Association pour la Recherche sur les Tumeurs de la Prostate

ARTP BULLETIN

November 17th, 2021

30th Annual Meeting Association pour la Recherche sur les Tumeurs de la Prostate

Foreword

With this 30th annual meeting, the ARTP continues a tradition of bringing together researchers, academics and clinicians from all over the world, experts in prostate cancer. This conference will particularly focus on microenvironment and metastases in prostate cancer, from diagnosis to therapy. Once again, the funding of the new projects selected for 2022 as well as the organization of this meeting would have not been possible without the generous contributions of Pierre Fabre Médicament, Astellas, Janssen Cilag, AstraZeneca, MSD, Ferring and the AFU foundation. We thank all speakers and participants for their contributions.

Prof Alexandre de la Taille
ARTP President

Program

Organizing Committee

Frédéric Bost, Jocelyn Céraline, Olivier Cuvillier, Vincent Goffin, Palma Rocchi & Alexandre de la Taille

9:05 a.m.
Welcome
Alexandre de la Taille
ARTP President

9:10 a.m.
Session I : ARTP 2020 laureates
Chairs : Vincent Goffin, Olivier Cuvillier

Edith Bonnelye
(UMR 9020 CNRS-UMR-S 1277, Lille)
'Involvement of ERR alpha in the response mechanisms to radiotherapy in prostate cancer'

9:30 a.m.
Session II : Clinical Session (Diagnostic, Imaging & Vaccination)
Chairs : Arnauld Villers, Alexandre de la Taille

Eric Tartour
(Hôpital européen Georges-Pompidou, Inserm U970, Paris)
'Cancer vaccines: rationale and potential clinical applications'

Steve Pascolo
(University Hospital Zurich)
'mRNA-based vaccines and cancer therapies'

10:30 a.m.
Coffee Break & Visit of Exhibition Booths

11:00 a.m.
Présentation ANAMACAP (in French) Chair : Alexandre de la Taille

Roland Muntz
(Président d'honneur ANAMACaP)

11:30 a.m.
ARTP General Assembly (Adherents ONLY)

Alexandre de la Taille, Président
Olivier Cuvillier, Trésorier

12:00 p.m.
Lunch

Restaurant Rural
by Marc Veyrat,
Palais des Congrès
niveau 0

1:30 p.m.

Session III : Microenvironment & Metastases

Chairs : Frédéric Bost, Stéphane Terry

Ewa Snaar-Jagalska

(Leiden University, The Netherlands)

'Microenvironment Elevates EMT and CSC-Like Phenotype of Engrafted Prostate Cancer Cells'

Catherine Muller

(IPBS CNRS UMR 5089, Toulouse)

'Progression of prostate cancer: a way paved of fat'

Juan Arriaga

(Columbia University, NY, USA)

'Identifying Drivers and Therapeutic Vulnerabilities of Prostate Cancer Bone Metastasis'

2:45 p.m.

Coffee Break & Visit of Exhibition Booths

3:00 p.m.

Session IV : Liquid Biopsies & Circulating Tumor Cells

Chairs : Gaëlle Fromont-Hankard, Palma Rocchi

Françoise Farace

(Institut Gustave Roussy, Villejuif)

'Genetic characterization of a unique neuroendocrine transdifferentiation prostate circulating tumor cell-derived eXplant (CDX) model'

Alexander Wyatt

(University of British Columbia, Vancouver, Canada)

'The emerging clinical utility of circulating tumour DNA in advanced prostate cancer'

4:00 p.m.

Session IV : Poster Session

Chairs of Selection Committee:
Jocelyn Céraline, Clémentine Le Magnen

5:00 p.m.

Session VI : 2019 ARTP Poster Prize Laureates

Chairs : Silvère Baron, Edith Bonnelye

Clément Paris

(CRCM, Marseille)

'Lipid antisense oligonucleotides nanoparticle: nanoplatform agent for the treatment of castration-resistant prostate cancer'

Charlotte Dubois

(Inserm U1003, Lille)

'Apoptosis mediated by mitochondrial Ca2+ overload requires inhibition of autophagy revealing a widespread vulnerability of cancer cells'

David Esteve

(IPBS CNRS UMR 5089, Toulouse)

'The adipose tissue that surrounds the prostate gland exhibits traits of hypoxic state that could contribute to its role in prostate cancer progression'

5:30 p.m.

Poster Prize distribution

5:45 p.m.

End of the meeting

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Session I :
ARTP 2020 Laureates

1

Edith BONNELYE

Institut de Biologie de Lille, UMR 9020 CNRS-UMR-S 1277, Lille, France

ERRα in hormone-related cancers: role in osteo-oncology

Bone metastases are one of the main complications of breast and prostate cancer. Indeed, up to 70 percent of patients with advanced breast cancer (BCa) and 80 percent of patients dying from prostate cancer (PCa) have developed bone metastases that are incurable, raising the need to improve their treatment and prevention. We identified the nuclear receptor ERRα ("Estrogen Related Receptor alpha") as an actor in bone metastases progression from breast and prostate cancer. First, we described ERRα as an inhibitor in BCa bone metastases by acting as an immunity modulator through the regulation of the chemokines CCL17, CCL20 and the TGFβ signaling allowing CD8+ T Lymphocytes recruitment and cytotoxic features. Second, we identified ERRα as a pro-metastatic factor in PCa by associating ERRα to the lethal castration resistant prostate cancer (CRPC) stage. Moreover, in PCa, we described ERRα as a pro-bone metastatic factor by impacting the bone remodelling and the tumor infiltrating fibroblasts (CAF) through the regulation of VEGFa, TGFβ and WNT signaling in tumor cells and periostin in CAF.

In conclusion, this new knowledge on ERRα suggest a dual role of this receptor in bone metastases from BCa and PCa. There also show that ERRα may constitute a new aggressiveness biomarker associated with high risk of CRPC progression and suggest that targeting ERRα in PCa may constitute a new therapeutic strategy in the treatment of the CRPC and their associated bone metastases.

