ARTP
Association pour la Recherche sur les Tumeurs de la Prostate

ARTP BULLETIN

November 20th, 2024

33rd Annual Meeting Association pour la Recherche sur les Tumeurs de la Prostate

Foreword

With this 33rd annual meeting, the ARTP continues a tradition of bringing together researchers, academics and clinicians from all over the world, experts in prostate cancer. Once again, the funding of the new projects selected for 2024 as well as the organization of this meeting would have not been possible without the generous contributions of Pierre Fabre Médicament, the Association Française d'Urologie, Astellas, AstraZeneca/MSD, Bayer, Viatris and the Fondation ARC. We thank all speakers and participants for their contributions.

Pr Arnauld VILLERS, ARTP President

33rd Annual Meeting
Wednesday 20 November 2024
Palais des Congrès de Paris
2 place de la Porte Maillot
75017 Paris

“Metabolic and immunosuppressive aspects of prostate cancer”

8:15 a.m. : Registration (3rd floor)

9:00 a.m. : **Welcome** Arnauld Villers, ARTP President

9:05 a.m : **Session I : ARTP & ESUR Laureates**
Chairs : Valério Farfariello, Damien Destouches

- **Vera CONSTÂNCIO** (Instituto Português de Oncologia do Porto, Portugal)
'A novel translational immunocompetent model for investigating prostate cancer bone metastasis’

- **Delphine MILHAS** (IPBS CNRS UMR 5089, Toulouse)
'Role of sex steroids in periprostatic adipose tissue in tumor progression and resistance of prostate cancer to anti-androgen therapy’

- **Manon BAURES** (INEM, CNRS UMR 8253, Inserm U 1151, Paris)
'Mouse LSCmed cells are a model of Club/Hillock Cells of the human prostate’

- **Darya YANUSHKO** (IGBMC, CNRS UMR 7104, Inserm U 1258, Strasbourg)
'IL6/JAK/STA3-mediated crosstalk between cancer associated fibroblasts and epithelial for cells promotes lineage plasticity and prostate cancer progression'

10:00 a.m. : Coffee Break & Visit of Exhibition Booths

10:20 a.m. : **Session II : Understanding and targeting prostate cancer metabolism**
Chairs : Frédéric Bost, Catherine Muller

- **Lisa M. BUTLER** (University of Adelaide, Australia)
'Novel approaches to target the prostate cancer lipidome'

- **Mark A. RUBIN** (University of Bern, Switzerland)
'Loss of PI5P4Kα slows the progression of a Pten mutant basal cell model of prostate cancer'

- **Anna DUBROVSKA** (Helmholtz-Zentrum Dresden-Rossendorf, Germany)
'Development of metabolism-related biomarkers for personalized radiation oncology'

12:00 p.m. : Lunch

1:15 p.m. : **Session III : Clinical Session**
Chairs : Charles Dariane, Guilhem Roubaud

- **Paul SARGOS** (Institut Bergonié, Bordeaux)
'Classification of risk of recurrence after local treatment'

- **Pierre-Jean LAMY (**Institut d'Analyse Genomique Imagenome, Inovie, Montpellier)
'Circulating biomarkers and treatment response'

- **David TAIEB** (Assistance Publique - Hôpitaux de Marseille)
'Targeted internal radiotherapy for CRPC: the potential of combination therapeutic approaches'

2:20 p.m : Coffee Break & Visit of Exhibition Booths

2:45 p.m. : **Session IV : The immunosuppressive mechanisms at play in prostate cancer**
Chairs : Vincent Goffin, Félicie Cottard

- **Andrea ALIMONTI** (Institute of Oncology Research, Bellinzona, Switzerland)

'Role of tumor-infiltrating neutrophils in prostate cancer'

- **Xin LU** (University of Notre Dame, IN, USA)

'Prostate cancer immunosuppression and how to conquer it'

- **David B. SYKES** (Harvard Medical School, Boston, MA, USA)

'Dissecting the immune suppressive human prostate tumor microenvironment via integrated single-cell and spatial transcriptomic analyses'

4:15 p.m. : **Session IV : Poster Session**
Chairs : Edith Bonnelye, Laurent Morel
Les candidats au Prix du Meilleur Poster auront 5 minutes pour présenter leur poster/Candidates for the Best Poster Award will have 5 minutes to present their poster.

5:30 p.m. : **Assemblée Générale ARTP**
Poster Prize Distribution
Arnauld Villers, ARTP President
Olivier Cuvillier, ARTP Treasurer'

5:45 p.m : End of the meeting

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Session I :
ARTP 2020 Laureates

1

Vera CONSTÂNCIO

Instituto Português de Oncologia do Porto, Portugal

From prostate cancer primary tumour to bone metastasis: Unveiling prostate cancer progression through the development and characterisation of a new translational model

Prostate Cancer (PCa) remains a significant global health challenge, with bone metastasis being the primary driver of morbidity and mortality. While existing translational models have advanced our understanding of PCa progression, they often fail to fully capture the complex immunobiological interactions during metastatic spread. To address these limitations, we developed and characterized a novel immunocompetent model of PCa bone metastasis, and established bone metastasis-derived cell lines. This model offers a valuable experimental platform for exploring molecular mechanisms underlying PCa bone metastasis, presenting new avenues for identifying novel therapeutic targets and biomarkers associated with disease progression.

Session I :
ARTP 2020 Laureates

1

Delphine MILHAS

IPBS CNRS UMR 5089, Toulouse

Periprostatic adipose tissue: a new source of androgens for castration resistant prostate cancer

Androgen deprivation is the treatment of choice for locally advanced prostate cancer (PCa) and involves the inhibition of testosterone secretion by the testes. However, the disease will progress into castration resistant PCa (CRPC) after a few years. An emerging mechanism of CRPC involves the ability of cells to find other sources of androgens in the tumour microenvironment in order to produce active forms of androgens, as recently shown for gut microbiota and cancer-associated fibroblasts.

