and Florian LESAGE

Nobuaki Takahashi (University of Kyoto, Japan) - *Oxidative Stress Defense in Cancer*

Rainer Schindl (University of Graz, Austria) - *Disease related STIM1 mutations that disturb store-operated channel activation*

Ivan Bogeski (University of Gottingen, Germany) - *Metabolic regulation of melanoma pathobiology: The role of calcium and redox signaling*

Selected speaker

David Crottès (University of Tours, France) - *Profiling of ion channels expression to investigate cancer heterogeneity*

Coffee break

15h-18h00 "Calcium signaling in carcinogenesis, ECS session"

Chaired by Jan PARYS and Jim PUTNEY

Keynote - Jim Putney (Scientist Emeritus, NIEHS, USA) - *Historical Perspective on Store-operated Calcium Channels*

Juan Rosado (University of Extremadura, Spain) - *Functional differences between Orai1α and Orai1β*

Mohamed Trebak (University of Pittsburg, USA) - *STIM proteins in colorectal cancer*

Jonathan Soboloff (Temple University, Phyladelphia, USA) - *Suppression of Ca2+ signaling enhances melanoma progression*

Selected speaker

Flore Sneyers (KU Leuven, Belgium) - *BAPTA directly inhibits PFKFB3, thereby impeding mTORC1-driven Mcl-1 translation and killing Mcl-1-addicted cancer cells*

20h00 Social event « Dinner »

WEDNESDAY, DECEMBER 7th

9h-10h30 Symposium 2: "Tumor growth"

Chaired by Loïc LEMONNIER and Bruno CONSTANTIN

Luis Pardo (Max-Planck-Institute, Germany) - *Cell biological roles of Kv10.1 in physiology and pathophysiology*

Olivier Soriani (University of Nice, France) - *SK2 channels set a signaling hub bolstering CAF-triggered Tumorigenic processes in pancreatic cancer*

Selected speakers

Isaac Jardin (University of Extremadura, Spain) - *Differential translocation ability of Orai1α and Orai1β to the plasma membrane*

Dimitra Gkika (University of Lille, France) - *Non genomic regulation of TRPM8: from thermosensation to cancer*

Coffee break

11h-12h30 Symposium 3: "Tumor cell migration and invasion"

Chaired by Dimitra GKIKA and Mustafa DJAMGOZ

Albrecht Schwab (University of Muenster, Germany) - *Ionic signaling in pancreatic stellate cell migration*

Konstantinos Konstantopoulos (Johns Hopkins, USA) - *Counterintuitive effect of extracellular fluid viscosity on enhancing motility and metastasis*

Selected speakers

Aubin Penna (University of Rennes, France) - *The mechanosensitive TRPV2 calcium channel controls human melanoma invasiveness and metastatic potential*

Rodrigo Cruz (New York University, USA) - *SOCE modulates dysplasia to cancer in human oral squamous cell carcinoma*

Lunch

13h40-14h Commercial presentation

14h-15h30 Symposium 4: "Therapy resistance"

Chaired by Charlotte DUBOIS and Olivier SORIANI

Barbara Ehrlich (Yale University, USA) - *Neuronal calcium sensor 1 (NCS1) and cancer progression and treatment*

Geert Bultynck (University of Leuven, Belgium) - *Bcl-2 family and IP3 receptor inhibition underlying cancer cell death resistance*

Selected speakers

Luca Matteo Todesca (University of Münster, Germany) - *KCa3.1 inhibition decrease non-small cell lung cancer (NSCLC) migration via increased β1-integrin expression*

Carlos Villalobos (University of Valladolid, Spain) - *Polyamine depletion reverses transcriptomic remodeling and changes in intracellular calcium homeostasis in colon cancer cells*

Coffee break

16h30-17h30 Plenary Lecture

Annarosa Arcangeli (University of Florence, Italy) - *The channel complexes landscape in tumours: a novel perspective in oncological studies*

17h30-19h30 Poster session

20h00 Dinner « Couvent des minimes »

THURSDAY, DECEMBER 8th

8h30-10h30 Symposium 5: "Tumor microenvironment"

Chaired by Morad ROUDBARAKI and Halima AHIDOUCH

Xi Huang (University of Toronto, Canada) - *Targeting ion channels in brain cancer*

Germain Gillet (University of Lyon, France) - *Role of Bcl-2 family proteins in development and tumor progression*

Stine Pedersen (University of Copenhagen, Denmark) - *Chronic acidosis rewires cancer cell metabolism through PPARalpha signaling*

Selected speakers

Tatiana Varanita (University of Padova, Italy) - *Myeloid cell-specific deletion of kv1.3 potassium channel determines tumor growth in vivo*

Silviya Radoslavova (University of Lille) - *Role of the extracellular matrix stiffness in pancreatic cancer cells and pancreatic stellate cells behavior*

Coffee break

11h-12h30 Symposium 6: "Metabolism"

Chaired by Valerio FARFARIELLO and Carlos VILLALOBOS

Kevin Foskett (University of Pennsylvania, USA) - *Pancreatic Ductal Cell Adenocarcinoma Growth, Proliferation, and Metastasis are Modulated by the Mitochondrial Ca^{++} Uniporter*

Mustafa Naziroglu (Suleyman Demirel University, Turkey) - *TRPM2 stimulation increases the antitumor action of cisplatin via the increase of mitochondrial oxidative stress and apoptosis in brain tumor cells*

Selected speakers

Jan Parys (KU Leuven, Belgium) - *Regulation of mitochondrial Ca2+ uptake and function by pyruvate kinase M2 (PKM2)*

Hilda C. Delgado De la Herrán (Helmholtz Zentrum München, Germany) - *Unbiased mapping of the MCU interactome reveals MCNR1 as a potential molecular target in cancer*

Lunch

13h45-14h00 Artem Kondratsky (University of Lille) - *Ion channels and cancer: global research trends, statistics, collaborations*

14h-16h00 Symposium 7: "Therapeutic Targeting"

Chaired by V'yacheslav LEHEN'KYI and Yaroslav SHUBA

Ildiko Szabo (University of Padua, Italie) - *Targeting the Achilles' heel of cancer cells: modulation of cell survival and migration by inhibition of mitochondrial ion channels*

Saverio Gentile (University of South Carolina, USA) -

Mustafa Djamgoz (Imperial College London, UK) - *Ranolazine: A voltage-gated sodium channel blocker with clinical potential*

Selected speaker

Nadine Déliot (CNRS, France) - *Role of calcium entries in the physiopathology of glioblastoma stem cells*

William J. Brackenbury (York Biomedical Research Institute, University of York UK) - *Targeting the Nav1.5 channel with antiarrhythmic drugs to reduce metastatic recurrence: evidence from retrospective patient cohort studies*

16h-16h15 Prizes ceremony and closure

SYMPOSIUM 1: "TUMOR INITIATION"

ORAL PRESENTATIONS

Oxidative Stress Defense in Cancer

Nobuaki Takahashi

Kyoto University

The unscheduled proliferation of cancer cells outside their natural niches subjects the cells to multiple insults, such as metabolic aberrations, detachment from the extracellular matrix (ECM), hypoxia, and immune cell attacks. Oxidative stress is a hallmark of cancer because these insults can all lead to the accumulation of reactive oxygen species (ROS) including H2O2. However, it remained largely elusive how cancer cells are able to adapt to harsh oxidative environments. In this symposium, we first provide evidence that cancer cells co-opt multiple ROS-sensing and adaptation programs, including the redox-sensitive TRPA1 channel, to tolerate highly oxidative environments by mitigating ROS-induced cell death (Takahashi N, Nature Chem Biol 2011; Cancer Cell 2018; Mol Cell 2020). We then introduce a tumor-targeted ROS probe (called "T-AP1") that we recently developed. T-AP1 not only revealed intratumor ROS heterogeneity but also identified a novel and surprising oxidative-stress defense

Keywords: TRPA1; Oxidative Stress

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Disease related STIM1 mutations that disturb store-operated channel activation

Rainer Schindl

Medical University of Graz, Austria

The stromal interaction molecule 1 (STIM1) has two important functions, Ca2+ sensing within the endoplasmic reticulum and activation of the store-operated Ca2+ channel Orai1, enabling plasma-membrane Ca2+ influx. We combined molecular dynamics (MD) simulations with live-cell recordings and structural biology techniques that determined the sequential Ca2+-dependent conformations of the luminal STIM1 domain upon ER Ca2+ store-depletion and luminal STIM1 di-/multi-merization. More-over, several luminal single point STIM1 mutations that cause tubular aggregate myopathy and are determined in cancer databases yield constitutive STIM1 activation. We will present a structural mechanism of STIM1 how luminal unfolding and dimerization processes of EF-SAM domains crucial for the initiation of SOCE activation cascade.