Session II : Clinical Session (Diagnostic, Imaging & Vaccination)

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Eric TARTOUR
Hôpital Européen Georges Pompidou, APHP, INSERM U 970 - PARCC. Université de Paris, France.

Cancer vaccines: rationale and potential clinical applications

In contrast to immunomodulatory drugs blocking the interaction of inhibitory receptors with their ligands, cancer vaccines have difficulties to find a clinical place. The first anti-cancer vaccine to obtain market authorization, sipuleucel (Provenge), was used in prostate cancer but its development in real life remain limited (modest effect, cost and complex production of cell product). In monotherapy, positive phase 2 trials of cancer vaccines have been reported in cancers with low tumor burden or in pre-neoplastic lesions. At an advanced stage, immunosuppression mechanisms (expression of inhibitory costimulatory molecules by T lymphocytes, presence of regulatory T cells, suppressive myeloid cells) may explain the resistance to vaccine efficacy. New antigenic targets (mutated antigens), new vaccine platforms (mRNAs), and the combination of vaccines with drugs that inhibit these suppressive mechanisms may allow future clinical application of these cancer vaccines.

Steve PASCOLO
University Hospital Zurich

mRNA-based vaccines and cancer therapies

Session III : Microenvironment & Metastases

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Ewa SNAAR-JAGALSKA
Leiden University, The Netherlands

Microenvironment Elevates EMT and CSC-Like Phenotype of Engrafted Prostate Cancer Cells

Catherine MULLER-STAUMONT
Institute of Pharmacology and Structural Biology
CNRS UMR5089

Dissemination of prostate cancer : a way paved of fat

Prostate is surrounded by a specific fat depot called periprostatic adipose tissue (PPAT) that contributes through paracrine mechanisms to prostate cancer (PCa) progression (for review Estève et al, Current Opinion in Endocrine and Metabolic Research, 2020). Like other white adipose tissues, PPAT stores lipids and is an endocrine organ. We and others have demonstrated that soluble factors secreted from PPAT promote PCa aggressiveness and dissemination using in vitro as well as in vivo (animal models, annotated tumor collections) approaches. PPAT participates to the early local invasion of cancer cells outside of the prostate gland through the ability of adipocytes to secrete the chemokine CCL7/MCP3, which chemoattracts the CCR3-expressing tumor cells (Laurent et al, Nature Communications, 2015). Once, the tumor cells infiltrate PPAT, a bidirectional cross-talk is established between adipocytes and cancer cells leading to a lipid transfer from adipocytes into cancer cells, which is responsible to an increased tumor cell invasion through the generation of reactive oxygen species (Laurent et al, Molecular Cancer Research, 2019). Homing of these invasive cells to the bones is also favored by the CCR3/CCL7 axis (Guerard et al, International Journal of Molecular Science, 2021). All the identified mechanisms are amplified in obesity, where the secretory and metabolic profile of PPAT is modified, obesity being associated with greater occurrences of aggressive diseases. Beyond obesity, the excessive accumulation of PPAT, independently of the ponderal status of the patients, is an emerging risk factor in aggressive diseases. I will present the latest results of our team concerning the biological characterization of these abundant PPAT and how they contribute to tumor progression. In conclusion, deciphering the role of human PPAT on PCa progression will undoubtedly provide, in the near future, new therapeutic strategies and new risk stratification factors in PCa.

Juan ARRIAGA

Columbia University, NY, USA

Identifying Drivers and Therapeutic Vulnerabilities of Prostate Cancer Bone Metastasis

Metastatic castration resistant prostate cancer (mCRPC) remains a lethal disease with few therapeutic options. Despite increasing knowledge of the molecular alterations that are present in mCRPC, much remains unknown on which of these alterations functionally impact metastasis. This is particularly true for bone metastasis, for which in vivo models are largely lacking.

In order to address this gap, we have developed a novel genetically engineered mouse model of spontaneous bone metastasis, as well as unbiased functional screening strategies in human cell lines that together identify new drivers of bone metastasis in prostate cancer. In particular, coactivation of PI3K and Ras pathways in the mouse prostate results in spontaneous development of castration resistant prostate cancer that develops bone metastasis in 45% of mice, therefore the most penetrant model known to date. We use this model to show that Myc and Ras signaling drive bone metastasis and to develop a gene signature significantly associated with metastasis recurrence in human patients. Second, by performing

first-in-class, genome-wide, *in vivo* CRISPR activation (CRISPRa) and inhibition (CRISPRi) screens in two non-metastatic human prostate cancer cell lines (LNCaP and 22Rv1), we identify CITED2 as a gene whose overexpression is sufficient for the development of prostate cancer bone metastasis.

In summary, our studies have identified key genes and signaling pathways that determine the development of bone metastasis from prostate cancer and pave the way for future studies directed at developing novel therapeutic strategies based on this knowledge.

Session IV : Liquid Biopsies & Circulating Tumor Cells

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Françoise FARACE
Institut Gustave Roussy, Villejuif

Genetic characterization of a unique neuroendocrine transdifferentiation prostate circulating tumor cell-derived eXplant (CDX) model

Despite advances in the treatments, the disease course of metastatic castration resistant prostate cancer (mCRPC) is almost invariably marked by evolution toward a therapy-resistant and lethal disease. In a substantial proportion of patients treated with anti-androgen receptor axis therapies, transdifferentiation of mCRPC into an aggressive neuroendocrine disease (CRPC-NE) is recognized as a mechanism of resistance. One of the challenges is the difficulty obtaining post-treatment tumor biopsy specimens and the lack of relevant experimental models.