The aim of our study was to determine if periprostatic adipose tissue (PPAT), an adipose depot surrounding the prostate has a specific steroid metabolism that could favour CRPC occurrence. We characterized the sex steroid content and the steroidogenic enzyme expression profile of human PPAT and abdominopelvic adipose tissue (APAT, as control) from patients with PCa who underwent a radical prostatectomy, by Gas Chromatography–Mass Spectrometry (GC-MS) and RT-qPCR. The effects of PPAT (conditioned medium (CM) and co-culture) on PCa cell growth and proliferation were evaluated by real-time imaging system Incucyte and BrdU incorporation.

We demonstrated that PPAT contained more steroid metabolites such as 5α androstanedione and epiandrosterone compared to the APAT, involved in the alternate routes for 5α-DHT synthesis in CRPC. Within PPAT, mature adipocytes appeared to be the main source of androgen metabolites. The regulation of steroidogenic enzymes expression could explain the higher content of 5α androstanedione and epiandrosterone in PPAT. Furthermore, we demonstrated that PPAT-CM and co-culture with PPAT isolated adipocytes stimulated cell proliferation and expression of androgen receptor (AR) target genes (KLK3 and FKBP5) of an androgen-dependent cell line LNCaP cultivated in androgen-deprived medium. The proliferative effect of PPAT was inhibited by an AR antagonist, bicalutamide, suggesting an activation of AR signaling. Altogether, these results bring arguments in favour of a functional effect of the steroid metabolites contained in PPAT on PCa cells and demonstrated that PPAT could represent a new source of androgens for CRPC.

Session I :
ARTP 2020 Laureates

1

Manon BAURES

INEM, CNRS UMR 8253, Inserm U 1151, Paris

Mouse LSCmed cells are a model of Club/Hillock Cells of the human prostate

Club and Hillock cells have been recently identified by scRNAseq as rare epithelial cell types in the healthy human prostate, but are emerging as potential contributors to prostate pathogenesis and therapeutic resistance. In parallel, we recently identified LSCmed (Lin-/Sca-1+/CD49fmed) cells as luminal cells of the mouse prostate that exhibit castration-resistance and progenitor properties. The aim of this study was to evaluate their human relevance.

We combined phenotypic and functional analyses of LSCmed cells FACS-enriched from WT and Pten-null mice (an acknowledged model of castration-resistant prostate cancer, CRPC), bioinformatic analyses of public transcriptomic databases and immunostaining studies of retrospective human prostate cancer cohorts (n=285).

We interrogated transcriptomic databases using a "LSCmed score" established from the transcriptomic signature of WT LSCmed cells. We found that LSCmed cells correspond to the Club/Hillock cells in the healthy human prostate. In scRNAseq datasets of naïve localized prostate cancer, we detected a small cell cluster enriched in LSCmed cell genes. Using KRT7 as a marker of LSCmed-like cells, we analyzed a cohort of localized prostate cancer and we found that KRT7 staining was predominant in benign peri-tumoral prostatic glands. Strikingly, KRT7 was associated with shorter bone metastasis-free survival. Mesenchymal stem-like prostate cancer (MSPC), a recently-identified prostate cancer subtype, is associated to castration-resistance and metastasis development. We found that MSPC is highly enriched in cells exhibiting high LSCmed score. Using CellPhoneDB, we identified EGFR, IGF-1R and MET as potential drivers of LSCmed proliferation, and we showed that pharmacological targeting of each receptor hampered organoid growth.

Thus, LSCmed cells represent a relevant preclinical model to investigate further the role of Club/Hillock cells in prostate cancer progression and to identify new therapeutic targets to prevent CRPC.

Session I :
ARTP 2020 Laureates

1

Darya YANUSHKO

IGBMC, CNRS UMR 7104, Inserm U 1258, Strasbourg

IL6/JAK/STA3-mediated crosstalk between cancer associated fibroblasts and prostatic epithelial cells promotes plasticity and metastatic dissemination.

The tumor suppressor genes PTEN and TP53 are frequently mutated in prostate cancer, and are predictive of an early metastatic dissemination and unfavorable patient outcome. The progression of solid tumors to metastasis is often associated with increased cell plasticity, but the complex events underlying TP53-loss induced disease aggressiveness remain incompletely understood. Using genetically engineered mice, we show that Trp53 deficiency in Pten-null prostatic epithelial cells (PECs) does not impact early cell proliferation and neoplasia formation, nor growth arrest and senescence entry at later time. However, Trp53-deficiency enhances invasive adenocarcinoma development and promotes metastatic cell dissemination. Importantly, our single-cell transcriptomic and chromatin accessibility analyses uncovered an epithelial cell population characterized by an induction of Jak/Stat3 signaling and displaying mesenchymal features. Using in silico analyses, prostate cancer organoids cultures, and spatial transcriptomic profiling, we provide evidence that PEC plasticity occurs through a bi-directional communication with cancer-associated fibroblasts (CAFs). Thus, our study demonstrates that combined PTEN and p53 loss induces a protumorigenic crosstalk between PECs and CAFs, and identifies new vulnerabilities that might be targeted to limit cancer progression.

Session II : Understanding and targeting prostate cancer metabolism

2

Lisa M. BUTLER

University of Adelaide, Australia

Novel approaches to target prostate cancer aggressiveness ia the lipidome.

Prostate cancer is the most frequently diagnosed malignancy in Western men, and identifying more aggressive tumours at diagnosis could result in earlier intervention and improved outcomes. Prostate cancer depends on lipid metabolism for growth and survival, but its role in disease progression after local therapy is unclear. This makes the tumour "lipidome" a promising source of potential prognostic markers and novel therapeutic targets. However, prostate cancer is a heterogeneous and multi-focal disease, necessitating the use of spatial techniques such as mass spectrometry imaging (MSI), which visualises the abundance and distribution of analytes in situ, to identify tumour-specific markers. Consequently, we employed MSI to analyse sections from prostate tumour specimens, and regions of tumour and stroma were compared between non-relapsed and clinically relapsed patients. We identified a lipid signature that robustly discriminated between patients based on clinical outcome, which included several species containing a 16-carbon monounsaturated fatty acid (FA 16:1; palmitoleic acid). As this fatty acid is produced by the enzyme stearoyl CoA desaturase (SCD), we confirmed that pharmacological inhibition of this enzyme suppressed the proliferation of prostate cancer cells and patient-derived tissue explants. This work provides evidence that cellular metabolism is an important readout of cancer aggressiveness and response to therapy, that may be targeted for clinical benefit..

