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Bulletin de l'Association pour la Recherche sur les Tumeurs de la Prostate

Editorial

Pour la 24ème fois, l'ARTP se réunit pour échanger sur plusieurs thèmes dont la place de la détection de l'ADN tumoral circulant et des miRNA, l'intérêt d'HSP70 comme marqueur diagnostique et la possibilité de surveiller la progression par des nouvelles générations de séquence de l'ADN plasmatique. L'après midi, la session ARTP sera commune avec l'INCa pour la restitution des projets subventionnés par le PAIR Prostate. Enfin les lauréats des prix ARTP 2014 viendront présenter l'avancée de leurs travaux.

Nous aurons aussi l'occasion de remettre plusieurs prix/subventions grâce au soutien de l'industrie pharmaceutique Pierre Fabre Médicament, Astellas, Janssen, Bouchara Recordati, Takeda, Ferring, GSK et l'Association Française d'Urologie.

Très bon congrès à tous.

Pr Alexandre de la Taille

Président de l'ARTP

Palais des Congrès de Paris
2 place de la Porte Maillot
75017 Paris

Comité d'Organisation

Alexandre de la Taille
Olivier Cuvillier
Palma Rocchi
Jocelyn Céraline

Programme scientifique de la 24ème journée

Marqueurs diagnostiques et pronostiques 'Diagnostic and Pronostic Markers'

Ce programme 2015 n'aurait pas été possible sans le dévouement des co-modérateurs et des membres du Comité d'Organisation. Nous tenons à exprimer notre reconnaissance pour les entreprises et les organisations qui ont fourni un soutien financier généreux pour la réunion annuelle 2015 de l'ARTP.

8h45 - 8h50
Message de bienvenue
Pr Alexandre de la Taille, Président de l'ARTP

8h50 - 10h00
Session I : Auditions Lauréats ESUR 2014 & ARTP 2013
Modérateurs : Dr O. Cuvillier, Dr F. Cabon

Orateurs :

Dr Ahmad Imran (Beatson Institute, Glasgow)
A Sleeping Beauty screen reveals PPARG activation in a PTEN null model of Metastatic Prostate Cancer

Dr Edith Bonnelye (Lyos, Inserm U1033, Lyon)
Involvement of ERRalpha in prostate cancer cell progression in bone metastases

Dr Thierry Capiod (INEM, Inserm U1151, Paris)
Dietary vitamin D3 prevents mouse prostate tumor progression induced by high calcium intake: a potential role for calcium sensing receptor and calcium channel TRPC6

Marie Henry de Villeneuve (CRCM, UMR 1068 Inserm, UMR7258 CNRS, Marseille)
TCTP inhibition by specific antisense oligonucleotide lipid moiety-modified as a new therapeutic strategy to restore hormone- and chemo-sensitivity for the treatment of therapy-resistant prostate cancer

10h00 - 10h20 Pause Café

10h30 - 12h20
Session II : miRNA, Exosomes, Circulating nucleic acids

Modérateurs : Dr P. Clézardin, Pr N. Prevarskaya

Orateurs:
Pr Ellen Heitzer (Medical University of Graz, Graz, Austria)
Circulating tumor DNA as a monitoring tool in metastatic prostate cancer patients
Dr Carmen Garrido (Inserm UMR U866, Dijon)
HSP70-exosomes: Biomarkers for cancer patients' follow-up and Therapeutic targets
Pr Mark Rubin (Weill Cornell Medical College, New York, USA)
Monitoring prostate cancer disease progression through next generation sequencing of plasma DNA
Pr Anders Bjartell (Skane University Hospital, Malmö, Sweden)
miRNAs in prostate cancer

12h30 - 14h00 Pause Déjeuner (réservé aux adhérents de l'ARTP)

14h00 -17h00
Session III : Séminaire de restitution des projets financés par le Programme d'Actions Intégrées de Recherche (PAIR) sur la prostate

14h00 - 14h15
Ouverture
François Sigaux, Directeur du Pôle Recherche et Innovation de l'INCa
Jean-Luc Descotes, Président de l'Association Française d'Urologie

14h15 - 14h30
Introduction
Olivier Cussenot

Modérateurs
Stéphane Culine, David Azria

14h30 - 14h45
Pr François Esinger (Institut Paoli-Calmettes, Marseille)
Mitigation du risque de cancer de la prostate dans les populations à risques
14h45 - 15h00
Dr José-Arturo Londono Vallejo (Institut Curie, Paris)
Instabilité télomérique et dérégulation des microARNs dans le cancer de la prostate
15h00 - 15h15
Dr Palma Rocchi (CRCM, Inserm UMR 1068, CNRS UMR 7258, Marseille)
Analyse des mécanismes d'actions d'Hsp27 responsables de l'évolution androgéno-indépendante des cancers de prostate
15h15 - 15h30
Dr Olivier Rouvière (Hospices Civils, Lyon)
Evaluation de la position, du volume et de l'agressivité des foyers de cancer de la prostate par imagerie multi-paramétrique

15h30 - 15h45
Dr Anne Chauchereau (IGR, Villejuif)
Détermination de biomarqueurs prédictifs de la réponse au docétaxel et identification de nouvelles cibles thérapeutiques dans la résistance à la chimiothérapie du cancer de la prostate

15h45 – 16h00 Pause Café

16h00 - 16h15
Pr Karim Fizazi (IGR, Villejuif)
Vers un traitement personnalisé des cancers de la prostate métastatiques « précoces » basé sur l'utilisation de biomarqueurs évalués sur la tumeur ou les cellules tumorales circulantes
16h15 - 16h30
Dr Stéphane Supiot (Institut de Cancérologie de l'Ouest René Gaudducheau, Nantes)
Optimiser la radiothérapie des cancers de la prostate par la caractérisation et la modélisation de l'hypoxie
16h30 - 16h45
Dr Anne-Valérie Guizard (Centre François Baclesse, Caen)
Qualité de vie à long terme des patients avec cancer localisé de la prostate : étude à partir de registres de population
16h45 - 17h00
Conclusion
François Sigaux