We present the establishment and characterization of a prostate CTC-Derived eXplant (CDX) model using CTCs obtained by leukapheresis from a mCRPC resistant to enzalutamide therapy. In addition to the CDX, a pair CDX/CDX-derived cell line was established. The permanent in vitro cell line was established using CDX dissociated tumour cells and conserved 86% of the genetic aberrations of the CDX. Both the CDX and the cell line mirrored patient response to standard of care CRPC therapies.The CDX and CDX-derived cell line expressed a neuroendocrine phenotype accompanied by expression of cancer stem cell features by the cell line. Only a small proportion (4%) of the mutations of the primary tumor was found in the CDX and associated with the tumorigenic activity of CTCs. An even smaller proportion (0.3%) of the mutations of CTCs supported their tumorigenicity. In contrast, the vast majority (83%) of the copy number aberrations (CNAs) of the primary tumour were conserved in tumorigenic CTCs. Importantly, phylogenic tree reconstruction enables to determine the evolution of tumorigenic CTCs and to identify the key drivers of the neuroendocrine transdifferentiation process which occurred in the patient.

While TMPRSS2-ERG fusion was clonal, subclonal TP53 loss was found in only one of the eight primary tumor specimens. Loss of TP53 and additional loss of PTEN and RB1 were acquired in CTCs and conserved in the CDX/cell line Therefore, the three genetic events which are hallmarks of neuroendocrine transdifferentiation were typically acquired in CTCs. Overall, the phenotypic and genetic characterization of our CDX is consistent with a neuroendocrine transdifferentiation model of CRPC where tumorigenic CTC have acquired phenotypic and genetic neuroendocrine features allowing them to resist to therapy. Our data provide unique insight into the genetic basis of the tumorigenic activity of CRPC CTCs and key genetic events that drive neuroendocrine transdifferentiation of CRPC in this clinical situation.

This CDX and CDX-derived cell line experimental model will be very useful tools for testing therapeutic approaches to reverse this process and drug resistance in mCRPC. in mCRPC.

Alexander WYATT
University of British Columbia, Vancouver, Canada

The emerging clinical utility of circulating tumour DNA in advanced prostate cancer

This presentation will cover the following topics:

1) Relative strengths and limitations of liquid versus tissue biopsy for clinical practice

2) Prognostic relevance of high plasma circulating tumour DNA (ctDNA)

3) Relationship between ctDNA abundance and detection of genomic alterations

4) Clinical relevance of selected genomic alterations, including DNA damage repair defects, and the ability to detect these in ctDNA

5) Evolution of Androgen Receptor alterations as captured in serial ctDNA samples

6) Emerging technologies for prostate cancer epigenetic profiling using ctDNA

Session V : Poster session

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CYTOKINE AND GROWTH FACTOR REGULATION OF CASTRATION-TOLERANT LUMINAL PROGENITORS OF THE MOUSE PROSTATE

Manon BAURES[1], Delphine DI MARTINO[1], Emilia PUIG LOMBARDI[2], Lucila SACKMANN SALA[1], Florence BOUTILLON[1], Jacques-Emmanuel GUIDOTTI[1], Vincent GOFFIN[1]

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[2]Bioinformatics Core Platform, INSERM UMR1163 / Imagine Institute, Université de Paris, 75015 Paris, France

Castration-resistant prostate cancer (CRPC) is a lethal disease. Once diagnosed, current therapeutic strategies do not improve overall survival more than a few months. The molecular and cellular mechanisms that drive cancer relapse remain poorly understood, which has prevented the development of efficient therapies for CRPC.

Our laboratory recently identified a population of castration-tolerant luminal progenitor cells that we called LSCmed according to their Lin-/Sca-1+/CD49fmed FACS profile. LSCmed cells are rare in WT mouse prostates, but are massively amplified in premalignant prostates driven by prolactin/STAT5 signaling (Pb-PRL mice), and even more in prostate cancer driven by loss of Pten tumor suppressor gene (Pten-null mice, a model of CRPC). This suggests that LSCmed cells contribute to pathological overgrowth of prostatic tissue. The goal of this study was to identify potential regulators of LSCmed progenitor ability.

We first used in silico approaches. Comparative transcriptome analysis of LSCmed, luminal and basal cells FACS-enriched from WT and Pb-PRL mice was performed in combination with an interactome study (CellPhone DB). These studies highlighted expression of several genes associated with EGFR, IGF-1R and c-Met pathways and their potential interactions, respectively. These growth factor signaling pathways have been shown to regulate stemness and proliferation in various contexts including cancer. The expression of the EGFR, IGF-1R and c-Met in LSCmed cells sorted from WT, Pb-PRL and Pten-null mouse prostates was confirmed by RT-qPCR. We then challenged the effects of these ligands on LSCmed cell progenitor and proliferative abilities using the organoid assay. As expected, EGFR signaling was mandatory for organoid formation by Pten-null LSCmed cells. Remarkably, our results show that IGF-1/IGF-1R and HGF/c-Met signaling pathways are able to rescue organoid formation and growth in the absence of EGF in culture medium, suggesting redundancy. While EGFR-targeting therapies have been proposed to affect cancer stem cells, our ongoing experiments using natural ligands and pharmacological inhibitors suggest that alternative pathways may overcome EGFR signaling blockade.

MECHANIMS OF EPITHELIAL MESENCHYMAL TRANSITION BY TGF-ß AND LXRs IN METASTATIC PROSTATE CANCER

Bouchareb E, Bunay J, Lobaccaro J.M , Degoul F, De Joussineau C, Morel L, Kocer A , Baron S

GReD, Clermont-Ferrand, France

Background

Most prostate cancer related deaths correlates with the metastatic potential of the tumor. However, the cellular and molecular mechanisms associated with the spread of tumor cells remain unclear. One of the main process involved in the metastatic process is the "Epithelial-Mesenchymal Transition" or EMT, in which epithelial cells lose their adhesive properties and acquire a mesenchymal-like morphology.

EMT therefore plays a key role in migration, invasion, allowing tumor cells to invade distant organs. The TGF-ß signaling pathway has been widely described as a key player in this process.