Session II : Understanding and targeting prostate cancer metabolism

2

Mark A. RUBIN

University of Bern, Switzerland

Loss of PI5P4Kα slows the progression of a Pten mutant basal cell model of prostate cancer.

While early prostate cancer (PCa) depends on the androgen receptor (AR) signaling pathway, which is predominant in luminal cells, there is much to be understood about the contribution of epithelial basal cells in cancer progression. Herein, we observe cell-type specific differences in the importance of the metabolic enzyme phosphatidylinositol 5-phosphate 4-kinase alpha (PI5P4Kα; gene name PIP4K2A) in the prostate epithelium. We report the development of a basal-cell-specific genetically engineered mouse model (GEMM) targeting Pip4k2a alone or in combination with the tumor suppressor phosphatase and tensin homolog (Pten). PI5P4Kα is enriched in basal cells, and no major histopathological changes were detectable following gene deletion. Notably, the combined loss of Pip4k2a slowed the development of Pten mutant mouse prostatic intraepithelial neoplasia (mPIN). Through the inclusion of a lineage tracing reporter, we utilize single-cell RNA sequencing to evaluate changes resulting from in vivo downregulation of Pip4k2a and characterize cell populations influenced in the established Probasin-Cre and Cytokeratin 5 (CK5)-Cre driven GEMMs. Transcriptomic pathway analysis points towards the disruption of lipid metabolism as a mechanism for reduced tumor progression. This was functionally supported by shifts of carnitine lipids in LNCaP PCa cells treated with siPIP4K2A. Overall, these data nominate PI5P4Kα as a target for PTEN mutant PCa.

Session II : Understanding and targeting prostate cancer metabolism

2

Anna DUBROVSKA

Helmholtz-Zentrum Dresden-Rossendorf, Germany

Metabolic biomarkers for prostate cancer radiotherapy

Reprogramming of cellular metabolism plays an essential role in prostate cancer progression and therapy resistance.

The talk will focus on developing clinically relevant biomarkers based on tumor metabolic pathways and explain their role in regulating prostate cancer stemness and radioresistance.

Session III : Clinical Session

3

Paul SARGOS

Institut Bergonié, Bordeaux

Classification of risk of recurrence after local treatment for prostate cancer

The aim of the presentation is to describe the natural history of recurrence after a local treatment.

We will analyse the different way to classify the risks related to recurrences, the way to prevent and to cure this event and also give the perspectives in the next futures based on ongoing clinical trials to improve outcomes and patient's quality of life.

Session III : Clinical Session

3

Pierre-Jean LAMY

Institut d'Analyse Genomique Imagenome, Montpellier

Circulating biomarkers and treatment response

Metastatic prostate cancer has complex genomic alterations that may be predictive of the efficacy of targeted therapies. These alterations can be identified on tissue but also directly on biologic fluids and mainly on blood. These circulating markers (also known as liquid biopsies) represent a safer and a less invasive alternative allowing monitoring of metastatic prostate cancer treated patients in the near future. The presentation will present the level of evidence for the use of circulating predictive biomarkers to improve precision medicine in metastatic prostate cancer.

Session III : Clinical Session

3

David TAIEB

Assistance Publique - Hôpitaux de Marseille

Targeted internal radiotherapy for CRPC: the potential of combination therapeutic approaches

Personalized medicine has already made a significant impact and holds the potential to further enhance patient management. It involves adapting healthcare strategies tailored to the individual characteristics of both the patient and the disease. In this regard, nuclear medicine plays a central role in personalized medicine through theranostic approaches. The concept of theranostics combines diagnostic and therapeutic functions within the same pharmaceutical platform (a theranostic pair).

In recent years, therapeutic nuclear medicine has become increasingly important in treating metastatic castration-resistant prostate cancer (mCRPC) that progresses after Docetaxel therapy. The outstanding results from the VISION trial demonstrated that 177Lu-PSMA-617 radioligand therapy significantly improved overall survival. This achievement has greatly accelerated the adoption of personalized treatments in mCRPC and has simultaneously driven substantial growth in the global nuclear medicine therapeutics market.

Currently, various perspectives are under evaluation, such as using alpha-emitting isotopes (e.g., Actinium-225, Lead-212, Astatine-211) or beta-minus (β^-) emitters that also emit short-range conversion and Auger electrons, such as Terbium-161. These are being explored in combination with synergistic therapeutic approaches, including radiosensitizing chemotherapy, epigenetic modifiers, PARP inhibitors, and immunotherapy.

To elevate the standard of care for patients with these tumors, it is essential to foster collaboration among healthcare organizations, industry leaders, academic institutions, and relevant professional and patient-related societies. This effort should manifest in global initiatives, including the creation of registries and databases, the organization of symposia and congresses, and other activities aimed at catalyzing clinical trials, advancing research programs, and disseminating vital information in the rapidly evolving field of theranostics.

Session IV : The immunosuppressive mechanisms at play in prostate cancer

4

Andrea ALIMONTI

Institute of Oncology Research, Bellinzona, Switzerland

Role of tumor-infiltrating neutrophils in prostate cancer

Recent research indicates that senescence plays a dual role in cancer, either suppressing or promoting tumor growth, depending on the context. Notably, cellular senescence can enhance metastasis formation in various cancers, including prostate cancer. Here, I will present recent studies demonstrating that therapies aimed at eliminating senescent tumor cells (senolytics) or reprogramming the senescence-associated secretory phenotype (SASP) hold promise in preventing metastasis.