17h00 - 17h30
Session IV : Session Poster

17h30
Remise des 3 prix Poster de l'ARTP 2015

17h30 - 18h00
Session V : Auditions Lauréats Prix Poster ARTP 2014

Orateurs:
Lucila Sackmann-Sala (Inserm U1151, CNRS UMR 8253, Paris)
Castration-resistant luminal progenitors are amplified in pre-cancerous prostates upon constitutive prl/stat5 activation

Carine Delliaux (CNRS UMR 8161, Lille)
Endothelin-1, a gene regulated by TMPRSS2:ERG fusion proteins in prostate cancer bone metastases.

Eric Vancauwenberghe (Inserm U1103, Villeneuve d'Ascq)
Involvement of the TRPA1 ion channel in epithelial-stromal interactions in human prostate cancer

18h00 - 18h30
Assemblée Générale de l'ARTP (réservé aux adhérents)

Prix Poster ARTP

Les 3 meilleurs posters recevront un prix Poster de l'ARTP d'un montant de 500 euros et présenteront leurs travaux lors de la 25ème Journée Scientifique l'ARTP

Dr Ahmad Imran
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A Sleeping Beauty screen reveals PPARG activation in a PTEN null model of Metastatic Prostate Cancer

Prostate cancer (CaP) is the commonest adult male cancer in the developed world. The paucity of biomarkers to predict tumour biology makes it important to identify key pathways that confer poor prognosis and guide potential targeted therapy. Using a novel murine forward mutagenesis screen in a low *Pten* background, we identified *Pparg*, a ligand-activated transcription factor, as a promoter of metastatic CaP through activation of lipid signalling pathways, including upregulation of lipid synthesis enzymes (FASN, ACC, ACLY). Importantly, inhibition of *Pparg* supressed tumour growth *in vivo*, with downregulation of the lipid synthesis program. We show that elevated levels of PPARG strongly correlate with elevation of FASN in human CaP, and that high levels of PPARG/FASN and low PTEN confer a poor prognosis. These data suggest that CaP patient could be stratified in terms of PPARG/FASN and PTEN levels to identify patients with aggressive CaP who may respond favourably to PPARG/FASN inhibition.

Dr Edith Bonnelye
LYOS, Inserm U1033, Lyon

Involvement of ERRalpha in prostate cancer cell progression in bone metastases

Bone metastases are one of the main complications of prostate cancer. Indeed 80% of patients dying from prostate carcinoma have developed bone metastases that are incurable, raising the need to improve their treatment or prevention. Therefore, in order to participate to a better molecular understanding of the metastatic process in bone, we investigated whether and how Estrogen receptor-related receptor alpha (ERRa) is involved in bone metastases associated with prostate cancer. We analyzed clinical specimens and gain-of-function/loss-of-function models in three prostate cancer cells models (PC3 (pure osteolytic model), PC3c and ACE-1 (mixed models that combine degradation and bone formation)) *in vivo*. Cellular and molecular studies *in vitro* were also performed to identify signaling pathways and target genes effects in tumors and the tumor microenvironment.
We demonstrate that ERRa acts as a pro-tumor factor in prostate cancer-derived bone lesions. Increased levels of ERRa in tumor cells in vivo led to both bone destruction and formation, and rapid tumor progression. ERRa overexpression in tumor cell had direct effects on osteoblasts and osteocytes and both direct and indirect effects on osteoclasts. New factors found to be regulated by ERRa in tumor cells, all of which may impact bone cell number and function, include COX2, ENDOTHELIN-1 and TGFβ1.
Notably, expression of all of these factors also significantly and positively correlated with ERRa expression in prostate patient specimens.

Finally, high levels of ERRa in tumor cells stimulated the pro-metastatic factor PERIOSTIN expression in the stroma, suggesting that ERRa regulates the tumor stromal cell microenvironment to enhance tumor progression. Taken together, our data demonstrate that ERRa is a regulator of prostate cancer cell progression in bone. Therefore, inhibiting ERRa may constitute a new therapeutic strategy for prostate cancer skeletal-related events.

Dr Thierry Capiod

PRL/GH Pathophysiology Laboratory and Phosphate Homeostasis Laboratory, Inserm U1151, Institut Necker Enfants Malades (INEM); Physiology Department, Hôpital Européen Georges Pompidou; Urology Department, Hôpital Cochin, Assistance Publique Hôpitaux de Paris; Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, Paris, France.

Dietary vitamin D3 prevents mouse prostate tumor progression induced by high calcium intake: a potential role for calcium sensing receptor and calcium channel TRPC6

The management of bone health in patients with prostate cancer is a concern for urologists. While calcium (Ca^{2+}) and vitamin D3 (VitD) supplementation is highly recommended as a supportive care option to reduce bone morbidity at all stages of the disease, the impact of these supplements on the progression of established prostate tumors is unknown. We used two transgenic mouse models of fully penetrant prostate tumorigenesis, Pb-Prl (enforced Stat5 signaling) and KIMAP (SV40 T antigen expression), to address the safety of dietary Ca^{2+} and VitD towards prostate tumor progression. Six week-old mice were fed with diets supplemented or not with moderate doses of VitD and/or high doses of Ca^{2+}. The human prostate cancer cell line PC-3 was used for mechanistic studies. We showed (histology, immunohistochemistry and qRT-PCR) that several cancer hallmarks including cell proliferation, inflammation, micro-invasion, expression of tumor markers, as well as Ca^{2+} channel TRPC6 and Ca^{2+} sensing receptor (CaSR), were significantly increased following Ca^{2+}-enriched diet and prevented by dietary VitD in mouse prostates. Stimulation of PC-3 cells with increasing concentration of extracellular Ca^{2+} resulted in an increase in cell proliferation rate, TRPC6 and CaSR expression (mRNA and protein) while VitD (10-100 ng/ml) reversed this effect. Silencing CaSR or TRPC6 expression in calcium stimulated PC-3 cells resulted in a decrease in cell proliferation rate. Our study suggests that Ca^{2+}-enriched diet drastically accelerated the progression of mouse prostate lesions towards more aggressive phenotypes while dietary VitD protected from these effects.