In this context, the finding of appropriate and effective treatments is a priority. LXRs (Liver X Receptors) are nuclear receptor that have been shown to downregulates TGF-ß signaling in many diseases, including cancer. In this project, we are defining how TGF-ß and LXRs pathways controls EMT in prostate cancer using ex vivo and in vivo models.

Methods

To study the underlying molecular mechanisms by which these signaling pathways control EMT, we use several prostate cancer cell lines and PTEN -/- mice for EMT mechanisms. We also use Nod-Scid Gamma immunodeficient mice to study metastatic spread.

Results

Activation of TGF-ß pathway increases migration of PC3 cells and EMT markers. LXRs activation inhibits TGF-ß induced migration, but does not affect EMT markers.

Conclusions

Our results suggest that LXRs pathway may counteract TGF-ß induced EMT. The next step is to study the exact mechanism by which LXRs are able to inhibit migration capacities, and its involvement in EMT process in prostate cancer.

ROLE OF LONG NON CODING RNAs IN PROSTATE CANCER PROGRESSION

R. Cipolla[1], M. Gabriel[1], V. Firlej[2], F. Vacherot[2], H. Beltran[3], M. Pinskaya[1] and A. Morillon[1]

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2 Université Paris Est Creteil, TrePCa, F-94010 Creteil, France.

3 Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA USA

BACKGROUND

Hormone therapies are the first-line strategies for treating this prostate cancer (PCa). Nevertheless, many patients receiving the androgen deprivation therapy (ADT) eventually develop the lethal castration-resistant prostate cancer (CRPC). It is frequently associated with neuroendocrine differentiation (NED) and acquisition of androgen independence (AI) by tumor cells. Neuroendocrine markers can be detected in many tumors subjected to ADT, but hardly detected in ADT naïve tumors, supporting the idea that ADT sets off the NED of PCa. Long non coding (lnc)RNAs play an important role in tumorigenesis, contributing to all hallmarks of cancer. Aberrant lncRNAs expression has been associated with different malignancies, PCa included. Recently, thousands of lncRNAs have been reported to be expressed specifically in neuroendocrine prostate cancer, but their role in NED is still unknown.

METHODS

To investigate the role of lncRNAs in the NED and AI, a dynamic in vitro LNCaP cell model was used. NED and AI-associated lncRNAs, hereby referred to as PROCAs (PROstate Cancer Associated lncRNAs), were identified by RNA-seq profiling of PCa tumors and LNCaP. Single candidate validation was carried by RT-qPCR. AR activity and changes in chromatin modifications throughout the NED was explored genome-wide using the CUT&RUN assay. To explore lncRNA functional relevance in NED, gain-of-function experiments were performed using ectopic expression of lncRNA.

RESULTS

We identified a set of novel NED and AI-lncRNAs, including PROCA11 whose expression starts after 72 hours of hormone deprivation and it is maintained throughout the NED in LNCaP. This lncRNA is also expressed in CRPC patients, both in adeno and neuroendocrine carcinomas. PROCA11 expression is regulated by AR. Its overexpression in LNCaP results in a decrease of mitochondrial membrane potential and the OXPHOS mitochondrial complexes.

CONCLUSIONS

PROCA11 is a novel lncRNA expressed at early stages of NED. Preliminary results suggest that PROCA11 might be under the transcriptional regulation of AR and might be involved in mitochondrial activity. Complementary approaches are needed to further validate these results and to fully characterize the mechanisms of action of this lncRNA in NED.

IS OXIDATIVE STRESS A RELEVANT TARGET IN BENIGN PROSTATE HYPERPLASIA?

Leïla DOS SANTOS[1], Emeline PACREAU[1], Manon BAURES1, Stefano PALEA[2], Marine LUKA[3], Francesco CARBONE[3], Mickaël MENAGER[3], Nicolas CAGNARD[4], Nicolas BARRY DELONGCHAMPS[1], Ahmed HAMAÏ[1], Jacques-Emmanuel GUIDOTTI[1], & Vincent GOFFIN[1]

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Background

Approximately half of patients with benign prostatic hyperplasia (BPH) remain unsatisfactorily addressed by current medical treatments. The hallmarks of oxidative stress are known to correlate prostate volume in BPH patients. The aim of this study was to use preclinical models of BPH to evaluate the beneficial effects of a small anti-oxidative compound (named Z1017) known to block ROS production from the complex I of the mitochondria respiratory chain (MRC).

Methods

For in vivo studies, we used Probasin-Prolactin (Pb-PRL) mice whose prostates exhibit several histopathological features of human BPH (Pigat et al, Frontiers Pharmacol, 2019). Z1017 treatment (versus vehicle) was administered per os daily during 28 consecutive days. Molecular (immunoblots, qPCR), histopathological (IHC) and functional (urinary parameter using metabolic cages) parameters were investigated. Single-cell RNA-seq was performed using 10x genomics technology. For in vitro studies, we used epithelial (BPH-1) and myo-fibroblastic (WPMY-1) prostatic cell lines to determine the effects of Z1017 on cell proliferation (Incucyte), viability (Dapi) and oxidative stress (DCFDA probe by FACS). mRNA profiling was performed using Clariom S arrays.

Results

Z1017 treatment reduced epithelial cell proliferation and improved urodynamics parameters of Pb-PRL mice (decreased frequency & increased urine volume per voiding). The decrease of the epithelial cell compartment was confirmed by cell clustering of single-cell RNA-seq data. Remarkably, BPH-1 & WPMY-1 cells exhibited different responses to the drug. The major effect observed in BPH-1 was a decrease of several markers of prostate luminal progenitors that are suspected to participate in BPH aetiology and/or progression. Lipid metabolism known to be crucial for prostate epithelial cell was also affected by Z1017 treatment of BPH-1, but not observed in WPMY-1 cells, suggesting metabolic reprogramming.