Keywords: STIM1

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Metabolic regulation of melanoma pathobiology: The role of calcium and redox signaling

Ivan Bogeski

University Medical Center, University of Göttingen, Germany

Melanoma is an aggressive cancer with a high tendency to metastasize to distant organs. In melanoma patients, mitochondria determine response rates to immune checkpoint therapies. However, the underlying molecular details regarding the mitochondrial contribution to melanoma pathobiology are not fully understood. As a major route for calcium into the mitochondrial matrix, the MCU complex is an important regulator of mitochondrial function. We found that MCUa expression correlates with melanoma patient survival and therapeutic sensitivity. Knockdown of MCUa induced melanoma phenotype switch by suppressing melanoma growth and by promoting invasion in vitro and in vivo in a redox dependent manner. Notably, MCUa expression affected melanoma cell resistance to immunotherapies and ferroptosis. Collectively, we demonstrate that mitochondrial calcium and redox signals are essential determinants of melanoma aggressive behavior and therapeutic sensitivity.

Keywords: calcium; redox; melanoma; mitochondria; MCU

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Profiling of ion channels expression to investigate cancer heterogeneity

David Crottès[1], Maxime Guéguinou[1], Karine Mahéo[1], Gaëlle Fromont-Hankard[1], Christophe Vandier[1], Yuh Nung Jan[2], Lily Jan[2]

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Cancers are highly heterogeneous diseases. The genomic and transcriptomic characterizations of thousands of tumors from different cancer types have revealed their molecular heterogeneity while identifying new subtypes of cancers with different outcomes. Ion channels are a protein family with an extraordinary diversity of structure, function or ion selectivity. In recent years, several ion channels have been associated to cancer development. Here, a genomic and transcriptomic pan-cancer analysis of ion channels and an unsupervised classification of cancers based on their expression reveal that the profile of expression of ion channels can be an interesting feature to classify cancer types and subtypes. Further characterization of the profile of the expression of ion channels in cancers will improve our understanding of the tumor heterogeneity, propose a new molecular classification of cancers and potentially highlight a contribution for underexplored ion channels in cancers.

Keywords: ion channels; cancer; tumor heterogeneity; unsupervised classification

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"CALCIUM SIGNALING IN CARCINOGENESIS, ECS SESSION"

ORAL PRESENTATIONS

Historical Perspective on Store-operated Calcium Channels

Jim Putney

National Institute of Environmental Health Sciences - NIH

Plasma membrane calcium channels play major roles in a wide variety of physiological and pathological processes. Aberrant calcium channel activity contributes to a multitude of pathological problems including cardiovascular disease and cancer. Among the various types of plasma membrane calcium channels, perhaps the most widely encountered are the store-operated calcium channels. Numerous studies have implicated these channels in the underlying mechanisms of growth factor and neurotransmitter signaling, and to the dysregulation of controlled cell growth and proliferation. This lecture will briefly annotate the historical development of the concept of store-operate calcium channels, and the discovery of the major underlying molecular players.

Keywords: Store-operated calcium channels; STIM1; Orai1; mouse models

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Functional differences between Orai1α and Orai1β

Juan A. Rosado

University of Extremadura

Two Orai1 variants are present in mammalian cells: Orai1α and a shorter form, Orai1β, generated by alternative translation initiation from methionine 64 in Orai1α. Both are equally capable of forming CRAC channels and participate in the ISOC current; however, they exhibit functional differences, i.e. both variants differ in their sensitivities to Ca2+-dependent inactivation and only Orai1α is required for the channels underlying Iarc. We have found that agonist stimulation evoke interaction of TRPC1 with Orai1α but not with Orai1β in HeLa cells, where Orai1α modulates TRPC1 plasma membrane expression and function, thus suggesting that the role of Orai1α and Orai1β in the formation of SOC channels is cell-specific. Furthermore, we have found that exclusively Orai1α is required for agonist-evoked NF-κB activation. This talk highlights the functional differences between both Orai1 variants. Supported PID2019104084GBC21 MCIN/AEI/10.13039/501100011033 and Junta Extremadura IB20007, GR21008.

Keywords: Orai1α; Orai1β; TRPC1; NF-κB; Ca2+ influx

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STIM proteins in colorectal cancer

Mohamed Trebak

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Ca2+ ions are universal second messengers that regulate nearly every aspect of cellular life. One of the most ubiquitous and evolutionarily conserved pathway of receptor-evoked Ca2+ entry is the store-operated Ca2+ entry (SOCE) pathway mediated by STIM and Orai proteins. Orai proteins, which consist of a family of three members (Orai1/2/3) encoded by distinct genes, form hexameric and highly Ca2+-selective channels at the plasma membrane. Orai channels are activated by stromal-interacting molecules (STIM1 and STIM2), which are Ca2+ sensing proteins located in the endoplasmic reticulum. Mutations or altered expression of STIM and Orai proteins are associated with several diseases, including immune, muscle, cardiovascular and airway diseases. Here, I will discuss our recent findings on the signaling functions of STIM/Orai proteins in colorectal cancer and their contribution to colorectal cancer growth and metastasis.

Keywords: STIM; Orai; Calcium signaling; Colorectal cancer

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Suppression of Ca2+ signaling enhances melanoma progression

Jonathan Soboloff

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Departments of Hematology/Oncology and Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA 19111, USA

The role of store-operated Ca2+ entry (SOCE) in melanoma metastasis is highly controversial. To address this, we examined UV-dependent metastasis, revealing a critical role for SOCE suppression. SOCE suppression was responsible for UV-dependent differences in gene expression associated with both increased invasion and reduced glucose metabolism. Functional analyses further establish that increased glucose uptake leads to a metabolic shift towards biosynthetic pathways critical for melanoma metastasis, particularly O-GlcNAcylation of proteins. Finally, examination of fresh surgically isolated human melanoma explants revealed low SOCE; invasiveness could be reversed by pharmacological SOCE potentiation or blockade of O-GlcNAcylation. Collectively, we provide evidence that, contrary to current thinking, Ca2+ signals can block invasive behavior, and suppression of these signals promotes invasion and metastasis.

Keywords: STIM1; Orai1; Melanoma; Invasion

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BAPTA directly inhibits PFKFB3, thereby impeding mTORC1-driven Mcl-1 translation and killing Mcl-1-addicted cancer cells

Flore Sneyers, Martijn Kerkhofs, Kirsten Welkenhuyzen, Femke Speelman-Rooms, Ahmed Shemy, Arnout Voet, Guy Eelen, Mieke Dewerchin, Stephen W. Tait, Bart Ghesquière, Martin D. Bootman, Geert Bultynck

KU Leuven

Intracellular Ca2+ signals control several (patho)physiological processes. A major tool to chelate intracellular Ca2+ is intracellular BAPTA (BAPTAi), introduced into cells as BAPTA-AM. We observed that BAPTAi induced apoptosis in Mcl-1 dependent lymphoma cells. BAPTAi provoked a rapid decline in Mcl-1 levels by inhibiting mTORC1-driven MCL1 translation. Overexpression of nondegradable Mcl-1 rescued BAPTAi-induced cell death. BAPTAi impaired glycolysis by directly inhibiting PFKFB3 activity, an up to now unknown effect of BAPTAi. All aforementioned effects of BAPTAi were also elicited by a BAPTAi analog with low affinity for Ca2+. Thus, we expose PFKFB3 inhibition as a Ca2+-independent mechanism by which BAPTAi impairs cellular metabolism and ultimately the survival of Mcl-1-dependent cancer cells. Also, cellular effects caused by BAPTAi are not necessarily related to due to Ca2+ buffering, urging a critical assessment of the role of Ca2+ in cell death and survival processes.

Keywords: Intracellular Ca2+ chelator; BAPTA; mTORC1; Mcl-1; Cancer; PFKFB3

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SYMPOSIUM 2: "TUMOR GROWTH"

ORAL PRESENTATIONS

Cell biological roles of Kv10.1 in physiology and pathophysiology

Luis A. Pardo

Max-Planck Institute for Multidisciplinary Sciences

Kv10.1, abundantly expressed in the brain while undetectable in other tissues, has been associated with cancer for many years. Still, the mechanistic link between the protein and its impact on cell physiology remains elusive. Increased expression (in cancer) or function (in neurodevelopmental diseases) of Kv10.1 has significant consequences. We recently showed that the channel is implicated in the final steps of cell division and that its expression is limited to a short time window around this key event. The role of Kv10.1 in cytoskeletal homeostasis around mitosis explains the phenotypic characteristics of patients carrying gain-of-function mutations. In the cancer context, tumor cells often show dysregulated (sustained) expression of the channel and thereby become more proliferative and aggressive, resulting in a correlation between the presence of the channel and a bad prognosis. We will discuss the strategies we currently follow to improve the efficacy of Kv10.1-targeted agents.