Marie Henry de Villeneuve

CRCM, UMR 1068 Inserm, UMR7258 CNRS, Marseille

TCTP inhibition by specific antisense oligonucleotide lipid moiety-modified as a new therapeutic strategy to restore hormone- and chemo-sensitivity for the treatment of therapy-resistant prostate cancer

We recently demonstrated that castration-resistant prostate cancer (CRCP) correlates with Translationally controlled Tumor protein (TCTP) overexpression and loss of p53. Human tissue microarray analysis showed that TCTP expression was found only in 10% of human PC before treatment that TCTP's expression become uniformly highly overexpressed in 75% of castration-resistant prostate cancer. Furthermore, no expression of TCTP is found in benign prostate hyperplasia and normal prostate cells. We developed and worldwide patented a first generation TCTP phosphorothioate backbone ASO that significantly downregulates mRNA and protein expression level (Patent PCT 10306447.3, 2010).

We demonstrated that specific inhibition of TCTP by ASO or siRNA showed a 50% decrease in PC-3 cell viability and apoptosis in a caspase-3 dependent manner, and a decrease of PC-3 cell growth. *In vivo*, systemic administration of TCTP ASO in athymic mice decreased PC-3 tumor progression and also significantly enhanced docetaxel chemosensitivity (Baylot, V. Molecular Therapy, 2012). We demonstrated that TCTP is involved in the Hsp27 cytoprotective role during CR evolution and that ASO-induced TCTP silencing restores the hormone- and docetaxel sensitivity by enhancing apoptosis and delaying tumor progression. TCTP is now recognized as a therapeutic target in several cancers including prostate, breast and lung cancers. The purpose of my work was to develop one second generation of TCTP ASO (TCTP-LASO) by using a lipid-conjugated oligonucleotides modification *via* « Click Chemistry » in order to improve stability, biodisponibility and delivery of the first generation TCTP ASO to be tested in clinics for PC patients.

Orateurs

Session II : **miRNA, exosomes, circulating nucleic acids**

Pr Ellen Heitzer
Institute of Human Genetics, Medical University of Graz, Graz, Austria

Circulating tumor DNA as a monitoring tool in metastatic prostate cancer patients

The plasticity and evolution of the metastatic prostate cancer genome is incompletely characterized due to the fact that cancer cells accumulate new genetic changes as a consequence of tumor progression and the selective pressure of cancer therapies. Therefore, metastases often show different changes than the primary and in most cases we are not able to monitor these changes with simple biopsies especially in prostate cancer that has an unusually high propensity for metastasizing to the bone. On possibility to overcome this limitation is the analysis of tumor-specific changes in cell-free circulating DNA (ctDNA).
We make use of the plasma-Seq approach in order to monitor metastatic prostate cancer patients under ADT and second line chemotherapy. Analysis of plasma DNA from prostate cancer patients revealed a variety of copy number changes characteristic for the prostate cancer. Although the prostate cancer genome was reported to be characterized by relatively few focal chromosomal alterations, we also demonstrate that newly occurring focal amplifications are a driving force in the progression to lethal, metastatic prostate cancer.

In approximately 70% of CRPC patients we were able to observe the emergence of AR gene amplification at the time of progression from CSPC (castration sensitive) to CRPC (castration resistant). Furthermore, plasma DNA analyses reflected the treatment response to ADT and second line treatment, i.e. cytotoxic chemotherapy, respectively. Moreover, we were able to monitor the evolution of novel focal amplifications and clonal shifts due to therapy changes in one third of the patients. Increases of neuron-specific enolase were accompanied by drastic clonal pattern changes in the tumor genome, most consistent with subclonal diversification of the tumor. Our analyses have significant implications for the clinical management of prostate cancer.

Dr Carmen Garrido

Inserm UMR U866, Dijon

HSP70-exosomes: Biomarkers for cancer patients' follow-up and Therapeutic targets

As cancer cells accumulate mutations, violate physiological laws and acquire sets of hallmarks, they require a constitutively high level of chaperones like HSP70 (heat shock protein-70) for their survival/maintenance. HSP70 is a major stress-inducible chaperone with intra- (cytoprotective) and extracellular (danger signal) functions. We have demonstrated that whereas cancer cells release exosomes with membrane-bound HSP70 (HSP70-exosomes), normal cells do not (Gobbo et al, J Natl Cancer Instit, 2015). We have developed a peptide aptamer (A8) that binds to the extracellular loop of membrane-bound HSP70 (Rerole et al, Cancer Res, 2011).
Using A8 as a high affinity ligand and a technique of interference biolayer (BLI), we have developed an easy optical approach to capture HSP70-exosomes from human fluids to demonstrate that the amount of HSP70-exosomes both in blood and urines is much higher in cancer patients than in healthy individuals (patent 2013-4 Inserm transfert). Since one single cancer cell can release hundreds of tumour-derived exosomes, HSP70-exosomes detection must precede the apparition of circulating tumour cells and therefore may be an interesting marker in cancer.
From a therapeutic perspective, we have demonstrated that HSP70-exosomes induce the activation of myeloid-derived suppressive cells (MDSC) and that this activation is blocked by the peptide aptamer A8. As a consequence, A8 induces a strong intra-tumour infiltration of immune cells (cytotoxic T-cells and macrophages) and the regression of the tumour (Gobbo et al, J Natl Cancer institute 2015). As most anticancer drugs induce the release of HSP70-exosomes, we believe they may benefit from a combination with a molecule like A8, able to restore the development of an anti-cancer immune response.