Additionally, I will present recent findings showing that senescence also occurs in immune cells, particularly in tumor-infiltrating myeloid cells (PMN-MDSCs). These senescent-like MDSCs exhibit heightened immune-suppressive and tumor-promoting activities compared to their non-senescent counterparts. These discoveries open up new therapeutic possibilities, as targeting both senescent cancer cells and senescent-like immune cells with senolytic treatments could offer a more effective approach to combating tumor progression and immune evasion.

Session IV : The immunosuppressive mechanisms at play in prostate cancer

4

Xin LU

University of Notre Dame, IN, USA

Prostate cancer immunosuppression and how to conquer it

T-cell-oriented cancer immunotherapy, most triumphed by immune checkpoint blockade (ICB) and CAR-T therapies, has transformed the cancer treatment landscape and benefited many patients. However, de novo and acquired resistance to these therapies remains a significant challenge especially for prostate cancer. Our recent works illuminate a number of key tumor-immune crosstalk mechanisms in prostate cancer, where both cancer-cell-intrinsic and -extrinsic pathways contribute to the formation of an immunosuppressive microenvironment, suggesting a concerted targeting strategy is required to overcome immunosuppression and enable immunotherapy efficacy. We identified emerging strategies, including molecularly targeted therapy and dietary interventions. The use of single-cell technologies greatly facilitates understanding the immunocyte changes in response to the experimental therapeutics and helps guide the following steps to improve the efficacy further. The objective of our research is to tip the survival curves to a complete “flat tail” – the ultimate goal of cancer immunotherapy.

Session IV : The immunosuppressive mechanisms at play in prostate cancer

4

David B. SYKES

Harvard Medical School, Boston, MA, USA

Immunosuppressive myeloid cells in the prostate tumor microenvironment: does these represent a therapeutic target?

We first approached the problem of prostate cancer bone metastases using fresh tumor samples directly from the operating room, removed from patients undergoing emergent spinal decompression due pathologic fractures. Our experimental approach of dissociation focused on the immune cells (rather than the tumor cells) within the tumor microenvironment (TME). This study was followed by a second study of primary prostatectomy specimens, to compare to the bone metastatic disease.

Tumor associated macrophages (TAM) were specifically and highly enriched in both metastatic and primary tumor samples and contributed to an immune suppressive and pro-tumorigenic TME. These TAMs are a subset of myeloid derived suppressor cells (MDSC) that inhibit the body's anti-tumor T-cell immune response.

These human findings were replicated in a syngeneic mouse model of prostate cancer, both localized disease and bone metastases. Understanding the heterogeneity and function of these myeloid cells is an essential step toward developing effective therapeutic targeting strategies and ultimately to enhance the anti-tumor immune response.

Among the many changes, the myeloid compartment was consistently dysregulated along the spectrum of normal tissue to metastatic disease. We characterized multiple MDSC subpopulations and revealed the dynamics of tumor associated macrophages (TAMs) during tumor progression and metastasis. A specific type of TAM (TREM2+SPP1+) is significantly enriched in metastatic tumors and transcriptionally like the TAMs found in the bone metastasis niche of prostate cancer. The SPP1+ TAMs localized near the tumor boundary within primary tumors, potentially indicating immune exclusion. We also noted that the burden of TREM2+SPP1+ TAM was predictive of prostate cancer recurrence after primary prostatectomy.

The importance of these TAMs was further evaluated in a mouse model of bone metastases. Specifically, the antibody depletion of SPP1+ TAMs enhanced the efficacy of anti-PD-1 treatment in mouse prostate cancer. Currently we are studying the role of TREM2+SPP1+ TAMs by focused analysis of their direct communication with T cells and tumor cells.

Our analyses provide a comprehensive picture of the myeloid cell linage across different stages of prostate cancer progression. We highlight the potential for therapeutic targets that disrupt the metastatic process via their effects on tumor associated macrophages.

Session V : Poster session

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STUDY OF THE MECHANISMS OF OCCURRENCE AND EVOLUTION OF EARLY EPITHELIAL TUMOR. IMPLICATIONS FOR PROSTATE CARCINOGENESIS

***Elissa Baabdaty*, Marine Vialat, Amalia Trousson, Françoise Degoul, Jean-Marc A. Lobaccaro, Silvère Baron, Laurent Morel & Cyrille de Joussineau**

iGReD – France

The Notch signaling pathway is evolutionarily conserved and plays a crucial physiological role in cell fate determination and tissue homeostasis, but also a pathological role in carcinogenesis. However, its implication in prostate tumorigenesis remains ambiguous, with contradictory observations regarding its promoting or inhibitory effect on tumor growth and evolution, without a comprehensive understanding of the underlying mechanisms. Our team has previously developed a model of prostate tumorigenesis in vivo, using a structural and functional equivalent of a prostatic acinus, the accessory gland of Drosophila melanogaster. This model is based on clonal expression of the oncogene EGFRλ which allows precise quantification of tumor formation following basal extrusion phenomenon, and the characterization of tumor cell progression based on their localization, number and expression of markers of aggressiveness. In this context, we have deciphered the influence of the different components of the Notch pathway on tumor initiation, progression and resistance. Remarkably, our results reveal the existence of two antagonistic signaling within the Notch pathway. On the one hand, canonical Notch-dependent signaling displays an anti-tumoral action. On the other hand, depending of Notch ligand Delta, a predominant and separated signaling occurs, which itself strongly promotes tumorigenesis. These findings rationalize previous contradictory observations and suggest targeted therapeutic avenues to achieve specific anti-tumor effects.