Keywords: Kv10.1; potassium channel; cytoskeleton; mitosis

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SK2 channels set a signaling hub bolstering CAF-triggered Tumorigenic processes in pancreatic cancer

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Context: • PDAC remains a therapeutic dead-end partially due to the lack of targeted therapy. • Intercellular communication between CAF and PCC largely contributes to PDAC aggressiveness. • Sig-1R is an ion channel chaperon involved in the remodeling of electrical signature in various diseases.
Results: • SK2 channel, chaperoned by Sig-1R, is a mediator of the intercellular communication. • SK2 activity is increased by direct AKT phosphorylation and stimulates a CAF-secretome-activated β-1-integrin-EGFR-AKT signaling hub. • The inhibition of this signaling hub leads to a decrease in metastasis spreading and an increase in survival in PDAC mouse models.
Conclusion • Our findings highlight the SK2 channel as an original target to counteract stromal-induced cancer cell aggressiveness in PDAC that can be targeted through Sig-1R, a druggable chaperone.

Keywords: Pancreatic adenocarcinoma; Cancer associated fibroblast; Potassium channels; SigmaR1; PI3K/AKT; signaling hub; intercellular crosstalk

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Differential translocation ability of Orai1α and Orai1β to the plasma membrane

Isaac Jardin, Sandra Alvarado, Joel Nieto-Felipe, Jose J Lopez, Gines M Salido, Juan A. Rosado

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At rest, Orai1 localizes both in the plasma membrane (PM) and intracellular vesicles and the latter translocates to the PM upon store depletion. Two Orai1 variants are expressed in mammals, Orai1α (long form) and Orai1β (short form) lacking the N-terminal 63 amino acids. By biotinylation and confocal microscopy in Orai1-KO HEK-293 cells expressing Orai1α or Orai1β we have analyzed the ability of Orai1 variants to translocate to the PM. We found that Orai1 variants are similarly expressed in the PM at rest and thapsigargin (TG) enhances exclusively Orai1α surface expression. In cells co-expressing Orai1α and Orai1β, TG enhanced PM expression of both variants. Orai1 variants translocation was Ca2+-independent but requires functional Arf6. These findings reveal differences in PM translocation abilities of Orai1α and Orai1β and suggest that Orai1α might facilitate TG-stimulated PM translocation of Orai1β.
PID2019104084GBC21 MCIN/AEI/10.13039/501100011033 & J. Extremadura IB20007, GR21008.

Keywords: Orai1α; Orai1β; Ca2+ influx; plasma membrane trafficking

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Non genomic regulation of TRPM8: from thermosensation to cancer

Dimitra Gkika

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TRPM8, a predominant detector of cold temperatures in vivo, is also expressed in sensory fibers innervating visceral organs and in epithelia such as prostate, bladder, testis and skin. In epithelia TRPM8 was involved in carcinogenesis and seems to be one of the most promising clinical targets for prostate cancer due to the variation in its expression. In an effort to characterize physiological factors other than cold playing a putative role in TRPM8 activation/modulation, several hormones were tested in our laboratory. In this context we have recently shown that testosterone regulates directly TRPM8 activity in both prostate carcinogenesis and cold thermosensation. In this presentation I will provide a mechanistic insight in the hormonal non genomic regulation of TRPM8 channel in two processes modulated during ageing, cold thermosensation and malignant transformation.

Keywords: TRPM8; androgen receptor; prostate cancer; testosterone

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SYMPOSIUM 3: "TUMOR CELL MIGRATION AND INVASION"

ORAL PRESENTATIONS

Ionic signaling in pancreatic stellate cell migration

Albrecht Schwab

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Pancreatic stellate cells are key players in the pathophysiology of pancreatic ductal adenocarcinoma (PDAC). They are responsible for the massive fibrosis in PDAC which in turn leads to massively increased tissue pressure and stiffness. The PDAC microenvironment is further characterized by a unique pancreatic pH landscape. The tumor with its extracellular aciditiy is surrounded by pancreatic tissue whose interstitium is acidified intermittently after each meal. Thus pancreatic stellate cells have to cope with important mechanical cues from the microenvironment that are overlaid by dynamic pH changes. pH-regulatory transporters as well as pH- and mechano-sensitive ion channels are major signaling hubs in detecting and transducing cues from the microenvironment. Here I will discuss how they shape the migratory behavior of pancreatic stellate cells in response to challenges from the microenvironment.

Keywords: pancreatic stellate cell; pH; mechanosignaling; migration

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Counterintuitive effect of extracellular fluid viscosity on enhancing motility and metastasis

Konstantinos Konstantopoulos

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Extracellular viscosity is a key physical cue that varies under (patho)physiological conditions. However, its impact on cancer biology and the mechanism by which cells sense and respond to changes in viscosity are unknown. Elevated viscosity counterintuitively increases the motility of various cell types on two-dimensional (2D) surfaces, in confinement, and cell dissemination from 3D tumor spheroids. Increased mechanical loading imposed by elevated viscosity induces a dense actin network, which enhances NHE1 polarization via its actin-binding partner ezrin. NHE1 promotes cell swelling and increased membrane tension which, in turn, activates TRPV4 and mediates calcium influx, leading to increased RhoA-dependent cell contractility. The coordinated action of actin remodeling, NHE1-mediated swelling and RhoA-based contractility facilitates enhanced motility. Moreover, breast cancer cells exposed to elevated viscosity exhibit increased migration in zebrafish and lung colonization in mice.

Keywords: mechanosensitive ion channels; ion transporters; viscosity; migration

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The mechanosensitive TRPV2 calcium channel controls human melanoma invasiveness and metastatic potential

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Cutaneous Melanoma (CM) is a highly aggressive cancer endowed with a unique capacity of rapidly metastasizing. Here, we uncover the prominent expression of the TRPV2 calcium channel as a distinctive feature of CM tumors, directly related to CM metastatic dissemination. In vitro as well as in vivo, TRPV2 activity was sufficient to confer invasive potentials, while conversely TRPV2 silencing or pharmacological inhibition in highly metastatic CM cells prevented aggressive behavior. In invasive CM cells, TRPV2 channel localizes at the leading edge, in dynamic nascent adhesions, and regulates calcium-mediated activation of calpain and the ensuing cleavage of the adhesive protein talin, along with F-actin organization. In human CM tissues, TRPV2 overexpression correlates with poor prognosis. Hence, by regulating adhesion and motility, the mechanosensitive TRPV2 channel controls CM cells invasiveness, highlighting a new therapeutic option for migrastatics in the treatment of metastatic CM.

Keywords: TRPV2 channel; melanoma; adhesion; calpain; metastasis

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SOCE modulates dysplasia to cancer in human oral squamous cell carcinoma

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Store-operated Ca2+ entry (SOCE) mediated by the ORAI channels is critical for essential cellular functions such as cell proliferation, cell death, and gene regulation. In most of non-excitable cells including various types of cancer cells, Ca2+ influx is strongly regulated by SOCE. Interestingly, the expression levels of ORAI (1-3) isoforms is up-regulated in various cancer types. However, the associations between SOCE and oral cancer progression are poorly understood. We found that ORAI1 and ORAI2 are up-regulated in tumors of oral cancer patients. Using human and murine oral cancer cells, we show that SOCE is important for Ca2+ influx. Moreover, we found that the expression of MMP genes considered markers in oral cancer progression, is unregulated by SOCE and show that over expression of ORAI1 in dysplastic oral keratinocytes increases cell invasion. These results suggest that SOCE is an important mediator in malignant transformation of oral dysplasia to oral cancer.