Pr Mark Rubin

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Monitoring prostate cancer disease progression through next generation sequencing of plasma DNA

Precision cancer care requires aligning the patient's clinical situation and therapy with genomic and epigenetic alterations[1]. In the Stand Up 2 Cancer/ Prostate Cancer Foundation Castration Resistant Prostate Cancer 500 Trial (SU2C/PCF CRPC 500), we have observed a host of novel mutations observed either only after androgen deprivation therapy (ADT) or occurring at significantly higher frequencies following treatment (Robinson et al., Cell 2015)[2].

Emerging work also indicates that the spectrum of disease resistance goes beyond the androgen receptor (AR) signaling pathway[3,4]. AR "indifferent" mechanisms of resistance are being observed and some cases can be characterized as CRPC with neuroendocrine differentiation (Beltran et al., ASCO 2015). As demonstrated in the SU2C/PCF CRPC500 Trial and at our Institute for Precision Medicine (Beltran et al., JAMA Oncology 2015)[5], obtaining metastatic biopsies is feasible and informative. However, in the setting of monitoring disease progression, the use of non-invasive approaches are needed. Recent studies from Demichelis and Attard (Science Translational Medicine)[6,7], support the feasibility of employing next generation sequencing (NGS) to interrogate plasma DNA for changes in mutations and clonality during the course of disease treatment. Important advances in computational analysis and NGS make it feasible to develop more sophisticated multi-gene panels that can capture the spectrum of novel mutations seen in the context of treatment. In addition, pilot work suggests that whole exome sequencing may also be a useful approach to monitoring plasma DNA. In summary, a combination of metastatic biopsies and non-invasive monitoring of plasma DNA for genomic alterations represent an emerging paradigm for precision cancer care for men with CRPC.

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Pr Anders Bjartell
Skane University Hospital, Malmö, Sweden

miRNAs in prostate cancer

Prostate cancer is a heterogeneous disease where the molecular mechanisms are still not fully elucidated. Prostate cancer research has traditionally focused on genomic and epigenetic alterations affecting the proteome, but over the last decade non coding RNAs, especially microRNAs, has been recognized to play a key role in prostate cancer progression. A considerable number of individual microRNAs have been found to be deregulated in prostate cancer and their biological significance elucidated in functional studies. This lecture will delineate the current advances regarding the involvement of microRNAs and their targets in prostate cancer biology as well as their potential usage in the clinical management of the disease. The main focus will be on microRNAs contributing to initiation and progression of prostate cancer, including androgen signalling, cellular plasticity, stem cells biology and metastatic processes. To conclude, implications on potential future microRNA based therapeutics based on the recent advances regarding the interplay between microRNAs and their targets are discussed.

NEUROPILINE-1, UN NOUVEAU BIOMARQUEUR D'AGRESSIVITÉ ET DE RÉSISTANCE THÉRAPEUTIQUE DU CANCER DE LA PROSTATE

Charly Blanc[1], Anissa Moktefi[2], Fannie Semprez[1,2], Pascale Maille[1,2], Pascale Soyeux[1], Virginie Firlej[1], Francis Vacherot[1], Alexandre De La Taille[1,3], Arturo Londono-Vallejo[4], Yves Allory[1,2], Jean Delbe[1], Yamina Hamma-Kourbali[1]

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Introduction

Dans le cadre du cancer de la prostate (CaP) localement avancé, l'hormonothérapie constitue le traitement de référence et permet une régression tumorale. Dans certains cas néanmoins, une forme de résistance s'installe et conduit à des formes plus agressives. Les mécanismes moléculaires impliqués dans la résistance associent l'activation du récepteur des Androgènes (RA), la surexpression de gènes anti-apoptotiques ou encore l'implication de gènes influençant la transdifférenciation neuroendocrine (NE).

La Neuropiline-1 (NRP1) est une glycoprotéine transmembranaire impliquée dans le développement embryonnaire mais aussi dans les processus physiopathologiques tels que l'angiogenèse et l'agressivité tumorale. En revanche, son rôle dans la carcinogenèse prostatique n'est pas clairement établi.

L'objectif de cette étude est de déterminer le rôle de NRP1 dans la progression du CaP et d'étudier les mécanismes moléculaires liés à la résistance aux traitements conventionnels.

Méthodes

Nous avons mis en œuvre le profilage moléculaire de 180 tumeurs à différents stades du CaP afin d'étudier le niveau d'expression de NRP1. D'autre part, l'utilisation de lignées cancéreuses prostatiques humaines hormono-sensibles ou hormono-résistantes a permis d'étudier le rôle de NRP1 et les mécanismes permettant l'acquisition de la résistance thérapeutique.

Résultats

L'analyse de l'ensemble de notre cohorte montre que l'augmentation de l'expression de NRP1 est corrélée avec l'évolution du CaP et en particulier avec l'acquisition de l'hormono-résistance (HR). L'étude des mécanismes moléculaires liés à la résistance indique que NRP1 est associée à l'expression de marqueurs NE.