Conclusion

Reduction of oxidative stress by Z1017 appears as a promising approach to reduce various BPH hallmarks. Ongoing investigations aim to better decipher the multiple downstream effects of the drug at the cell and molecular levels.

HYPOXIC MITOCHONDRIA, VDAC1-ΔC AND PRIMARY CILIUM IN PROSTATE CANCER

Yingbo GUO, Siyong PENG, Victor TIROILLE, Abigaïl MAZZU, Julie CONTENTI, Frederic BOST, Nathalie M. MAZURE.

INSERM U1065, University of Côte d'Azur (UCA), C3M, 151 Route de St Antoine de Ginestière, 06200 NICE

Stabilization of Hypoxia-Inducible Factor-1**α** (HIF-1**α**) in hypoxia followed by interactions between mitochondria and endolysosomes, results in truncation of the mitochondrial voltage-dependent anion channel C-terminal, VDAC1, into VDAC1-ΔC. Oxidative phosphorylation and glycolysis are then upregulated, resulting in increased resistance to chemotherapy. Recently, our team linked the regulation of ciliogenesis, processes by which the primary cilia (PC) is formed, to VDAC1-ΔC and tumor aggressiveness. This small sensorial antenna has an important role in signaling pathways, anion transport and cell cycle regulation. An emerging role of PC is in the regulation of cancer development. In clear cell renal cell carcinoma (ccRCC), we characterized a PC signature with two markers, IFT20/Gli1.

The presence of PC, IFT20+/Gli1+, was associated with more aggressive cancer and patients died faster.

Our hypothesis is that such a signature can be extended to other types of cancer, including prostate cancer (PCa). We observed a group of patients with strong similarities to the previously described group. Do these patients present a more aggressive cancer? Our objectives are therefore to force the re-expression of PC in 2D and 3D culture systems.

P69 (prostate epithelial cell) and DU145 (PCa metastasis cell) were used as 2D cell models and RWPE1 (prostate epithelial cell) and WPE1NB26 (Tumor-like RWPE1-derived human PCa cells) as 3D models. Gefitinib, an inhibitor of EGFR, and clofibrate, an agonist of PPAR, were used to restore PC as described previously. Different O2 concentration were used to culture cells: normoxia (Nx) 21%-, physioxia 6%-, hypoxia 1%- and 0.1%- O2.

In 2D hypoxic culture, the percentage (%) of PCs decreased in P69, RWPE-1 and WPE1NB26 compared to Nx. Gefitinib only increased % of PC in RWPE-1 and WPE1NB26 while clofibrate restored a higher % of PC in P69. Percentage of PC remained consistently low and unchanged in DU145. In 3D, in the first step, structures of the acini and tumor-like were modified. In a second step, preliminary results showed little % of PC in untreated cells in Nx. Gefitinib limited the growth of the model but did not restore PC.

We have now established the cell model that will allow us to come close to PCa patients expressing the IFT20/Gli1 dual signature. Metabolic and aggressiveness measurements will be performed soon.

HYPUSINATION REGULATES MITOCHONDRIAL METABOLISM AND PROLIFERATION IN PROSTATE CANCER CELLS

Michel KAHI[1], Abigaïl MAZZU[1], Mathieu CARLIER[1], Sandra LACAS-GERVAIS[2], Issam BEN-SAHRA[3], Nathalie MAZURE[1] and Frédéric BOST[1]

1 Université Côte d'Azur, C3M, INSERM U1065 Equipe Targeting Prostate cancer cell metabolism, Nice, France

2 Université Côte d'Azur, Centre Commun de Microscopie Electronique, Nice, France

3 Northwestern University, Chicago, USA

Background

Prostate cancer (PCa) is a public health problem, despite great advances it is still difficult to treat advanced stages. Cancer cells reprogram their metabolism to resist various stresses and treatments and to provide the metabolites, energy and co-factors required for their proliferation and progression. Our team is interested in innovating therapeutic approaches targeting cancer cell metabolism. Here, we focus on hypusination which is associated with poor prognosis in PCa. Hypusination is a unique post-translational modification of the eukaryotic translation initiation factor 5A (EIF5A) that modulates its activity. This reaction requires a polyamine (spermidine) and the action of two enzymes: deoxyhypusine synthetase (DHPS) and deoxyhypusine hydroxylase (DOHH). Hypusination is involved in several cellular processes such as autophagy, metabolism, senescence and differentiation. The mechanism by which this pathway is implicated in tumor growth and metastasis is unclear. To elucidate its role in PCa, we pharmacologically inhibited the enzymes that catalyzes this reaction and investigated the effect on cell growth and metabolism

Methods

To study the effect of hypusination on cell growth, we inhibited this reaction with a pharmacological compound GC7 and Ciclopirox and performed cell counting and cell cycle analysis by flow cytometry. To explore the role of hypusination on the metabolism of PCa cells, we performed steady state metabolomics and measured mitochondrial respiration with the Seahorse Bioanalyzer, glucose consumption and lactate production. We also studied the phenotype of mitochondria by electron microscopy.

Results

Our results showed that inhibition of hypusination decreased cell growth and blocked the cell cycle in G0/G1.

Interestingly, it also altered cell metabolism by inhibiting the Krebs cycle and cellular respiration. Finally, we showed that the deregulation of the mitochondrial function induced a metabolic shift with an increase of glycolysis and is associated with alteration of mitochondrial phenotype.

Conclusions

Inhibition of hypusination decreases cell growth and mitochondrial respiration two biological processes implicated in PCa aggressiveness and metastasis. Our results highlight a potential therapeutic opportunity for PCa that target hypusination and could be used for clinical applications.

IMPACT OF VITAMIN D SIGNALING ON PROSTATIC PRECANCEROUS LESIONS

Kateryna Len[1], Justine Gantzer[1], Elise Grelet[1], Mohamed A. Abu el Maaty[1], Celine Keime[1], Darya Yanushko[1], Regis Lutzing[1], Daniel Metzger[1], Gilles Laverny[1]

1 Institute of Genetics and Molecular and Cellular Biology, CNRS UMR 7104, Inserm U1258, University of Strasbourg, France.