Keywords: SOCE; oral cancer; cancer progression

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SYMPOSIUM 4: "THERAPY RESISTANCE"

ORAL PRESENTATIONS

Neuronal calcium sensor 1 (NCS1) and cancer progression and treatment

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Neuronal calcium sensor 1 (NCS1) is a calcium sensor protein that binds to the inositol trisphosphate receptor (ITPR). NCS1 also is an off-target binding protein for chemotherapeutic agents that alter microtubule assemblies to kill cancer cells. This binding leads to off-target toxicities. The addition of taxanes increases calcium release from intracellular stores to activate calpain which initiates a neurodegenerative environment resulting in chemotherapy-induced peripheral neuropathy (CIPN) and cognitive impairment (CICI), or "chemo brain". There are no approved, disease-modifying treatments for CIPN or CICI. NCS1 is also critical for cell motility where high levels of NCS1 lead to higher tumor load in mice. We found compounds and peptides that prevent taxane-induced neuronal changes. We now are working to prevent NCS1-dependent increased cell motility. Our goal is to prevent the off-target effect of chemotherapy to protect nerve function and to retard tumor growth.

Keywords: Neuronal calcium sensor 1; chemotherapy; neuronal function

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Bcl-2 family and IP3 receptor inhibition underlying cancer cell death resistance

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Anti-apoptotic Bcl-2/Bcl-XL proteins execute part of their function by directly inhibiting IP3 receptors, thereby preventing pro-apoptotic Ca2+ fluxes and cell death. Recent work revealed the converging role of Bcl-2 and Bcl-XL in inhibiting IP3 receptors through a common Lys amino acid residue. Here, we will discuss recent advances on how Bcl-2 and Bcl-XL proteins affect IP3 receptor function, thereby contributing to the cell death resistance of cancer cell models including B-cell malignancies for IP3R/Bcl-2 complexes and breast cancer for IP3R/Bcl-XL complexes. We will highlight strategies to antagonize IP3R/Bcl-2 or IP3R/Bcl-XL complexes including peptides & small molecules to evoke cancer cell death. We will present ongoing work indicating how acquired venetoclax-resistance mutations in Bcl-2 found in venetoclax-treated CLL cancer patients impact the IP3 receptor modulation by Bcl-2 and how this may provide opportunities for potential BH4-domain antagonists of Bcl-2.

Keywords: IP3 receptor; Bcl-2; cancer cell death; cell death resistance; BH3 mimetics

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KCa3.1 inhibition decrease non-small cell lung cancer (NSCLC) migration via increased β1-integrin expression

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KCa3.1 channels play an important pathophysiological role in non-small cell lung cancer (NSCLC) by regulating some cancer cell functions like migration and invasiveness. Moreover, these channels are also involved in the EGFR-TKIs resistance mechanism (i.e. erlotinib resistance). The aim of this study is to unravel mechanisms by which blocking KCa3.1 channels with senicapoc contributes to overcome erlotinib-resistance. Using single-cell force spectroscopy, 3D migration and Western blot techniques we focused on the impact of KCa3.1 inhibition on cell-matrix adhesion and migration, and the role that β1-integrins have in these processes. Our results indicate that KCa3.1 channel inhibition in erlotinib-resistant NSCLC cells increases cell adhesion by an elevated β1-integrin expression that depends on mitochondrial ROS release. As shown with migration experiments, this can help to overcome erlotinib resistance by decreasing motility of the NSCLC cells.

Keywords: non-small cell lung cancer; KCa3.1; β1-integrin; erlotinib resistance; cell migration

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Polyamine depletion reverses transcriptomic remodeling and changes in intracellular calcium homeostasis in colon cancer cells

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The common activation of c-Myc oncogene in colon cancer induces overexpression of ornithine decarboxylase (ODC), the limiting step in polyamine synthesis, a process blocked by α-Difluoromethylornithine (DFMO), a suicide ODC inhibitor and potential cancer treatment. In addition, intracellular Ca2+ homeostasis is remodeled in colon cancer. We asked whether polyamine depletion induced by DFMO may reverse calcium remodeling in colon cancer and the molecular basis. For this end we used calcium imaging, transcriptomic analysis in HT29 cancer cells and NCM460 normal cells. HT29 cells show enhanced resting and store-operated Ca2+ entry (SOCE) but decreased Ca2+ store content relative to normal cells. HT29 cells displayed differential expression of 56 genes involved in Ca2+ transport. DFMO treatment reversed Ca2+ remodeling and expression of several SOCE modulators, SPCA2 and PMCA4 pumps and TRPC1, TRPC5 and TRPV6 channels in cancer cells but not in normal cells.

Keywords: Colon cancer; transcriptomics; c-myc; polyamines; DFMO

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SYMPOSIUM 5: "TUMOR MICROENVIRONMENT"

ORAL PRESENTATIONS

The channel complexes landscape in tumours: a novel perspective in oncological studies

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During neoplastic transformation, several ion channels are up- or de-regulated and contribute to trigger or modulate different aspects of cancer cell behaviour. Recent evidence indicates that ion channels often operate within macromolecular complexes, both in normal excitable and non-excitable tissues, as well as in transformed cells. Channel macromolecular complexes which occur in tumours, often comprise "non canonical" proteins. A prototype is represented by hERG1 and its propensity to form complexes with cell adhesion receptors (e.g. integrins) or growth factor receptors (e.g. EGF-R), besides different ion transporters or channels. Another peculiar aspect of channel complexes in tumours is their localisation in those highly dynamic membrane microdomains, called lipid rafts (LRs). In addition, when ion channels operate within multiprotein complexes in tumours, they often work in a non-conductive way, to trigger and activate intracellular signalling cascades mainly through e.g. conformational coupling.
From a pharmacologic standpoint, the multiprotein complexes which occur in tumours will offer unique opportunities for cancer cell targeting by using e.g. bispecific antibodies which can simultaneously bind two or more proteins. In addition, the occurrence of non-conductive channels in multiprotein complexes in tumours paves the way for targeting different channel conformational states. Overall, the ion channel complexes landscape might represent a novel pathophysiological and therapeutic approach in oncology.

Keywords: ion transporters; channel complexes; signaling

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Targeting ion channel in brain cancer

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Brain cancer is among the most challenging cancers to treat. A major obstacle is the blood-tumor barrier (BTB), which restricts the delivery of most therapeutic agents into the brain. Due to the BTB, chemotherapy drugs are used at dosages that result in toxicity yet providing limited benefit to patients. Mechanotransduction, the conversion of mechanical cues into cellular signaling, underlies physiological processes such as touch, pain and hearing. While tumor cells experience pervasive mechanical cues, whether and how mechanotransduction regulates BTB permeability is unknown. Medulloblastoma (MB) is the most common malignant brain tumor in children. We discovered that Sox2+ tumor cells directly ensheathe blood vessels to construct the BTB in MB. Genetic deletion of Piezo2, a force-activated ion channel, decreases tumor cell coverage on blood vessels, increases BTB permeability, and markedly enhances MB chemosensitivity. Mechanistically, MB develops tissue stiffness gradient as a function of distance to capillaries. Sox2+ tumor cells perceive substrate stiffness to sustain local intracellular calcium to promote cellular process growth. Furthermore, Piezo2 knockout reverses WNT/β-Catenin signaling states between Sox2+ tumor cells and endothelial cells to compromise the BTB. Collectively, we show that mechanosensitive tumor cells construct the BTB to mask tumor chemosensitivity. Targeting Piezo2 addresses BTB properties that underlie therapy failures in brain cancer patients.

Role of Bcl-2 family proteins in development and tumor progression

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Bcl-2 family proteins have long been described as regulators of programmed cell death. However, depending on the intra- and extra-cellular environment, they are involved in a multiplicity of pathways, controlling, among others, cell metabolism, migration and differentiation. Recent data from our laboratory shed light on some of the underlying molecular mechanisms. In this review we will focus on the interactions between Bcl-2 proteins and ion channels at the level of the mitochondria and the endoplasmic reticulum in the context of cancer and development.

Keywords: Bcl-2; Mitochondria; Endoplasmic reticulum; Breast cancer; Neurodevelopment

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Chronic acidosis rewires cancer cell metabolism through PPARalpha signaling

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The mechanisms linking tumor acidosis to disease progression are not understood. Adapting cancer cells to growth at a pHe mimicking acidic tumor niches (6.5) increases acid extrusion capacity and elevates pHi at physiological pHe. The acid adapted phenotype is characterized by oxidative metabolism, increased lipid droplet-, triacylglycerol-, peroxisome content, and mitochondrial hyperfusion. PPARa activity is upregulated, at least in part by fatty acid uptake. PPARa upregulates genes driving increased mitochondrial and peroxisomal mass and beta-oxidation capacity, including mitochondrial lipid importers CPT1A, CPT2, electron transport chain components, peroxisomal proteins PEX11A and ACOX1, and TXNIP. This endows acid-adapted cells with increased capacity for utilizing fatty acids while limiting glycolysis, and renders them highly sensitive to PPARa inhibition. We conclude that PPARa is a key upstream regulator of metabolic changes favoring cancer cell survival in acidic niches.