Session IV : **Posters**

Par ailleurs, nous avons défini pour la première fois que l'expression de NRP1 est sous le contrôle du RA. L'inhibition de la voie du RA conduit à un phénotype NE associé à la surexpression de NRP1. Enfin, nous avons montré que NRP1 favorise l'acquisition d'une HR, la surexpression de marqueurs NE, l'activation de voies de survie cellulaire et par conséquent la résistance aux traitements.

Conclusion

La NRP1 semble être une nouvelle voie d'étude intéressante pour concevoir de nouvelles thérapies dans le cadre des CaP agressifs HR.

IMPLICATION OF NPM1 PHOSPHORYLATION IN PROSTATE CANCER

Damien Destouches[1,2,3], Stéphane Terry[4], Charles Marchand[1,2], Pascale Maillé[1,2,5], Gilles Carpentier[1,3], Yves Allory[1,2,5], José Courty[1,3], Alexandre De La Taille[1,2,6] and Francis Vacherot[1,2]

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Background: Despite the advent of several new treatment options over the past years, advanced/metastatic prostate carcinoma (PCa) still remains incurable, which justifies the search for novel targets and therapeutic molecules. Nucleophosmin (NPM1) is a shuttling nucleoprotein involved in tumor growth and its targeting could be a potential approach for cancer therapy. We previously demonstrated that the multivalent pseudopeptide N6L binds to NPM1 potently affecting *in vitro* and *in vivo* tumor cell growth of various tumor types as well as angiogenesis. Furthermore, NPM1 binds to androgen receptor (AR) and modulate its activity. In this study, we investigated the implication of the NPM1 and its Thr199 and Thr234/237 phosphorylated forms in PCa.
Methods: Colocalization of phosphorylated NPM1 with AR, using immunofluorescence and immunoprecipitation assays, and effects of N6L on the phosphorylated NPM1 expression and AR activity were investigated *in vitro* in LNCaP cells. Finally the expression of NPM1 and its phosphorylated forms was evaluated in patient tissues.
Results: We showed that phosphorylated forms of NPM1 interact with androgen receptor (AR) in nuclear speckles. N6L treatment of prostate tumor cells led to inhibition of NPM1 phosphorylation in conjunction with inhibition of AR activity. We also found that total and phosphorylated NPM1 were overexpressed in castration-resistant PCa.
Conclusions: Our findings reveal the role of Thr199 and Thr234/237 phosphorylated NPM1 in PCa progression and their potency as targeting molecules for PCa therapy.

OVEREXPRESSION OF THE EMBRYONIC GENE CRIPTO PROMOTES EPITHELIAL - MESENCHYMAL TRANSITION AND IS ASSOCIATED WITH TUMOR AGGRESSIVENESS IN PROSTATE CANCER

Ihsan El Sayed[1,2], Pascale Maillé[1,3], Fannie Semprez[1], Damien Destouches[1], Cynthia Pimpie[1], Guillaume Ploussard[1], Arturo Londoño-Vallejo[4], David S. Salomon[5], Ahmad Daher[2], Yves Allory[1,3], Alexandre de la Taille[1,6], Francis Vacherot[1] and Stéphane Terry[1,7]

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Background: Prostate cancer (PCa) is the most common malignancy and a prevalent source of cancer-related morbidity and mortality in men. Identification of tumor biomarkers may be able to help distinguish clinically significant from indolent PCa and select patients at high risk of relapse for more aggressive treatment. The epidermal growth factor-related peptide, CRIPTO (also referred to as human Cripto-1, abbreviated CR-1) is the founding member of the EGF-CFC (Cripto, FRL-1, Cryptic) protein superfamily. CR-1 and its orthologs play crucial roles in embryonic development. In humans, CR-1 can also be expressed in a wide spectrum of human tumors, but its implication in prostate cancer has remained unexplored. Here, we investigated the expression pattern of CR-1 and the consequences of its expression in the prostate cancer setting in order to assess its potential impact on progression of prostate malignancy.
Methods: Different prostate normal and cancerous tissue specimens were examined by immunohistochemistry. Various prostate cancer cell lines were employed in experimental studies, and analyzed using techniques commonly used in biochemistry, cellular and molecular biology.
Results: we found significant CR-1 expression in 37.9% of PCas, while CR-1 expression was absent or marginally detected in benign conditions. In addition, elevated CR-1 expression in primary prostate tumors was found to be an independent prognostic factor for disease recurrence in PCa patients who had previously underwent radical prostatectomy as primary management. Experimental studies demonstrated that CR-1 overexpression plays a functional role in PCa cells by promoting an epithelial-mesenchymal transition (EMT) associated with enhanced migration capacity and survival under various stress conditions, and these effects rely in part to its propensity to stimulate PI3K/AKT and FGFR1/ERK signaling pathways.
Conclusion: In sum, these findings reveal a previously unknown function of CR-1 in PCa, emphasize a potential prognostic value for CR-1 in PCa and suggest that inhibiting these pathways may be useful in a subset of CR-1 expressing prostate tumors.