Prostate cancer is the second leading cause of male cancer-related deaths in western societies. Due to late diagnostics and poor treatment efficiency of aggressive forms, a better understanding of prostate cancer initiation and progression are required to improve the prevention and therapy. As PTEN (Phosphatase and tensin homolog) is the most frequently mutated or deleted tumor suppressor in prostate cancer, we generated PTEN(i)pe-/- mice, with a selective inactivation of PTEN in prostatic epithelial cells at adulthood. These mice develop prostatic intraepithelial neoplasia (PIN) with full penetrance during the first month after gene inactivation (AGI), followed by 6-8 months of latency phase characterized by senescence and recruitment of myeloid derived suppressive cells (MDSC). Adenocarcinoma in PTEN(i)pe-/- mice are formed one year AGI.

Epidemiological studies indicate that prostate cancer risk and severity correlate with low levels of circulating vitamin D and reduced expression of vitamin D receptor (VDR).

Moreover, supra-physiological doses of bioactive vitamin D decrease the severity of symptoms in various mouse models of cancer, and our recent investigations demonstrate that a vitamin D analog reduces the severity of prostatic precancerous lesions in PTEN(i)pe-/- mice.

To investigate the role of VDR signaling in prostatic tumorigenesis, we generated PTEN/VDR(i)pe-/- mice in which PTEN and VDR are selectively inactivated in the prostatic epithelium at adulthood. Our results show that the epithelial cell proliferation is 2-fold higher in prostates of PTEN/VDR(i)pe-/- mice 1-months AGI than those of PTEN(i)pe-/- mice. In addition, immunophenotyping at 3 months AGI revealed that the number of MDSC is 2-fold higher in PTEN/VDR(i)pe-/- prostates than in PTEN(i)pe-/- ones. Moreover, single-cell analysis of PTEN(i)pe-/- and PTEN/VDR(i)pe-/- dissociated prostates indicate the presence of cells expressing simultaneously epithelial (Krt8) and fibroblasts (Vim) markers, highlighting the role of VDR signaling in epithelial–mesenchymal transition. Thus, vitamin D signaling in PTEN-deficient prostatic epithelial cells limits their proliferation and plasticity, as well as MDSC recruitment in PINs.

REGULATION OF TMPRSS2 BY THE ANDROGEN PATHWAY AND IMPLICATIONS IN SARS-COV-2 INFECTION

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Background

TMPRSS2 is a cellular protease regulated by androgens in prostate cells. Entry of SARS-CoV2 by membrane fusion ("early-entry") into cells of the respiratory epithelium requires cleavage of Spike by TMPRSS2.

Our hypothesis is that the level of androgens and the presence of the androgen receptor (AR) in lung cells may regulate the expression of TMPRSS2 and thus influence the membrane fusion entry of SARS-CoV-2.

Methods

The regulation of TMPRSS2 and AR was studied in two lung cell lines (A549 and Calu-3) and in control prostate cell lines (LNCaP or VCaP) by androgen deprivation and supplementation experiments as well as by transfection of AR-targeted siRNAs. The regulation of TMPRSS2 and AR expression was studied by RT-qPCR and Western blot. SARS-CoV2 infection in Calu-3 cells was studied under AR blocking conditions.

Results

Our results show that both lung cell lines used (A549 and Calu-3) express TMPRSS2 and AR at mRNA and protein level. In these lines there is also a regulation of TMPRSS2 and AR expression by androgens. This effect is well known and found in prostate cell lines. Finally, we were able to show that in lung cells, the rate of infection by SARS-CoV2 was lower when the AR pathway was previously blocked.

Conclusions

Blocking TMPRSS2 limits the infection of the virus in vitro. Our results suggest that TMPRSS2 expression is regulated by androgens in lung cells and that testosterone may play a role in SARS-CoV2 infection. Blocking AR could be a therapeutic avenue to explore to limit COVID19.

ROLE OF TRPM4 IN PROSTATE CANCER: FROM METASTASIS TO DIAGNOSIS

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Background

Transient Receptor Potential Melastatin 4 (TRPM4) is a Ca2+-activated Na+ Channel that depolarizes the plasma membrane modulating Ca2+ influx. TRPM4 protein expression level was shown to be upregulated in premalignant human PIN and cancerous prostate tissue, with the highest staining found in PCa. Cellular senescence was introduced as a possible link between prostate diseases of the aging males. Studies evaluating the presence of cellular senescence in human prostate were discussed both in BPH and PINs and that the latter predicts early relapse in PCa. Although senescent cells lose their ability to replicate, they remain metabolically active and their secretome- known as senescence associated secretory phenotype (SASP) - contributes to inflammatory microenvironment. Therefore, we aim to investigate the role played by TRPM4 both in tumor microenvironment (TME) and early stages of PCa.

Methods

Senescence was induced by (H2O2, hRAS, and Etoposide) in stromal cells and screened for TRPM4 de-regulation and variants by qPCR mapping. Boyden Chamber invasion assay was done to evaluate the effect of SASP secreted in the presence and absence of TRPM4 in senescent stromal cells on PCa cell lines. Ca2+ dynamics were examined by Ca2+ imaging. The in vitro model of PTEN-induced cellular senescence was established in primary prostate epithelial cells (PrEpiCs) by both PTEN KD and inhibition (pharmacological) followed by screening for TRPM4 by qPCR.

Results

Here, we show that TRPM4 variant 5 is commonly upregulated not only in senescent stromal cells regardless of the type of senescent inducer, but also in our in vitro model of PTEN induced senescence. Treating PCa cells with conditioned medium from senescent cells, show significantly lower invasion capacity when TRPM4 is KD. We demonstrate a significant increase in basal Ca2+ levels and significant decrease in store-operated Ca2+ entry (SOCE) after TRPM4 KD in WT cells.