Keywords: tumor microenvironment; acidosis; metabolism; fatty acids; PPARa

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MYELOID CELL-SPECIFIC DELETION OF Kv1.3 POTASSIUM CHANNEL DETERMINES TUMOR GROWTH IN VIVO

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Myeloid cells in the tumor microenvironment and increased neutrophil-to-lymphocyte ratio (NLR) in the peripheral blood actively support tumor growth and progression. The voltage-dependent potassium channel Kv1.3 located mainly in the plasma and inner mitochondrial membranes is expressed in many cell types. In the immune system, Kv1.3 plays important roles in regulating immune cell function, and in cancer cells, this channel is emerging as a promising oncological target. We established a novel mouse model of myeloid lineage-specific Kv1.3 deletion. Mice develop normally and are indistinguishable from their littermates. However, they show higher NLR and increased tumor burden. Collectively, Kv1.3 modulates macrophage activation and the immune composition of the tumor microenvironment. Its expression in the myeloid compartment is required for anti-tumor immunity.

Keywords: Kv1.3; myeloid cells; tumor microenvironment

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Role of the extracellular matrix stiffness in pancreatic cancer cells and pancreatic stellate cells behavior

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Pancreatic ductal adenocarcinoma is one of the most lethal cancers, characterized by an extensive fibrotic stroma. This latter is formed by an abundant extracellular matrix (ECM) deposition, leading to an increase in tissue stiffness, and by a cellular component, mainly represented by the pancreatic stellate cells (PSCs). Hence, we aimed to investigate firstly the effect of the stiff ECM on the behavior of pancreatic cancer cells (PCCs) and PSCs. To address this, we fabricated type I collagen hydrogels with two different stiffnesses (1kPa and 34kPa). We demonstrate that the genotype and secretome of PCCs and PSCs are modified in high compared to low stiffness. These modifications are followed by an increase of PCCs and PSCs migration in 34kPa, which seems to be linked to store-operated calcium entry-dependent and -independent mechanisms in PSCs and PCCs, respectively. These data are a guideline for the study of the ECM stiffness in the dialogue between PCCs and PSCs, currently under investigation.

Keywords: extracellular matrix; stiffness; pancreatic cancer cells; pancreatic stellate cells; calcium

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SYMPOSIUM 6: "METABOLISM"

ORAL PRESENTATIONS

Pancreatic Ductal Cell Adenocarcinoma Growth, Proliferation, and Metastasis are Modulated by the Mitochondrial Ca^{2+} Uniporter

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Despite improved outcomes in many cancers due to advances in targeted therapies and immunotherapeutics, pancreatic ductal adenocarcinoma (PDAC) remains a cancer with a particularly poor prognosis. This may be at least partially attributable to the early metastasis of these tumors contributing to mortality. Previously, our lab has demonstrated that cancer cell lines of various tissue types may be "addicted" to constitutive uptake of Ca2+ by mitochondria through the mitochondrial calcium uniporter (MCU) at endoplasmic reticulum-mitochondria contact sites. The resultant mitochondrial Ca^{2+} (mCa^{2+}) influx through MCU may similarly promote cancer development, proliferation, and metastasis in PDAC. Here, we show an association between high MCU expression and poor survival outcomes, as well as with Kras mutations (the most common driver of PDAC). We used the Pdx1cre; KrasLSL-G12D/+; p53fl/+; Rosa26LSL-YFP/LSL-YFP (KPCY) murine model of PDAC with or without expression of Mcufl/fl alleles to isolate tumor tissues, then leveraged CRISPR/Cas9 techniques and stable re-expression to generate isogenic cell lines with or without MCU expression for further analysis. KPCY-McuKO pancreatic cell lines (via Cre or CRISPR) lacked mCa2+ uptake in a manner rescued by stable re-expression of MCU. Wound healing, self-renewal capacity, and proliferation rate were increased in MCU+ over MCU-KO isogenic lines. MCU-KO reduced tumor growth and metastasis as compared to MCU+ cells in both immunocompetent and immunocompromised orthotopic models of PDAC, utilizing both Cre- and CRISPR- mediated isogenic lines. Key differences in gene expression related to specific pathways, including epithelial to mesenchymal transition and metabolism, were identified by nonbiased transcriptomic screening. We therefore suggest that MCU-mediated mCa2+ uptake contributes significantly to PDAC growth, proliferation, and metastasis and may thus present a therapeutic target for cancer treatment. This effect may be through increased EMT and pro-growth metabolic activity, which could be induced due to changes in mCa++ flux.

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Keywords: MCU; pancreatic cancer; pancreatic stellate cells; calcium

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TRPM2 stimulation increases the antitumor action of cisplatin via the increase of mitochondrial oxidative stress and apoptosis in brain tumor cells

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Cisplatin (CSP) induced-overload Ca2+ entry results in the increase of mitochondrial oxidative stress and apoptosis in the glioblastoma multiforme (GBM) cells. However, the success rate of the treatments is limited in the patients with GBM. The cytosolic ADP-ribose and ROS stimulate TRPM2 cation channel activation. The high content of PUFA in the brain is a main target of ROS. Eicosapentaenoic acid (EPA) induces oxidant action via the enhance of PUFA content in the glioblastoma (DBTRG) cells. Silver nanoparticles (AgNPs) are particularly intriguing for cancer therapy. Recently, my groups indicated that combinations of CSP and EPA or AgNPs may offer potential therapies in the DBTRG cell by exerting the antitumor (cell number and viability), oxidant, and apoptotic, tumor death, and stimulating Ca2+ influx and TRPM2 activity. In conclusion, anticancer action of CSP was further increased via the activation of TRPM2 channel in the DBTRG cells by the treatment of EPA and AgNPs.

Keywords: Apoptosis; Cisplatin; Glioblastoma; Oxidative stress; TRPM2 channel.

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Regulation of mitochondrial Ca2+ uptake and function by pyruvate kinase M2 (PKM2)

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PKM2 is highly expressed in cancer cells. In addition to its metabolic role, PKM2 shows non-metabolic effects, including regulation of intracellular Ca2+ signaling. Using HeLa PKM2 knock-out cells, we demonstrate that PKM2 suppresses inositol 1,4,5-trisphosphate receptor (IP3R)-dependent Ca2+ release without interfering with either ER Ca2+ store content, IP3R expression levels or store-operated Ca2+ entry. Interestingly, PKM2 also impacts mitochondria in multiple ways: loss of PKM2 in cells resulted in fewer ER-mitochondria contact sites, increased respiration, a more negative mitochondrial membrane potential, and increased mitochondrial Ca2+ uptake. The structure and post-translational modifications of PKM2 are presently being investigated to understand how PKM2 interacts with IP3Rs, and how it affects Ca2+ signaling and mitochondria. Our results indicate modulation of Ca2+ signaling as a new function of PKM2, which can contribute to survival and/or proliferation of cancer cells.

Keywords: IP3R; PKM2; Ca2+ signaling; mitochondria

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Unbiased mapping of the MCU interactome reveals MCNR1 as a potential molecular target in cancer

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Mitochondria play a key role in Ca2+ homeostasis and thus the regulation of metabolism and cell death. The MCU is an ion channel that mediates the rapid and highly selective uptake of Ca2+ into the mitochondrial matrix. However, an in-depth characterization of the molecular links that couple MCU-dependent Ca2+ entry with mitochondrial function is lacking. We performed 50 pulldowns from MCU complex reporter cell lines and built a protein network of statistically significant interactors. Among these, we identified MCNR1 as a novel MCU regulator. MCNR1 is a soluble EF-hand containing protein localized to the mitochondrial intermembrane space, documented to be highly expressed in breast, ovarian and cervical cancers. Knockdown of MCNR1 in cancer cells results in an increased MCU-mediated calcium uptake, a slower cell proliferation and a higher sensitivity to apoptotic stimuli. This presents a novel link between calcium signaling and cancer and a promising candidate for molecular targeting.

Keywords: MCU; Calcium; Cancer; Mitochondrial Calcium Uniporter

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Ion channels and cancer: global research trends, statistics, collaborations

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ION CHANNEL LIBRARY, ionchannellibrary.com

The “Ion channels and cancer” field has evolved rapidly over the last two decades. Here we provide a comprehensive overview of global research output in this field. We demonstrated the evolution of research output over time and highlighted key research topics and trends. We also identified leading authors, universities, countries, and journals, as well as collaboration networks and patterns. Finally, we performed patent analysis and identified biotech companies working in this field. These results will be useful to anyone wishing to better understand the evolution of the “Ion channels and cancer” field, find potential partners, identify current trends, and make data-informed strategic decisions about their research.