IDENTIFICATION OF LIVER X RECEPTOR ENVIRONMENTAL CHEMICAL DISRUPTORS INVOLVED IN THE OCCURRENCE OF PROSTATE CANCER

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Background: Recent decades have been marked by an increased incidence of metabolic diseases and cancer. Molecules present in the environment, environmental chemical disruptors (ECDs), by continuous exposure to low doses, have been suspected of being involved in this phenomenon. Among nuclear receptors superfamily, *Liver X receptor* (LXR) have a protective role in prostate epithelial carcinogenesis due the control of proliferation/apoptosis balance. We wondered whether ECDs could, in part, alter LXR signaling pathways.
Methods: From a library of molecules, an *in silico* screening was performed through molecular modeling and bibliographic researches. The selected molecules were tested in cell culture using a UAS-GAL4 system to evaluate their effects on the ligand binding domain of the LXRs. Molecules were then studied for their abilities to affect the LXR-RXR activity. LXRs target genes transcription were measured on HeLa cell incubated with the related ECDs.
Results: Both Bisphenol A and Chlordecone have antagonistic effects on the LXRs. They act on the ligand binding domain and thereby disturb the LXR-RXR functioning and thus transcription of regulated genes. IC50 have been calculated as 3.34 µM for Chlordecone and 0.75 µM for Bisphenol A on LXRa and 1.06 µM for Chlordecone and 2.12 µM for Bisphenol A on LXRβ. These IC50 are in accordance with the concentrations found in human.
Conclusions: Even though these results have to be validated *in vivo*, we have shown that Bisphenol A and Chlordecone, two chemicals involved with risk to develop prostate cancer, are ECDs for both LXRs isoforms.

FKBP7: A NEW THERAPEUTIC TARGET IN TAXANE RESISTANT PROSTATE CANCER

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Background: Prostate cancer is the most common malignancy among men worldwide and its incidence has been increasing recently in western countries. Docetaxel and Cabazitaxel are taxane chemotherapies used for the management of Metastatic Castrate-Resistant Prostate Cancer (mCRPC). Despite survival benefits observed in patients, the major challenge in clinic remains the chemoresistance, leading inexorably to death. Therefore, efforts are needed to identify new therapeutic targets in order to overcome taxane-resistance.
Methods: We developed a series of Docetaxel-resistant cell lines (IGR-CaP1-R, PC3-R, 22RV1-R, LNCaP-R) and we generated a signature of 1,006 highly differentially expressed genes potentially implicated in chemoresistance. Moreover, we performed a high throughput siRNA screening in IGR-CaP1, allowing us to select 60 genes with a functional role in Docetaxel resistance. We also established Cabazitaxel resistant cell lines to extend the study to taxanes.
Results: We focused our attention on the role of FKBP7, a protein belonging to the FK506 binding proteins which are known as immunophilins. Members of this family are chaperons exhibiting a peptidyl-prolyl cis/trans isomerase (PPIase) activity. This protein is highly overexpressed in prostate tumors from patients and in taxane-resistant prostate cancer cell lines.
Specific inhibition of FKBP7 with siRNA significantly blocked the growth of chemoresistant cells. Moreover, knock-down of this protein was accompanied by a sensitization of chemoresistant cells to taxane treatment. In addition, although this protein is highly expressed in several non cancerous cells, its extinction does not affect cell growth suggesting a different function of the protein between chemoresistant cells and non-cancerous cells. Furthermore, proteomics experiment allowed us to identify its localization within intermediate filaments in cells which are directly linked to microtubules, the target of taxane.

Conclusion: We identified a new protein which could be a relevant therapeutic target in chemoresistant CRPC. We are now focusing on the validation of this therapeutic target in a Docetaxel-resistant prostate cancer mice model established within the laboratory.

THE MEDULLARY ADIPOCYTES CONTRIBUTE TO THE BONE METASTASIS OF PROSTATE CANCER AND THIS EFFECT IS REGULATED BY OBESITY

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Background: We have recently demonstrated that mature adipocytes of the periprostatic adipose tissue (PPAT) act as a driving force for the local dissemination of prostate cancer (PCa) through the secretion of the CCL7 chemokine, and that this effect was amplified by obesity (Laurent, Guerard et al, Nature Communications). Once present in PPAT, PCa cells will have the ability to enter to the circulation and to metastasize to distant sites and preferentially to bone. Our main hypothesis was that chemokines (and more specifically CCL7) secreted by mature adipocytes in the yellow bone marrow (BM) contribute to the homing of PCa cells to bone, and that this effect could be amplified in obesity, as suggested by the clinical evidences of increased bone metastasis in obese patients.
Methods: We investigated the ability of the conditioned medium from human medullary adipocytes (MedAd-CM) obtained from lean and obese patients undergoing orthopedic surgery to support the directed migration of a series of PCa cell lines *in vitro* (Boyden chamber assay).
To validate this effect *in vivo*, we used a murine cell line RM1-BM able to localize to the bone after intra-cardiac injection.
Results: Using a series of 23 samples of men between 45 to 65 years, we first showed that MedAd-CM were able to specifically chemoattract PCa cells (by contrast to paired conditioned medium obtained from subcutaneaous adipocytes) with a strong amplification of this effect in a context of obesity. Interestingly our preliminary results suggest that aging could also amplify this effect.
The chemoattractive potential of medAd-CM was mediated by the presence of the chemokine CCL7 able to interact with one of its receptor CCR3 expressed by tumor cells, as shown using pharmacological inhibitors, blocking antibodies and gene repression strategies. Interestingly, we also demonstrated *in vivo* that the loss of CCR3 in tumor cells abrogates the bone metastatic homing of the RM1-BM cell line.
Conclusions: This study show for the first time a mechanism that could explain the increased bone metastatic dissemination of prostate cancer linked to obesity. These data highlight the fact that medullary adipocytes, using the CCR3/CCL7 axis, are able to control the distant dissemination of PCa cells to the bone. In a context of obesity, medullary adipocytes show a different phenotype leading to an increased secretion of CCL7 and enhanced bone dissemination *in vivo*.

A DROSOPHILA MODEL OF HUMAN PROSTATE CANCER FOR DECIPHERING MECHANISMS THAT COORDONATE RAS/MAPK AND AKT/mTOR SIGNALING PATHWAYS.