Conclusion

Our results represent TRPM4 as a regulator of SOCE in TME. Decreased SOCE signals contribute to several hallmarks of cancer, here we demonstrate TRPM4 as a regulator of PCa microenvironment yielding PCa invasion. Additionally, we suggest the possible use of this channel as a prognostic biomarker in the early stages of PCa, potentially prior the onset of invasive disease.

PROSTATE CANCER PATIENT-DERIVED ORGANOIDS: DETAILED OUTCOME FROM A PROSPECTIVE COHORT OF 81 CLINICAL SAMPLES

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Background

The establishment of prostate cancer (PCa) patient-derived organoids has been hampered by poor success-rates, which limits their broad use for translational research applications. There is an unmet need to identify determinants of success and failure in organoid generation

Methods

We attempted to derive organoids from 81 primary or metastasis samples obtained from 75 PCa patients with diverse clinical features. Organoid growth was assessed using bright-field imaging and was correlated with histological features of the matched tumor samples (Gleason score, tumor content, proliferation index). Tumor-organoid pairs were phenotypically and molecularly characterized using immunohistochemistry, immunofluorescence, fluorescence in situ hybridization, and targeted sequencing.

Results

We identified improved culture conditions favoring the generation of PCa organoids, yet no specific intrinsic tumor feature (i.e. histological or molecular) was broadly associated with sustained organoid growth. Morphological and immunohistochemical profiles of whole organoids altogether provided a fast read-out to identify the most promising ones. Primary samples were associated with an initial take-rate of 83 % (n=60 / 72) in culture, with maintenance of cancer cells displaying common PCa alterations, such as PTEN loss and ERG overexpression. These cancer-like organoids were however progressively overgrown by organoids with a benign-like phenotype. Out of 9 metastasis samples, we established a novel organoid model derived from a hormone-naive lung metastasis, which displays alterations in the PI3K/Akt and Wnt/ß-catenin pathways and responds to androgen deprivation.

Conclusions

Taken together, our comprehensive study explores determinants of outcome and highlights the opportunities and challenges associated with the establishment of stable tumor organoid lines derived from PCa patients. Building upon this study, we will now explore the contribution of distinct growth factors to organoid generation with the ultimate goal of developing optimal organoid models.

BASAL EXTRUSION, A CRITICAL STEP OF EARLY TUMORIGENESIS, DIRECTLY DEPENDS ON CHOLESTEROL AVAILABILITY IN THE PROSTATE-LIKE DROSOPHILA ACCESSORY GLAND

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Several epidemiological studies indicated a probable implication of cholesterol in prostate cancer progression and aggressiveness. The most aggressive tumors also appear to be sensitive to therapies designed to decrease hypercholesterolemia such as statins. Nevertheless, whether cholesterol levels and its metabolism are important for early tumorigenesis remains unknown.

Drosophila accessory gland is a functional equivalent of human prostate. In this organ, we have defined the conditions to reproduce early epithelial tumorigenesis by mimicking initiation, where rare clones of cells expressing oncogenic hits are surrounded by normal cells. These clonal cells then undergo a basal extrusion, the first step of invasion, to form primary tumors outside the epithelial compartment represented by the gland.

These tumors accumulate lipids, and especially esterified cholesterol, as in human late carcinogenesis. Moreover, while a high cholesterol diet increases the risk to develop tumors, clonal-cell specific alteration of different enzymes implicated in cholesterol metabolism and transport impairs the basal extrusion.

We conclude that, in vivo, accessory gland early epithelial tumorigenesis relies on cholesterol. Furthermore, whether systemic levels of cholesterol do influence tumorigenesis, this is the actual cholesterol availability within the clonal cells that correlates with basal extrusion.

Our aim is now to understand which molecular mechanisms are promoted by cholesterol to induce early tumorigenesis and to evaluate their relevance for human pathology.

INTRATUMORAL SEX STEROID SYNTHESIS IS INVOLVED IN BASAL EXTRUSION DURING PROSTATE-LIKE TUMORIGENESIS, AND ITS DEPRIVATION PROMOTES THE EMERGENCE OF A NEW TUMOR CELL POPULATION

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Sex steroids and particularly androgens trigger prostate development, differentiation, but also sustains prostate cancer progression. Hormonal therapy based on androgen deprivation is then used to treat prostate cancer in its localized, locally advanced and metastatic stages. However, the role of deprivation in the appearance of castration resistant prostate cancer remains uncertain.

Drosophila accessory gland is a functional equivalent of human prostate. In this organ, we have defined the conditions to reproduce early epithelial tumorigenesis by mimicking initiation, where rare clones of cells expressing oncogenic hits are surrounded by normal cells. These clonal cells then undergo a basal extrusion, the first step of invasion, to form primary tumors outside the epithelial compartment.

Ecdysone is the steroid hormone that sustains accessory gland reproductive function. In the adult fly, this steroid is produced by the accessory gland itself, and interacts with its specific Ecdysone Receptor (EcR). By RNAi interference, we have downregulated either ecdysone receptor or ecdysone synthesis only in the clonal cells.

In both cases, we observe an impairment of basal extrusion and extraepithelial tumor formation, a phenomenon to compare to prostate tumor regression in human during androgen deprivation therapy. However, a new kind of tumorigenesis appears independently of the previously observed tumors, baring characters of higher aggressiveness.

We conclude that accessory gland early tumorigenesis relies on steroids. We furthermore demonstrate that, in vivo, this is an intratumoral ecdysone synthesis that sustains basal extrusion. Finally, we show that clone-specific ecdysone deprivation induces the emergence of a new type of resistant tumorigenesis, two phenomena that are reminiscent of the suspected mechanisms of resistance to androgen deprivation therapy.