Keywords: Ion channels; Cancer; Bibliometric analysis; Research topics; Collaboration

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SYMPOSIUM 7: "THERAPEUTIC TARGETING"

ORAL PRESENTATIONS

Targeting the Achilles' heel of cancer cells: modulation of cell survival and migration by inhibition of mitochondrial ion channels

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Mitochondria are hubs for cellular energetics and metabolism. In accordance, deregulation of mitochondria function might profoundly change cell fate via different mechanisms, including high ROS production and cytochrome c release. To date, a number of ion channels that show an altered expression in cancer cells were found to reside in both the plasma membrane and mitochondria. Pharmacological modulation of such channels specifically in mitochondria thus can add a layer of specificity in modulating cancer cell behaviour with respect to drugs that affect mitochondrial metabolism or permeabilization in general. Our strategy of fusing a mitochondria-targeting moiety to specific channel inhibitors was exploited for three potassium channels (mtKv1.3, mtKCa3.1; mtTASK-3). In two cases, depending on the concentrations used, these agents were able to modulate cancer-cell specific functions in vitro and in vivo, leading to drastic reduction of tumor volume and migration, without toxicity.

Keywords: mitochondrial ion channels; mitochondria-targeted channel inhibitors; apoptosis; metastasis

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Calcium signaling unveils cancer vulnerability: From bench science to clinical trial

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Changes of ionic gradients is a fundamental factor to control a variety of cellular events ranging from cell motility to proliferation. Living cells regulate their ionic environment through the coordinated activities of a variety of ion channels/transporters proteins. Nevertheless, Ca^{2+}-dependent signaling appears to be one of the most important factor in cell signal transduction. Remarkably, aberrant Ca^{2+} signaling is increasingly recognized as a central pathological mechanism in a variety of disorders afflicting millions of people. Nevertheless, little is known about the role of Ca^{2+} signaling in cancer biology and direct targeting Ca^{2+} channels for therapeutic purposes is still a important challenge. We discovered that manipulation of potassium ion channels produce a significant change in Ca^{2+} dynamics in non-excitable cancer cells. Our research brought to light new mechanisms linking changes in Ca^{2+} gradients to function of specific oncogenes (i.e. cyclin E2) as well oncosuppressors (i.e. p21), mitochondria and/or cell motility (i.e. TGFb signaling). Remarkably, these events translate in a significant inhibition in a variety of hallmarks of cancer including growth, metastasis and cancer cell metabolism independently of the cancer histogenesis. Also, in this talk we will provide first evidence supporting the hypothesis that pharmacological targeting K^+ channels to interfere with Ca^{2+}-driven signaling can be considered as an effective and safe anticancer therapeutic strategy.

Keywords:

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Ranolazine: A voltage-gated sodium channel blocker with clinical potential

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A wealth of data suggests strongly that voltage-gated sodium channels (VGSCs) are expressed in several carcinomas and promote disease progression (metastasis). In fact, VGSC expression appears early in metastasis and may even initiate it. We have focused on the channel's persistent current component (INaP) which develops under hypoxic conditions which occur commonly in growing tumours. As a result, an excessive amount of sodium enters the cells, and this can be detected by clinical 23Na-MRI. Ranolazine blocks INaP selectively, inhibits Matrigel invasiveness and metastasis in rodent models of breast and prostate cancer. Accordingly, ranolazine which is already in clinical use as an anti-angina drug, can be repurposed as a safe anti-metastatic agent. In addition, the VGSC expression offers distinct advantages as a 'companion diagnostic'.

Keywords: Sodium channel; hypoxia; persistent current; ranolazine; metastasis

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Role of calcium entries in the physiopathology of glioblastoma stem cells

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Transcriptome analysis showed that glioblastoma stem cells (GSC) are enriched in calcium signaling genes that suggest a role of calcium (Ca2+) in GSC regulation. To mimic the different substrates that GSC will find in the brain, tridimensional environments have been used. Biocompatible polyacrylonitrile-derived nanofibrous scaffolds have been developed in « Institut Européen des Membranes » with two nanofibers organizations and stiffnesses to analyze their impact on SOCE (store operated Ca2+ channel entries) in GSC as well as in proliferation and migration. Our previous study showed a role of SOCE in proliferation, self-renewal and stemness in GSC. Next, we analyzed ROC (receptor operated Ca2+ channel) expression especially TRPC3 and TRPC6 and ROCE (ROC entries) . The inhibition of ROC has an impact on proliferation and self-renewal. Our data indicate that calcium signaling plays a crucial role in GSC physiopathology and could be an interesting therapeutical target to regulate GSC.

Keywords: glioblastoma stem cells; SOCE; ROCE; 3D migration

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Targeting the Nav1.5 channel with antiarrhythmic drugs to reduce metastatic recurrence: evidence from retrospective patient cohort studies

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Solid tumours have abnormally high Na+. Using 23Na-MRI, we show that this is driven by elevated intracellular Na+. The Nav1.5 voltage-gated Na+ channel (VGSC) may underlie this Na+ accumulation. We show in a breast cancer tissue microarray that high Nav1.5 expression strongly correlates with metastasis and shortened cancer-specific survival. We also show that Na+ currents are detectable in patient-derived cells. To study therapeutic value, we investigated associations between VGSC inhibitor use and survival in a cohort of breast, bowel, and prostate cancer patients. Exposure to VGSC-inhibiting tricyclic antidepressants, local anaesthetics, and anticonvulsants was associated with increased mortality. In contrast, exposure to slow/late current-inhibiting Class 1c and 1d antiarrhythmics was associated with significantly improved cancer-specific survival. These data support previous preclinical findings and suggest a positive impact of certain VGSC inhibitors on metastasis-free survival.

Keywords: Antiarrhythmic; Metastasis; Nav1.5; Sodium; Therapeutics

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POSTER PRESENTATIONS

Role of the MICU2 protein in colorectal cancer hallmarks

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Since the last decade, the role of mitochondrial Ca2+ homeostasis has been highlighted in colorectal cancer (CRC). The mitochondrial Ca2+ uniporter (MCU) plays a prominent role in intra-mitochondrial Ca2+ uptake. MCU functions as a large multimolecular complex consisting of MCU pore-forming proteins and mitochondrial Ca2+ regulatory proteins (MICU1, MICU2, MICU3 and EMRE). The set of these regulatory proteins remains poorly studied in cancerology. The main objective of our study is to determine the role of MICUs in the different CRC cancer hallmarks. Dataset analysis has shown increased expression of the MICU2 in metastatic stage in CRC. We reported that MICU2 plays an important role in mitochondria calcium homeostasis, cellular respiration and metabolic reprogramming. We also described that MICU2 significantly regulates CRC cell proliferation and migration. For the first time, we demonstrate a pivotal role of MICU2 in cancer progression, and specifically in CRC.

Keywords: cancer colorectal; calcium signalling; mitochondria; metabolism; MICU2

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Involvement of the calcium channel TRPV6 in the migratory and invasive potential of metastatic prostate cancer cells

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The progression of prostate cancer is accompanied by the establishment of a more aggressive phenotype, resulting in formation of metastasis, located at 91% in the bones. The data in vivo demonstrate that TRPV6 is abundantly expressed in cancer tissue and is located at the edge of the tumor. Further, PCa cells overexpressing TRPV6 were shown in the bone marrow of patients having osteoblastic lesions. Thus, the role of the TRPV6 in the migratory and invasive potential in PCa cells remains to be determined. To study the role of TRPV6, we have generated a metastatic prostate cancer cell line, PC3Mtrpv6-/- . In vitro, PC3Mtrpv6-/- cells as compared to PC3Mtrpv+/+ showed significant decrease in cell migration and invasion. Moreover, mechanistic studies have demonstrated that PC3Mtrpv6-/- cells possessed a decreased rate of motility and tracked distance, which may be partially explained by an altered transcriptomic and proteomic profile of the Ca2+-dependent pathways involved in motility.