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Background: Analyses of human *prostate cancer* specimens have revealed that Ras/MAPK and AKT/mTOR signaling pathways are hyperactive and functionally cooperate to promote tumor growth and progression to metastatic and advanced castration resistant forms of the disease. **Methods:** To uncover the mechanisms by which molecules of these signaling pathways operate during development and progression of the disease, we took advantage of engineered *Drosophila* with hyperactive Ras/MAPK and/or AKT/mTOR signaling in the accessory gland, a functional homolog of the mammalian prostate, to unravel how these pathways interconnect at a molecular level.
Results: Ras^{V12} overexpression induces formation of cell masses which recapitulate many cancer cell hallmarks including uncontrolled cell growth and proliferation; enhanced matrix metalloproteinases expression; *switch* from *E- to N-cadherin* induction, endothelium extravasation and neovascularization-like tracheogenesis.

Although expression of myristoylated AKT did not promote tumor formation, our data clearly show that hyperactive Ras^{V12} enhances AKT/mTOR signaling and supports tumorigenesis. Interestingly, EGFR ligand Spitz expression is also induced by Ras^{V12} expressing cells thus showing that AKT/mTOR activation may rely on the setting of an autocrine feedback loop (EGFR dependent signaling), mimicking *in vivo* the EGF loop described in cultured prostate cancer cells.
Conclusions: Collectively, our data show that both Ras/MAPK and AKT/TOR pathways are required to induce tumor development in the accessory gland epithelium. This model may then be used to screen mediators that support the crosstalk between these two pathways, and which could be attractive therapeutic targets for prostate cancer treatment during late stage disease.

ANDROGEN RECEPTOR VARIANTS AND MICROENVIRONMENT IN PROSTATE CANCER

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Background: Progression of hormone-dependent prostate cancer (PCa) is driven by androgens. Thus, the most common treatment for patients with advanced PCa consists in androgen ablation therapy. However, the majority of patients relapse and develop a castration-resistant PCa. This failure of androgen deprivation is related to the emergence of androgen receptor (AR) variants. Nevertheless, the tumour microenvironment is another necessary feature to PCa progression and metastatic process. In fact there's a strong cooperation between cancer cells and cells surrounding in the stroma, through cancer associated fibroblasts (CAFs).
CAFs represent a very heterogeneous population. They can derive from different cell types but up to approximately 25% of CAFs originate from bone marrow, especially from bone marrow-derived mesenchymal stem cells (MSCs).
In this way, we study the effects of AR variants on the surrounding prostate tumour microenvironment by focusing on MSCs differentiation into CAFs.

Methods: We use the prostate tumour cell line PC3 as a differentiation positive control, and LNCaP cells expressing or not AR variant through lentiviral transduction. We then use an *in vitro* co-culture system of human MSCs together with PC3 or LNCaP that express or not AR variants. Next, expression of differentiation factors and markers are measured with Bio-Plex® assay in LNCaP, and with RTq-PCR and immunofluorescence in MSCs.

Results: We first noticed that VEGF secretion, a factor known to be secreted by tumour cells and involved in MSCs differentiation into CAFs, was increased in presence of ARQ640X variant. Preliminary data revealed an upregulation of several markers such as α-SMA, PDGFR-β, SDF-1 and FSP-1 in MSCs, suggesting a positive impact of AR variants on MSCs differentiation into CAFs. Further experiments are going on to understand more deeply the mechanisms underlying these interactions.

Conclusions: Our study would highlight an unknown property of AR variants in prostate tumour cells, that is their ability to promote corruption of the microenvironment to favour tumour progression.

PROPOLIS EXTRACTS ALTER SURVIVAL OF PROSTATE CANCER CELLS LNCAP

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Background. Propolis or bee glue is a resinous mixture collected by honey bees from various botanical sources that has been in traditional medicines for thousands of years, notably for its antioxidant properties.
In vitro, propolis induces cell cycle arrest, apoptosis and reduces expression of growth and transcription factors, which makes it as a good candidate for pharmacological approach in prostate cancer. Flavonoids and phenolic compounds appear to be the principal components responsible for the biological activities. Based on these bibliographical elements, we have analyzed the effects of propolis extracts on the survival of cultured LNCaP cells

Methods. LNCaP cells were cultured for 24 to 48 hours with increasing amount of propolis extract diluted with ethanol. Anti-proliferative effect was assayed by the measurement of MTT. Accumulation of the androgen receptor (AR) was investigated by western blot. PSA secreted in the media was measured throughout the incubation.
Results. 1) Propolis blocks survival of LNCaP cells after 48 hours of treatment with an IC50 of 0.05 mg/ml. 2) Propolis inhibit androgen signaling as accumulation of AR decreases as well as PSA secretion by LNCaP cells. 3) Cellular effects of propolis extract seem to induce apoptosis.
Conclusions. Propolis extract affect LNCaP cell survival by an anti-androgen effect. Effect of these extracts on accumulation of androgen regulated genes will be measured in LNCaP cells. A putative presence of a natural anti-androgen with the propolis will be investigated by transient transfection with a luciferase promoter gene under the control of tan androgen response element. Altogether these results justify the interest of deciphering the role propolis on LNCaP cells and open a new field of investigation in the characterization of molecules present in this complex compound in the pharmacological treatment of prostate cancer.