DECIPHERING AND TARGETING CASTRATION-INDUCED PLASTICITY OF LUMINAL PROGENITOR-LIKE CELLS IN PROSTATE CANCER

Manon Baurès[1], Anne-Sophie Vieira Aleixo[1], Emeline Pacreau[1], Aysis Koshy[1], Marc Diedisheim[2], Martin Raigel[3], Yichao Hua[4], Charles Dariane[1], Florence Boutillon[1], Lukas Kenner[3], Jean-Christophe Marine[5], Gilles Laverny[6], Daniel Metzger[6], Florian Rambow[4], Jacques-Emmanuel Guidotti[1], Vincent Goffin[1]

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[6] Université de Strasbourg, CNRS, Inserm, IGBMC UMR 7104 - UMR-S 1258, F-67400 Illkirch, France.

Background

Mesenchymal stem-like prostate cancer (MSPC) is an aggressive prostate cancer molecular subtype associated to tumor recurrence following chemical castration. The transcriptomic signature of MSPC is enriched in mouse prostate luminal progenitor cells named LSC^{med}. The latter are tumor-initiating and castration-tolerant cells. As luminal progenitor cells pre-exist in naïve tumors, understanding castration's effects on these cells is crucial in order to develop therapeutic strategies to prevent emergence of castration-resistant prostate cancer.

Methods

The tumoral prostates of Pten-null mice are highly enriched in LSC^{med} cells. We performed scRNA-Seq on LSC^{med} cells sorted from both naïve and castrated Pten-null mice. Based on bioinformatics analyses we elaborated a therapeutic strategy to target the castration-resistant cells.

Results

ScRNA-Seq results predicted that castration leads to transcriptomic reprogramming in Pten-null LSC^{med} cells resulting in increased stemness and EMT signature enrichment. Pharmacological inhibition of FOSL1 and PIM1, identified as master regulators of this post-castration aggressive state, efficiently blocked cell proliferation and induced cell death in tumorosphere assays involving both Pten-null LSC^{med} and human MSPC-like cell lines.

Combined FOSL1/PIM1 inhibition in castrated Pten-null mice induced a significant decrease of prostate weight associated with a reduction of histopathological phenotypes. Strikingly, LSC^{med} cells sorted from these tumors were virtually unable to generate organoids. Accordingly, the drug combination significantly delayed tumor growth of MSPC-like human PC-3 cells grafted in castrated immunodeficient mice.

Conclusion

This study shows that, contrary to prior assumptions, luminal progenitor cells are not intrinsically androgen-independent. Instead, they respond to castration by a transcriptomic reprogramming into a castration-tolerant cell state that exhibits elevated aggressive features. We identified a therapeutic strategy that suppresses cell stemness and tumor growth in a castration context, providing a strong rationale for the development of therapies targeting human MSPC subtype.

Session V : Poster session

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IDENTIFICATION OF NEW PHARMACOLOGICAL EIF5A INHIBITORS AGAINST PROSTATE CANCER USING A NEW ENZYMATIC ASSAY – THE HYP'ASSAY

Oumayma Benaceur[1]#, Paula Ferreira Montenegro[2], Michel Kahi[1], Fabien Fontaine-Vive[2], Nathalie M. Mazure[1], Mohamed Mehiri[2], Frederic Bost[1]*, Pascal Peraldi[1]*

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Background

The latest epidemiological studies predict that by 2040 the incidence and mortality associated with prostate cancer (PCa) will double. The search for a new therapeutic approach, and the development of new pharmacological strategies, appears to be the only way to curb the PCa mortality curve. Our laboratory has demonstrated that eIF5A plays an important role in PCa. eIF5A is a translation factor that must be hypusinated to be active. Hypusination is a unique post-translational modification, affecting only eIF5A. It is dependent on two enzymes: DHPS and DOHH. So far, only a few pharmacological inhibitors of hypusination have been described and none of them are used in the clinic. The paucity of new inhibitors is probably due to the hurdle of testing DHPS and DOHH activities. Classical assays require radioactive molecules coupled with HPLC.

Methods:

We set up the Hyp'Assay, a non-radioactive cell-free assay to measure eIF5A hypusination without chromatography. Hypusination is performed in 96 or 384 wells using recombinant human eIF5A, DHPS, and DOHH and is revealed by a specific hypusinated eIF5A antibody. The Hyp'Assay is sensitive, quantitative, fast, easy to use, and can be used to find DHPS and DOHH inhibitors.

Results

Pharmacological results obtained with the Hyp'Assay for established DHPS or DOHH inhibitors were similar to those published with classical radioactive assays. We used the Hyp'Assay to test the ability of crambescines, a polyamine-like molecules. Treatment of DU145, a PCa cell line, indicates that crambescines inhibit hypusination in intact cells. Our assay also shows that crambescines are a new family of DHPS inhibitors.

Conclusions

Together, the Hyp'Assay is a very convenient and sensitive assay that could be used for large- scale screening of DHPS and DOHH inhibitors that could be used for the treatment of cancer and other pathologies associated with increased activity of eIF5A. The Hyp'Assay will be used to do a screening of 10,000 molecules from a chemical library specializing in protein-protein interaction inhibitors. The potential molecules found could be chemically improved. These results should provide leads for the development of new molecules to treat PCa.

Session V : Poster session

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NK CELLS PLAY A KEY ROLE IN CASTRATION RESISTANT PROSTATE CANCER

Bouhelier Léa, Julie Terzic, Graciela Ruiz, Lucie Maerky, Dr. Daniel Metzger

IGBMC, Institut de Génétique Moléculaire et Cellulaire, 1 rue Laurent Fries, Illkirch, 67400

Background

Prostate cancer (PCa) is one of the deadliest and the second most common cancer globally. It typically progresses slowly, evolving from prostatic intraepithelial neoplasia (PIN) to adenocarcinoma. In its advanced stages, PCa is treated with androgen deprivation therapy and chemotherapy. However, many patients eventually develop castration-resistant prostate cancer (CRPC) and become resistant to chemotherapy after an initial period of treatment responsiveness. While immunotherapies have become a significant cancer treatment in the 21st century, prostate cancer is classified as a 'cold' tumor, rendering it unresponsive to most current immunotherapy approaches. Therefore, it is crucial to identify new therapeutic strategies for CRPC patients.