Keywords: Prostate Cancer; Calcium; TRPV6; Metastasis

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SODIUM-CALCIUM SIGNALLING NETWORK UNDERLYING METASTATIC POTENTIAL OF PROSTATE CANCER CELLS

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A new model has been generated from circulating tumor cells (CTC) which will help us to have deeper insights in understanding the metastasis mechanism. And, we have recently performed bioinformatic analysis on prostate tumor samples, revealing several mutations of NALCN, a sodium channel which we previously described as an actor of invasion during prostate cancer (PCa). Analysing the RNA sequencing (Faugeroux et al. 2020) on CTC derived cells, a differential expression of a number of ion channels in comparison to LNCaP is noticed. Understanding the ion homeostasis of CTC derived cells, from calcium imaging, it is observed that the store mediated calcium entry (SOCE) of these cells is lower than the SOCE release in LNCAP and LNCaP C4-2 cells. It is crucial to discover new and effective therapies for advanced PCa and in this study, we have preliminary evidences of role of ion channels in regulating cell-survival mechanisms of highly metastatic cells to resist cell death.

Keywords: Circulating Tumor Cells; Ion Channels; Metastasis; Cell Death Resistance

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Evaluation of the therapeutic efficacy of a bispecific antibody targeting the hERG1/β1 integrin complex (ScDb) in combination with Gemcitabine (GEM) in a mouse model of pancreatic ductal adenocarcinoma (PDAC)

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We generated an orthotopic xenograft mouse model in which we tested the antineoplastic efficacy of scDb, proven to affinity target PDAC cancers, in combination with GEM at therapeutic and subtherapeutic concentrations. The development of the PDAC has been characterized and monitored by US imaging. The treatment started after 2 weeks from the cell injection (PANC-1) and continued for the next 3 weeks. In terms of tumor growth, we observed a similar effect between scDb and GEM at the lower dose (0.1 mg/kg-subtherapeutic), but the most relevant result was obtained in the group treated with scDb+GEM 0.1 mg/kg. In time, the specificity provided by scDb combined with subtherapeutic dose of GEM increased their efficacy, reflecting the same impact as therapeutic dose gemcitabine. In addition, the difference of effects provided by combinatorial treatment against GEM 0.5 mg/kg (therapeutic) and scDb alone, suggests a synergic effect between the bifunctional antibody and GEM.

Keywords: PDAC; ANTIBODIES; ULTRASOUND IMAGING; hERG1

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PHARMACOLOGICAL MODULATION OF THE MITOCHONDRIAL POTASSIUM CHANNEL Kv1.3 TRIGGERS APOPTOSIS OF CANCER STEM CELLS AND PREVENTS MAMMOSPHERE FORMATION

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Triple Negative Breast Cancer (TNBC) is a heterogenous, recurring cancer. TNBC express high level of the mitochondrial Kv1.3 ion channel. We investigated the effects of Kv1.3 inhibitors that are either membrane-impermeant acting on the plasma membrane-located channels, or two inhibitors that act on the mitochondria-located channel. The mitochondrial inhibitors, PAPTP and PCARBTP, were able to trigger apoptosis in 2D cultures and acted synergistically with gemcitabine. Sublethal doses of mtkv1.3 inhibitors were very efficient in mammosphere models, while membrane-impermeant toxin inhibitors of Kv1.3 were without effect. Efficiency of mitochondrial inhibitors to inhibit mammosphere formation, increased in combination with gemcitabine and abolished CSC population. Biochemical experiments highlighted that PAPTP combining with gemcitabine affected cellular pathways that are crucial for cancer stemness. Our results shows mtKv1.3 inhibitors with gemcitabine are promising agents against TNBC.

Keywords: Triple Negative Breast Cancer (TNBC), mitochondrial ion channel, PAPTP and PCARBTP, mammosphere, cancer stem cells

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Kv10.1 channel involvement in breast tumor microenvironment sensing

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The aggressive phenotypes of breast cancers are responsible of death due to the development of metastasis. Furthermore, hypoxia has been shown to promote this aggressivity. We demonstrated that Kv10.1 potassium channel regulates proliferation or motility of different breast cancer models in normoxia. Kv10.1 also favors collagen-1-induced cell survival suggesting its capability to sensing the tumoral environment. However, few information is available about its role in response to hypoxia. In severe hypoxia conditions (1% O2), Kv10.1 increased MDA-MB-231 cell migration by affecting integrin expression. Its silencing or pharmacological inhibition reduced the EMT markers (e.g. vimentin…). In addition, the Kv10.1-dependent secretome favors angiogenesis. Finally, Kv10.1 expression was found in hypoxic sections of breast cancer tissues. In conclusion, Kv10.1 favors cell migration, EMT and angiogenesis under hypoxic conditions.

Keywords: Kv10.1 potassium channel; tumor microenvironment; hypoxia; migration; angiogenesis

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TRPV6 modulates Panc-1 cell aggressiveness and chemotherapeutic resistance

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Increasing evidence suggests that the overexpression of the Ca2+ channel TRPV6 is a common event in cancers of epithelial origin. Our work aims at studying the role of TRPV6 channels in pancreatic ductal adenocarcinoma (PDAC) cells. We generated four different stable clone models of the Panc-1 cell line. These clones either under- or overexpressed TRPV6. Using MTS cell survival assays, cell count, ATP quantification and cell cycle analysis for sub-G1 peak quantification we found that TRPV6 overexpression leads to an increase of cell viability and proliferation, whilst the knockdown of the channels leads to cell cycle retention. Moreover, the knockdown of TRPV6 made cells more susceptible to chemotherapeutics like gemcitabine, cisplatin and 5-Fluorouracil, as assessed by Annexin V staining and quantification of intracellular ATP. Overall, our results suggest that TRPV6 plays a protective role in Panc-1 cells and increases their aggressiveness.

Keywords: TRPV6; PDAC; chemotherapeutics

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TRPV6 TARGETING BY MONOCLONAL ANTIBODY INDUCES APOPTOSIS IN VITRO AND TUMOR REGRESSION IN VIVO

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Increasing evidences suggest that the overexpression of TRPV6 is a common event in cancers of epithelial origin. TRPV6 was observed to be up- regulated in various tumors. Thus, TRPV6 represents an attractive therapeutic target against many cancers. To efficiently target TRPV6 calcium channel, we have generated a monoclonal antibody against the pore region of the channel. In vitro, the incubation of prostate cancer cells with anti-TRPV6 antibody showed a significant decrease in cell growth. Moreover, it has shown a considerable inhibition of the TRPV6-mediated currents. Finally, the incubation of prostate cancer cells with this antibody showed a highly increase of apoptosis, suggesting that this antibody inhibits TRPV6 and induces cell death by apoptosis. In vivo, experiments have been done in immunodeficient mice xenografted with prostate cancer cells. Treatment with TRPV6 antibody significantly reduces tumor growth suggesting its therapeutic potential in humans.

Keywords: TRPV6 CALCIUM CHANNEL; ANTIBODY; PROSTATE CANCER

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TRPM4 regulates cytosolic Ca2+ oscillations and secretome in chemotherapy-induced senescence

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Cellular senescence is characterized by a stable cell cycle arrest, various macromolecular changes, and a pro-inflammatory phenotype- the senescence-associated secretory phenotype (SASP). Here, by q-RT-PCR, we show that TRPM4 is upregulated in response to DNA-damaging chemotherapeutic drugs in prostate stromal cells. By western blot analysis, we identify that the isoform that is upregulated represents the channel's dominant negative, short isoform, rather than the wild type, full-length isoform. TRPM4 appears to reshape Ca2+ homeostasis and control the oscillatory behavior of persistent DNA damage-induced-senescent cells. Moreover, we show that conditioned medium from senescent stromal cells enhances the invasive capacity of epithelial prostate cancer cells, which can be limited by silencing TRPM4 in stromal cells. Our results suggest TRPM4 as a novel tumor microenvironment regulator in prostate cancer progression in response to chemotherapy.

Keywords: Chemotherapy; Senescence; SASP; tumor microenvironment; Ca2+; oscillations

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Identification of the reticulo-membrane complex Orai3/STIM1/IP3R3 (OSIR) in the formation of breast metastases

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Breast cancer is the most common and deadliest cancer in women. At the cellular level, dysregulation of calcium homeostasis is one of processes involved in metastasis. Among the proteins modulating this calcium homeostasis, three of them, ORAI3, STIM1 and IP3R3, acting close to each other, could form a functional complex ORAI/STIM/IP3R (OSIR). Many studies have shown an involvement of these proteins individually in cancer cell behaviours such as migration, invasion, proliferation and angiogenesis. However, the presence of this complex has never been established in cancer cells. Our aim is to provide proof of concept that by modulating the migratory and secretory capacities of breast cancer cells, the reticulo-membrane complex Orai3/STIM1/IP3R3 could also promote the occurrence of metastases, making it possible to assign a predictive character of tumor aggressiveness in case of strong expression of these actors in the primary tumour.