Our aim is to understand which molecular mechanisms are promoted by ecdysone to induce early tumorigenesis and which ones induce the emergence of a new tumoral cell population in case of ecdysone deprivation, and then to evaluate their relevance for human pathology.

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LIPID ANTISENSE OLIGONUCLEOTIDES NANOPARTICLE: NANOPLATFORM AGENT FOR THE TREATMENT OF CASTRATION-RESISTANT PROSTATE CANCER

Clément PARIS
CRCM, Marseille

Prostate cancer (PC) is one of the most common causes of death by cancer in the Western World. Once diagnosed, androgen deprivation is the first line therapy. However, the disease progresses to a castration-resistant state (CRPC), and chemotherapy used prolongs life span of a few months. Our laboratory has previously demonstrated that translationally controlled tumor protein (TCTP) is overexpressed in CRPC and is implicated resistance to treatment. TCTP protein is involved in a plethora of important cellular processes related to cell growth, cell cycle progression, malignant transformation and inhibition of apoptosis. Therefore, TCTP is now recognized as a potential therapeutic target in several cancers including breast, lung cancers and prostate. We previously reported specific inhibition of TCTP with lipid-antisense oligonucleotides (LASO) in vitro and in vivo. LASO properties lead to their auto-organization in micelles allowing then to self-internalization in cells without transfecting agent. In this project, we used the advantage of the unique supramolecular properties of LASO nanomicelle for active PC targeting using radionuclides and PSMA ligand. In addition to the therapeutic and self-internalization properties of LASOs, further functionalization for imaging and specific targeting was introduced and synthesized during the project. Heteronanomicelle was then formulated, combining TCTP-LASO and both lipid-conjugates. Heteronanomicelle characterization was performed using dynamic light scattering and biologically evaluated in vitro showing the specific uptake of the nanoparticle decorated PSMA ligand in prostate cancer cells.

Personalized (e.g., precision) medicine has already made its mark and has the potential to enhance patient management using companion tests such as genetic screening for treating patients with targeted therapies. Nuclear medicine has a central role in precision medicine by allowing direct visualization of molecular target and for some very well linked to treatment options, selective deposit/delivery of radionuclides (also called targeted internal radiotherapy, TIR).

APOPTOSIS MEDIATED BY MITOCHONDRIAL CA2+ OVERLOAD REQUIRES INHIBITION OF AUTOPHAGY REVEALING A WIDESPREAD VULNERABILITY OF CANCER CELLS

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Background:

Intracellular calcium (Ca2+) dynamics determine cell fate and mitochondrial Ca2+ overload is considered as a major way of inducing the intrinsic apoptotic pathway. Thus, targeting mitochondrial Ca2+ homeostasis is considered as a promising anti-cancer strategy to sensitize cancer cells to apoptosis and overcome drug resistance. In this work, we challenge this crucial paradigm redefining targeting of mitochondria in cancer treatment.

Methods:

Ca2+ dynamics were examined by Ca2+ imaging and time domain-fluorescence lifetime imaging microscopy. Apoptotic, autophagic and mitochondrial status were investigated by using Western blotting analysis, electron microscopy, subcellular fractionation, and immunocytochemistry. Mitochondrial membrane potential and permeability transition pore opening were evaluated by flow cytometry and confocal imaging. Drugs combinations were evaluated in vitro using cell lines, in vivo using mouse xenograft model and ex-vivo from clinical specimens.

Results:

Here, we report that mitochondrial Ca2+ overload is largely ineffective in inducing cell-death by itself and require a concomitant inhibition of autophagy to counteract its pro-survival action in prostate cancer.

In such condition, an acute mitochondrial stress occurred -revealed by a DRP1-mediated mitochondrial dynamic remodeling- inducing mitochondrial depolarization, release of cytochrome c and finally efficient apoptosis. This priming mediated by mitochondrial Ca2+ overload and inhibition of autophagy can sensitize several cancer cells types to different chemotherapies. The translational relevance of this dual-targeting strategy was confirmed with a promising drug under clinical evaluation: The G-202 (Mipsagargin).

Conclusions:

These findings challenge a crucial paradigm in cell death revealing a widespread vulnerability of cancer cells to enhance chemosensitivity via novel combined therapeutic strategies.

PERIPROSTATIC ADIPOSE TISSUE DISPLAYS A CHRONIC HYPOXIC STATE THAT LIMITS ITS EXPANSION IN OBESITY AND RESULTS IN FEATURES KNOWN TO FAVOR TUMOR PROGRESSION

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Recent evidence indicates that periprostatic adipose tissue (PPAT) plays an important role in the progression of prostate cancer. Unlike all other adipose depots, PPAT secretes pro-inflammatory cytokines even in lean individuals and does not increase in volume during obesity. These unique features remain unexplained due to the poor structural and functional characterization of this tissue. By using pre-operative magnetic resonance imaging of patients undergoing prostatectomy for prostate cancer, we found that PPAT volume was independent of BMI. Abdominopelvic adipose tissue (APAT) volume, by contrast, did depend on BMI; thus, we used this tissue as a control for further studies. Confocal microscopy followed by 3D reconstructions showed a sparse vascular network in PPAT when compared with that in APAT, suggesting that this tissue is hypoxic. Unbiased comparisons of PPAT and APAT transcriptomes found that most differentially expressed genes were related to the hypoxia response. High levels of the hypoxia-inducible factor HIF-2a confirmed the presence of an adaptive response to hypoxia in PPAT. This chronic hypoxic state was associated with inflammation and fibrosis, which were not further upregulated by obesity. This fibrosis and inflammation explain the failure of PPAT to expand in obesity and both probably contribute to prostate tumor progression.

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Notes

A jury evaluates the quality of the posters using mainly the following three criteria: clarity, self-explanatoriness and layout.

The 3 best poster awardees (PhD students or Postdocs) will receive a prize of 300 euros and will present their work during the 31st ARTP Meeting in 2022

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