As the tumour suppressor PTEN is frequently mutated in PCa, we generated genetically-engineered Pten(i)pe-/- mice in which Pten is selectively inactivated in adult prostatic epithelial cells. The Pten(i)pe-/- mice develop PIN and CRPC characterized by an immunosuppressive microenvironment. In contrast, Pten/Hif1a(i)pe-/- mice develop less aggressive tumors that are castration-sensitive and infiltrated with a higher numbers of natural killer (NK) cells. These findings suggest that HIF1A may contribute to tumor progression and castration resistance by inhibiting NK cell infiltration and/or NK cell-mediated cytotoxicity.

Methods

Castrated Pten/Hif1a(i)pe-/- mice were treated with anti-NK1.1 neutralizing antibodies for two weeks post-castration, whereas castrated Pten(i)pe-/- mice were treated with IL-15 for one month. Prostate tumors were analyzed histologically.

Results

NK cells depletion in Pten/Hif1a(i)pe-/- mice via anti-NK1.1 antibodies increased tumor aggressiveness. In contrast, IL-15 treatment of Pten(i)pe-/- mice promoted NK cells infiltration and/or proliferation, leading to tumor regression.

Conclusion

Our data indicate that the NK cells stimulation boosts the anti-tumor immunity in CRPC and thus open new perspectives for personalized medicine.

Session V : Poster session

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ECM-FREE PATIENT-DERIVED ORGANOIDS PRESERVE DIVERSE PROSTATE CANCER LINEAGES AND UNCOVER IN VITRO-ENRICHED CELL TYPES

Robin Dolgos[1,2,3], Romuald Parmentier[1,2,3], Jing Wang[1,2,3], Raphaëlle Servant[1,2,3], Arnoud J. Templeton[4], Tobias Zellweger[5], Alastair Lamb[6,7], Kirsten Mertz[8], Svetozar Subotic[9], Tatjana Vlanic[1], Helge Seifert[2], Ashkan Mortezavi[2], Cyrill A. Rentsch[2], Lukas Bubendorf[1], Clémentine Le Magnen[1,2,3]

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Background

Patient-derived organoids (PDOs) offer new opportunities to model various cancers. However, their application in prostate cancer (PCa) has been hampered by poor success rates and overgrowth of cell types which are not representative of the patient samples. Here, we aimed at modulating culture conditions and investigating in vitro-associated cellular heterogeneity to identify refined PCa PDO culture conditions.

Methods

A cohort of 162 PCa patient samples was used to establish PDOs in various extracellular matrices (ECM) and medium compositions. PDOs were characterized using immunofluorescence, immunohistochemistry, and FISH. Single-cell RNA sequencing (scRNA-seq) was performed on 11 tumor and organoid samples, followed by unsupervised clustering, differential gene expression, cell type annotation, and CNV analysis. Published spatial and bulk transcriptomic data were re-analyzed to validate specific markers. A prostate PDO scRNA-seq atlas was generated by integrating three published datasets together with our newly-generated data.

Results

Out of 5 ECM conditions, an ECM-free culture system increased the take-rate of PDOs with luminal-like and PCa features, while standard Matrigel-based culture conditions yielded basal-like benign organoids. ECM-free PDOs comprised cell populations associated with known PCa signatures, exhibited transcriptomic resemblance with their respective parental tumors, and maintained patient-specific epithelial populations. Furthermore, we defined organoid-associated cell type signatures and identified markers discriminating tumors versus benign cells ex vivo and in situ. Finally, our integrative single-cell atlas highlighted that Matrigel-based organoids derived from primary PCa are essentially composed of benign epithelial cells, irrespective of the dataset or the malignant nature of the tissue of origin. In contrast, ECM-free conditions preserved heterogenous tumor-like cell populations and enriched in intermediate cell types.

Conclusions

ECM-free PCa PDOs exhibit improved fidelity and in vitro-enriched cell populations. Our work contributes to significantly enhancing the potential of PDOs in PCa research.

Session V : Poster session

5

BONE MARROW ADIPOCYTE-DERIVED ANDROGENS: A ROLE IN PROGRESSION AND CASTRATION RESISTANCE OF BONE METASTATIC PROSTATE CANCER

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Prostate cancer (PCa) is the second most frequent cancer in the world. Survival rates plummet from over 90% for localised PCa to 30% for metastatic PCa. As PCa is a hormone dependent cancer, the standard treatment is androgen deprivation therapy. However, most patients will develop resistance called castration resistant prostate cancer (CRPC) which carries an even worse prognosis. One emerging mechanism of CRPC is the ability of PCa cells to find other sources of androgens in the tumour microenvironment in order to produce active androgens. PCa mainly metastasises to the bone. The bone is an organ rich in adipocytes, called bone marrow adipocytes (BMAds), which can take up to 70% of medullary spaces in adults. These adipocytes differ from classical white adipocytes as they have a specific metabolism and are deprived of lipolytic activity.

As it has been shown that adipose tissue is a site of androgen production, the aim of our study was to determine if BMAds have a specific steroid metabolism that could favour metastatic CRPC development in the bone. We worked with primary human adipocytes isolated from BMAT collected during hip replacement surgeries in collaboration with Toulouse hospitals. We evaluated steroidogenic enzyme protein levels in BMAds compared to subcutaneous adipocytes by proteomic analysis. After validating a 3D culture model of human BMAds, we co-cultured them with PCa cells to evaluate cell growth and proliferation through cell counting, real live imaging and BrdU incorporation.

Proteomic data indicated that BMAds contain steroidogenic enzymes whose activity regulate the production of 5α-androstanedione involved in alternative pathways to produce the active androgen 5α-DHT in CRPC. AKR1C2 and AKR1C3 enzymes were under-represented and HSD17Bs over-represented in BMAds compared to paired subcutaneous adipocytes, this could favour the accumulation of 5α androstanedione in BMAds. We validated a 3D culture system of BMAds, as they maintained their morphology, size and adiponectin secretion over 5 days of culture. Preliminary results indicated that BMAds co-culture increased androgen-dependent LNCaP cell number and proliferation in an androgen depleted medium. This effect was inhibited by an androgen receptor antagonist, bicalutamide.