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Castration-resistant luminal progenitors are amplified in pre-cancerous prostates upon constitutive prl/stat5 activation

Resistance to androgen-deprivation therapies in prostate tumors remains the major cause of death by prostate cancer. Recent studies have demonstrated the existence of castration-resistant luminal cells in human primary tumors [1], suggesting a critical role of these cells as initiators of disease recurrence. Very little information is available concerning prostate luminal cells that can survive castration in humans or mice. Our FACS analyses of a mouse model of prolactin overexpression in the prostate (Pb-PRL mice, which present constitutive Stat5 activation in the prostate epithelium), have evidenced the amplification of a new subpopulation of luminal cells that express Sca-1 (stem cell antigen 1). Initial studies showed that these cells expressed luminal cytokeratin 8 and not cytokeratin 5, and that they could generate few but large prostaspheres in 3D culture. In addition, expression of Sca-1 was lost upon in-vitro androgen stimulation, suggesting that they could differentiate into mature luminal cells in these conditions [2]. We have now tested whether these putative luminal progenitor cells survive castration, and shown that their prevalence is significantly increased after 14 days of castration in Pb-PRL prostates.
Even though very few of these cells are present in the prostate epithelium of wild-type (WT) mice, an increased prevalence of luminal progenitors was observed after 14 days of castration in WT mice as well. A transcriptomic analysis of sorted luminal progenitors from Pb-PRL and WT prostates indicates that their gene expression profiles are distinct from those of sorted luminal and basal cells. Candidate markers are currently under validation using immunohistochemistry on prostate slides from Pb-PRL mice and other mouse models of prostate cancer. The mechanisms underlying the amplification of luminal progenitors in Pb-PRL mice are presently under study. Human cohorts will soon be assayed in an effort to establish the presence of these luminal progenitors in human prostates, their prevalence and possible correlation to disease states.

1. Toivanen R et al, Sci Transl Med. 5(187):187ra71, 2013.
2. Sackmann-Sala L et al, Am J Pathol. 184(11):3105-19, 2014.

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Endothelin-1, a gene regulated by TMPRSS2:ERG fusion proteins in prostate cancer bone metastases.

Bone metastases are frequent and severe complications of prostate cancer (PCa). Recently, the *TMPRSS2:ERG* gene fusion, which results in the aberrant androgen-dependent expression of the ERG transcription factor, has been shown to be the most common gene rearrangement in PCa. This study investigates a potential role of the gene fusion in the development and phenotype of PCa bone metastases.

We previously established cell clones from a PCa cell line (PC3c), over-expressing different levels of TMPRSS2:ERG. *In vivo* analysis of bone lesions induced by intra-tibial injections of PC3c-TMPRSS2:ERG clones in mice showed an increase of osteoblastic phenotype compared to control cells. Furthermore, a transcriptomic study of these clones showed a change of expression in many genes, including *endothelin-1* (*ET-1*). Since ET-1 is known to be involved in osteoblast proliferation and in osteoblastic metastasis formation in PCa, we therefore investigated the transcriptional regulation of *ET-1* by fusion proteins. *In vitro*, we have shown that this gene was overexpressed in PC3c-TMPRSS2:ERG clones, depending on ERG expression levels, and was inhibited by ERG silencing. *In silico* analysis of the promoter of *ET-1* revealed the presence of several potential binding sites of ERG. ChIP experiments demonstrated a direct binding to one of them. Moreover, using a cohort of human carcinoma prostate samples, we were able to establish a correlation between the expression of *ET-1* and the expression of the fusion gene *TMPRSS2:ERG*, reinforcing the link between *ET-1* and the fusion.

Taken together, these results strongly suggest that the *TMPRSS2:ERG* gene fusion contributes to the osteoblastic phenotype of PCa bone metastases and that ET-1 is a crucial target gene regulated by the transcription factor ERG.

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Involvement of the TRPA1 ion channel in epithelial-stromal interactions in human prostate cancer

Accumulating data show that the development and progression of human prostate carcinoma (PCa) is dependent on tumor microenvironment (TME) in particular the cancer associated fibroblasts (CAF). A reciprocal signaling exists between tumor cells and CAF, via secretion of growth factors, leading to the growth, differentiation, migration and in the resistance of PCa cells to chemotherapeutic agents. These observations suggest that the tumor stroma also has to be considered as a potential therapeutic target in PCa therapies. In this context, our recent works showed that TRPA1 ion channel is exclusively expressed in PCa myofibroblasts. The activation of this channel may allow an increase in intracellular free calcium leading to the secretion of factors and may participate in epithelial-stromal interactions of PCa. It is therefore important to study the role of this channel in the epithelial-stromal interactions of PCa.
We studied first the functionality and role of TRPA1 channel in primary cultured PCa myofibrobasts. Using calcium imaging and electrophysiological techniques we showed that TRPA1 channel is functional in these cells and is involved in calcium entry induced an epithelial agonist, ET-1 (Endothelin-1) which in turn modulates the expression of the TRPA1 channel in CAF. Interestingly, the activation of the channel induced the secretion of Hepatocyte Growth Factor (HGF). In the context of the epithelial-stromal interactions, we also studied the effects of PCa myofibroblasts CM and HGF on epithelial cancer cell lines. The myofibroblasts CM and HGF induced an epithelial-mesenchymal transition (EMT) of the human PCa androgen-independent cell line DU145, the process being accompanied in these cells by a gene expression remodeling, cell migration and resistance to chemotherapeutic agents.
Taking into account the relevance of the tumour stroma, antineoplastic therapeutic strategies must be tuned to target the 'cancer tissue', e.g. not only tumour cells, but also the cellular constituents of the TME. In this context, deciphering the role of ion channels and transporters proteins in the crosstalk between the tumour cells and the various constituents of the TME merits particular attention, also from a therapeutic viewpoint. Our work shows the importance of the stroma-specific TRPA1 ion channel in epithelial-stromal interactions in human prostate cancers. The TRPA1 channel is involved in the secretion of growth factors such as HGF, a factor able to promote cancer cell migration and resistance to apoptosis by inducing an EMT, a process involved in the metastasis of tumor epithelial cells. Thus, TRPA1 channel could be a particularly attractive therapeutic target to disrupt the epithelial-stromal interactions in prostate cancers.

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