Keywords: calcium signaling; breast cancer; endoplasmic reticulum; cytoskeleton

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pHe-sensitive Store-Operated Ca2+ signals contribute to tumor acidic microenvironment-induced PDAC cells' selection to more aggressive phenotypes

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Acidosis is a key chemical signature of Pancreatic ductal adenocarcinoma. Ca2+-permeable ion channels are deregulated in cancer and their pHe-sensitivity makes them drivers of tumor aggressiveness. To verify the hypothesis that acidic TME employs Ca2+ signaling as a preferential route for sustaining PDAC progression, we evaluated how tumor acidosis modulates Ca2+ signals during acid selection, with a focus on Ca2+ oscillations and SOCE. During early stages of selection, cells show slow orai1-dependent Ca2+ oscillations and orai1 downregulation with respect to control, while long exposure to acidic pH and recovery to neutral pH shows a recover of faster Ca2+ oscillations and orai1 upregulation. These data correlate with SOCE. ORAI1-mediated Ca2+ entry plays a key role in promoting migration and invasion of all acid phenotypes but not control cells, as orai1 silencing and chemical inhibition didn't affect control cells' invasion and migration.

Keywords: Acidic tumor microenvironment; PDAC; Ca2+-permeable ion channels; Store-Operated Ca2+ entry; Ca2+ oscillations

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A novel target of EWS-Fli1, the potassium channel KCNN1, regulate Ewing sarcoma cell proliferation via intracellular calcium signaling

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Ewing sarcoma (ES) is the second most common primary pediatric bone tumor, characterized by the EWS-Fli1 fusion protein, acting as an oncogene. Our goal is to better understand the ES biology, by studying the involvement of potassium channels. Indeed, studies showed their hijack to promote the tumor development. RNA-seq analyses from ES patients have shown a high expression of KCNN1, encoding for the potassium channel SK1, which led us to wonder about its involvement in ES development. These results have been confirmed by qPCR on ES cell lines. ChIP-Seq analyses also proved that KCNN1 expression is transcriptionally regulated by EWS-Fli1. Then, using inducible shRNAs, we showed the involvement of SK1 in the regulation of cell proliferation and cell cycle of ES cells by modulating membrane potential and calcium flux. All these results suggest SK1 as a potential therapeutic target.

Keywords: Ewing sarcoma, SK1, potassium channel, EWS-Fli1, Cell proliferation

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Targeting TRPV6 Channel as a Novel Autophagy Modulator and Therapeutic Strategy to Sensitize Prostate Cancer to Abiraterone Acetate

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The role of calcium (Ca2+) in regulation of cancer death and survival is well known. However, the potential players in Ca2+ signaling related to the progression of resistance to cancer therapies and their mechanism of action is still limited. We investigated the Ca2+ signature of abiraterone acetate (AA) treatment in regulating prostate cancer (PCa) cell fate. We observed that AA upregulates key proteins associated with Ca2+ signaling and promotes Ca2+ entry through TRPV6 channel into LNCaP prostate cancer cells. AA treatment to androgen-sensitive human prostate adenocarcinoma cells led to activation of CAMKK2 and its downstream effector AMPK thus linking Ca2+ signaling to autophagy induction and suppression of cell death. We showed that the silencing of TRPV6 lead to inhibition of autophagy and therefore, enhance AA efficiency and increase cell death. We suggest TRPV6 channel as a novel autophagy modulator and target for improving the effect of AA in PCa patients.

Keywords: abiraterone acetate; calcium; TRPV6; autophagy; resistance to therapy

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hERG1 POTASSIUM CHANNEL AND HYPOXIA IN BLADDER CANCER: IMMUNOHISTOCHEMISTRY AND IN SILICO ANALYSES

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hERG1 potassium channels encoded by the KCNH2 gene are deregulated in different human cancers including clear cell renal cancer (ccRCC) where they predict recurrence in surgically-treated patients. Moreover, we showed that hERG1 and CA IX are physically associated in ccRCC (Lastraioli E et al., 2020) and in other cancers connections between hERG1 and Glut1 (Lastraioli E et al., 2012) and between hERG1 and VEGF-A also exist (Crociani O et al.,2014). Basing on these premises we performed a pilot study aimed at unravelling the expression of hERG1 in Urothelial bladder cancer (UBC) samples. We performed immunohistochemical analysis (IHC), to evaluate the expression of hERG1, CA IX, Glut1 and VEGF in UBC samples with anti-hERG1, anti-Glut1, anti-VEGF and anti-CAIX antibodies. Moreover, in order to define a molecular landscape of the hypoxic niche, an in-silico analysis was performed using publicly available databases, analyzing the expression of KCNH2, GLUT1, VEGFA and CAIX genes in UBC.

Keywords: hERG1; bladder cancer; immunohistochemistry; in silico analysis; hypoxia

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Blocking the Ca2+-activated K+ channel KCa3.1 in pancreatic ductal adenocarcinoma

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The KCa3.1 channel is massively overexpressed in pancreatic ductal adenocarcinoma (PDAC). The aim of this project is to better characterize its role. In vivo experiments were performed using the KrasLSL−G12D/+Trp53fl/flPdx1Cre/+ PDAC mouse model. Mice were treated with vehicle, gemcitabine, the KCa3.1 inhibitor TRAM-34 or a combination of the two. Pancreata were sliced, stained, and analyzed to assess tumor size and the extent of fibrosis. This was complemented through the assessment of migration in a spheroid model of PDAC. The inhibition of KCa3.1 in combination with gemcitabine leads to a moderate decrease in tumor size and a reduction of gemcitabine-induced fibrosis. This could mean that the combined effect makes the tumor tissue more accessible to treatment. In PDAC spheroids, KCa3.1 inhibition in combination with gemcitabine decreases the invasive potential. This is accompanied by a change from an elongated to a round morphology of the migrating cells.

Keywords: Pancreas, Cancer, KCa channels

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The Role of the Na+/Ca2+-Exchanger in the Migration of Pancreatic Stellate Cells in the Tumor Microenvironment

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Pancreatic stellate cells (PSCs) remodel the tumor microenvironment (TME) of the pancreatic ductal adenocarcinoma. This leads to altered physico-chemical properties of the TME. Moreover, PSCs co-metastasis with pancreatic cancer cells. The Na+/Ca2+ exchanger (NCX) is an important Ca2+ regulatory transport protein. Here, we studied whether migration of PSCs is regulated by the NCX in the different physico-chemical properties of the TME. Migration of PSCs was monitored with live-cell imaging. [Na+]i, [Ca2+]i and membrane potential were determined with fluorescent imaging. Cells were treated with hypoxia, pressure, acidic pH and growth factors. Migration of PSCs depends on cues from the TME. The Na+/Ca2+ exchanger plays a differential role in translating these cues into an altered migratory behavior. When NCX operating in the forward mode (Ca2+exit) is inhibited, PSCs migrate faster in most conditions. Thus, NCX-mediated extrusion of Ca2+ contributes to a slow mode of migration of PSCs.

Keywords: Na+/Ca2+ exchanger (NCX); Ca2+; migration; tumor microenvironment (TME); PDAC

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KCa and Nav channels mediate hyperpolarizing fluctuations in MDA-MB-231 human breast cancer cells

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It is widely known that cancer cells have a depolarized membrane potential (Vm) compared to non-tumorigenic cells. Furthermore, Vm and ion channels are associated with cancer cell processes including metastatic behaviors. We recently found that the Vm of MDA-MB-231and 7 other breast cancer cells fluctuates, mainly with transient hyperpolarizations1. In contrast, non-tumorigenic breast epithelial MCF-10A cells possess a stable Vm. Tetrodotoxin (TTX) decreased the hyperpolarizing fluctuations in MDA-MB-231 cells. Blockade of BK or SK KCa channels both decreased hyperpolarizing events in MDA-MB-231 cells. Because Nav channel blockade by TTX is known to hyperpolarize resting Vm, we hypothesize that this reduces the voltage-sensitive BK channel contribution to the hyperpolarizing transients. These results suggest that both KCa and Nav conductance contribute to the generation of hyperpolarizing Vm transients in MDA-MB-231 cells. Quicke, P. et al. Commun. Biol. 5, 1–14 (2022).

Keywords: Calcium-activated potassium channel; membrane potential; cancer; voltage imaging; voltage-gated sodium channel

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