These preliminary data suggest that BMAds could be a neglected source of androgens at the bone metastasic site participating in castration resistance.

Session V : Poster session

5

A NOVEL COMPOUND WITH STRONG ANTI-CANCER EFFICACY FOR PROSTATE CANCER TREATMENT

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Background

Prostate cancer is the third leading cause of cancer death in men worldwide. This is because the disease ultimately progresses to metastatic castration-resistant prostate cancer (mCRPC), which is currently incurable. Our recent work has described a novel theranostic compound, which demonstrated extraordinary biological activity at very low concentrations for combating prostate cancer. Nevertheless, the poor solubility of the compound presents a huge limitation for clinical applications, particularly since the solvent DMSO used is toxic to the cell.

Objectives

We aim to perform chemical modifications on published compound to improve its solubility while maintaining its anti-cancer activity.

Methods

Cell sensitivity assay: evaluate the cytotoxicity of the new compounds (NC1, NC2) compared to our currently published compound on PNT1A (normal cell line), LNCaP (CSPC cell line), PC-3 and C4-2 (CRPC cell lines).

Western blotting: To analyze the expression of proteins involved in HSP27 signaling on PC-3 and LNCaP cell line after treatment with NC1.

Cell cytometry: To evaluate the internalization of the compounds in different PC cells.

Results

NC1 shows as strong anti-cancer efficacy as the published compound when tested on cancer cell lines (LNCaP, PC-3 and C4-2) while being less toxic to normal cell lines (PNT1A). Notably, NC1 was more efficiently internalized by the PC-3 cancer cell than by the normal cell PNT1A and showed a good inhibitory effect on the growth of the PC Patient-derived Organoids after three days of the treatment.

Interestingly, the action mechanism of NC1 is different between LNCaP and PC-3. On LNCaP, NC1 significantly down-regulates the expression of Hsp27 and partner proteins, while Hsp27 expression is not affected by NC1 when tested on PC-3.

Conclusion

The new compound NC1 could be a potential anti-tumor agent for PC treatment with good solubility and strong anti-cancer efficacy.

Session V : Poster session

5

CDO1 IS A NEW BIOMARKER FOR AGRESSIVE FORMS OF PROSTATE CANCER

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Prostate cancer (PCa) is the men leading cancer with an incidence of 70,000 new cases per year in France. While most PCa progress favourably, a significant proportion will develop an aggressive disease with metastases, directly affecting the prognosis for patients. Yet it is still impossible to differentiate aggressive from indolent cancers. At the diagnosis level therefore, we need to clearly define the risk of developing a lethal cancer. New markers would enable us to differentiate between these two forms, to better adapt diagnosis and avoid any over-treatment that could lead to significant side effects.

Previous data identified CDO1 as under expressed in patients with an aggressive form of PCa. We thus hypothesized that CDO1 could be a predictive marker of aggressiveness. As CDO1 is downregulated after castration, we wondered whether CDO1 expression might be regulated through the androgen receptor (AR) pathway.

First, using our RNAseq and HTA2.0 array data (PAIR cohort), TCGA and GTex RNAseq data, we have analysed CDO1 expression between relapsing and non-relapsing forms of PCa.

Then, we have cultivated VCaP cells, an androgen-dependant PCa cell line expressing CDO1, in androgen-free conditions or with addition of androgens to analyse the regulation of CDO1 expression. To confirm these results on CDO1 expression, we have used two AR antagonists and siRNA targeting AR.

Finally, we have assessed CDO1 implication in the tumoral process. We used siRNA targeting CDO1 in order to inhibit his expression and investigated cell proliferation, migration and growth.

CDO1 was found under expressed in patients with relapse associated with poorer survival prognostic. Concerning androgen regulation, starvation has resulted in a decrease in CDO1 expression which was rescued when adding androgens. These results were confirmed by transfection using siAR and AR antagonist treatment, showing that CDO1 is positively regulated by androgens. Finally, CDO1 inhibition was found to be associated with increased cell growth and migration but with no effect on proliferation.

This study highlights CDO1 as a potential new biomarker for aggressive forms of PCa. To understand how CDO1 is involved with PCa aggressivity, we aim to investigate the signaling pathways involved by RNAseq.

Session V : Poster session

5

TARGETING PROSTATE CANCER CELLS GROWTH AND METABOLISM WITH CRO15 A NEW BIGUANIDE DERIVATIVE

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Background: Prostate cancer is a major public health challenge, particularly in advanced stages where treatment resistance is universal. Identifying new therapeutic strategies is critical for improving patient outcomes.

Methods: This study investigates the effects of CRO15, a novel compound derived from biguanides, on prostate cancer cells. We employed vitro assays to assess cell proliferation, viability, mitochondrial metabolism, and pyrimidine synthesis, as well as in vitro studies using patient-derived tumoroids.

Results: CRO15 demonstrated a dose-dependent reduction in the proliferation of prostate cancer cells, with significant effects observed at concentrations starting from 5 µM. The compound particularly affected the PC3 aggressiveness, decreasing cell viability and inducing apoptosis. Additionally, CRO15 inhibited mitochondrial metabolism and pyrimidine synthesis in these cells, leading to reduced growth in patient-derived tumoroids.

Conclusions: Our findings indicate that CRO15 holds promise as a novel therapeutic agent targeting the metabolism of prostate cancer cells, warranting further investigation into its potential clinical applications.

Session V : Poster session

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INVESTIGATING PROSTATE CANCER CELLULAR HETEROGENEITY AND TREATMENT RESPONSE AT SINGLE-CELL LEVEL

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Background

Androgen deprivation therapy (ADT) is the mainstay of treatment for advanced castration-sensitive prostate cancer (CSPC); however, most patients eventually relapse, progressing to lethal castration-resistant prostate cancer (CRPC). Our study aimed to generate single-cell transcriptomic profiles from advanced CSPC samples and ADT-treated patient-derived organoids (PDOs) to investigate cellular dynamics associated with androgen deprivation response at single-cell resolution.

Method

We collected and processed nine radical prostatectomy or metastasis resection specimens from treatment-naïve high-grade CSPC patients, preparing single-cell suspensions. Single-cell RNA sequencing (scRNA-seq) was conducted on six specimens meeting required quality criteria. When possible, we established and characterized PDO lines using whole exome sequencing, IHC, and immunofluorescence, culturing them in androgen-deficient conditions to simulate ADT. A viability assay confirmed treatment efficacy before performing scRNA-seq with a lipid-based multiplexing method (MULTI-seq).

Results

Our work generated an atlas capturing transcriptomic profiles of over 20,000 cells from rare tissue material. While highlighting patient-specific tumor features and integrating cells from the microenvironment, this atlas also diverse epithelial subtypes, including a subset of intermediate cells, known as club/hillock cells, previously implicated in tumor progression. Notably, PDOs derived from non-metastatic tissue retained these cells, while those from metastatic tissue consisted solely of tumor-like cells.

The response of PDOs to ADT varied by model and specific cell subtypes present in each. Yet, responsive models showed notable pathway alterations, including the Androgen Response Signature. Current analyses are investigating whether these altered populations pre-exist within the tumor or are progressively acquired during treatment.

Conclusion

PDOs reliably reflect primary prostate tumor characteristics and serve as functional models of castration-sensitive disease. Using the generated atlas, we aim at tracking putative transcriptomic shifts that may drive tumor heterogeneity and favor castration tolerance onset.

Session V : Poster session

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TUMOR SUPPRESSOR MENIN SWITCH TO ONCOGENE DURING PROSTATE CANCER PROGRESSION LEADING TO TREATEMENT RESISTANCE THROUGH MIRNAS REGULATION

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Background

In our previous data, the tumor suppressor (TS) Menin has been shown to be overexpressed in high-grade PC and Castration-resistant PC (CRPC). Menin knockdown using antisense oligonucleotides restores chemosensitivity in CRPC cells. We performed Chip-seq analysis in normal (PNT1A), hormone-sensitive (HS, LNCaP) and androgen-independent (AI, PC-3) cells to understand how TS can switch to oncogene during PC progression. We demonstrated different Menin DNA binding in each cell line that could explain the Menin switch of function. Chip-seq results analysis demonstrates that Menin plays a TS role in normal model PNT1A by regulation of miRNA known for their TS roles. In the AIPC model, we found that Menin activates genes involved in PI3K/Akt signaling pathway largely known to be associated with disease progression and resistance to castration.

Objectives

To better understand the switch of the TS menin to an oncogene during PC progression, we performed a whole human miRNA profile regulated by Menin in normal and PC cells.

Methods

HTG EdgeSeq miRNA whole transcriptome Assay: To measure the expression of whole human miRNA transcripts using NGS.

Total mRNA-Seq: Sequencing and bioinformatics analysis were performed by the Genomics and Bioinformatics facility from the U1251/Marseille Medical Genetics lab.

Functional analysis using KEGG pathway database: to identify functions or signaling involved by identified menin-regulated miRNAs in PC.

Results

Our study highlights Menin's dual regulatory role in PC progression, impacting both miRNA expression and key signaling pathways. Menin knockdown across PNT1A, LNCaP and PC-3 cell lines shows distinct miRNA deregulation profiles. Specifically, Menin acts as a TS in normal cells, where its inhibition up regulates oncogenic miRNAs linked to cell cycle progression. In contrast, in PC cells, Menin inhibition primarily enhances TS miRNAs associated with apoptosis and chemosensitivity. Furthermore, KEGG analysis reveals Menin-regulated miRNAs activating the PI3K/AKT pathway, contributing to CRPC and chemoresistance. Integrated miRNA-seq and ChIP-seq analyses confirm that Menin directly modulates critical miRNAs involved in survival and therapy resistance pathways, establishing it as a pivotal regulator and potential therapeutic target in PC.

Conclusion

Tacken together, our results show that the function of the tumor suppressor menin switch to an oncogene implicated in treatment resistance during PC progression via miRNAs regulation.

Session V : Poster session

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MET'CONNECT : UNE ACTION STRUCTURANTE POUR MIEUX COMPRENDRE LE MÉTABOLISME DES CELLULES TUMORALES

Plateforme

Mots clés : métabolisme, cancer, instruments

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Le métabolisme tumoral constitue un domaine fondamental de la recherche en oncologie. La compréhension du métabolisme cellulaire est cruciale pour élaborer des stratégies thérapeutiques qui ouvrent la voie à des traitements plus efficaces permettant de contourner les résistances aux traitements.

Met'Connect vient en aide aux projets en lien direct avec le métabolisme tumoral. Cette action structurante s'appuie sur des instruments de pointe qui offrent une compréhension approfondie du métabolisme. Ces approches expérimentales sont mises en œuvre pour faciliter l'obtention rapide et optimisée de résultats. Les instruments disponibles sur la plateforme pour vous aider dans vos projets sont : l'Omnilog qui permet un criblage phénotypique des cellules cultivées en présence de différents métabolites afin de déterminer les voies métaboliques importantes pour la prolifération cellulaire. Le Seahorse qui effectue une analyse fonctionnelle du métabolisme and analysant la respiration mitochondriale et l'acidification du milieu (un reflet de la glycolyse). L'automate YSI effectue le dosage du glucose, lactate, glutamine et glutamate en format 96 puits. Enfin, nous avons la possibilité de réaliser des expériences en hypoxie grâce à deux enceintes qui nous permettent de faire varier la concentration en oxygène.

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 34th ARTP Meeting in 2025

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