Association pour la Recherche sur les Tumeurs de la Prostate

Session I :
ARTP 2021/ESUR 2022 Laureates

Benoît MIOTTO (Institut Cochin, Paris)

'Molecular and prognostic study of the transcription factor ZBTB38 in metastatic progression and treatment resistance in prostate cancer'

Prostate cancer is one of the most common malignancies in men. The mechanism of how prostate cancer initiates and develops is still not clear. Here, we show that expression of the gene ZBTB38 is associated with poor prognosis in localised prostate cancer and could help discriminate aggressive localised prostate tumours from those who can benefit only from observation. Low expression levels of ZBTB38 associate with increased levels of chromosomal abnormalities and more aggressive pathological features, including higher rate of biochemical recurrence of the disease. ZBTB38 recognizes two different methylated consensus sequences found upstream of long and active CpG islands, for housekeeping and cell cycle genes. ZBTB38 abundance is regulated by deubiquitinase USP9X, an important gene in prostate cancer, and regulates reactive oxygen species. Our study shows that ZBTB38 is involved in prostate cancer pathogenesis and may represent a useful marker to identify high risk and highly rearranged localised prostate cancer.

Gilles LAVERNY (Institut de Génétique et de Biologie Moléculaire et Cellulaire, Illkirch)

'Role of HIF1A signaling in aggressive prostate cancers'

Prostate cancer (PCa), when locally confined, is of good prognostic, but the current treatments affect the quality of life. Therapies of advanced PCa are based on the inhibition of androgen receptor signaling. However, the majority of PCa-related deaths are due to a metastatic disease and no curative treatment is currently available, as patients will develop resistances. Thus, there is a need for a better characterization of PCa progression to aggressive and metastatic forms to improve patients care. Using genetically engineered mouse models, we have recently demonstrated that HIF1a signaling plays a key role during prostate tumorigenesis induced by Pten loss and represents a promising therapeutic target. In addition, we have unraveled that p53 loss induces prostate cancer progression by promoting epithelial cell plasticity and metastasis. However, the contribution of HIF1A signaling to the severity of aggressive tumors remains unknown. To address this question, we took advantage of the Pten/$Trp53^{(i)pe-/-}$ mouse model, in which the tumor suppressor genes Pten and Trp53 are selectively inactivated in prostatic epithelial cells at adulthood, that develop invasive adenocarcinoma and metastases. Using pharmacological and genetic approaches, we demonstrated that HIF1a signaling plays minor role in the progression of primary tumors in Pten/$Trp53^{(i)pe-/-}$ mice. In contrast, we show that HIF1a inhibition impairs the metastatic potential of these tumors. Thus, the results gained from this study improve our understanding on the mechanisms underlying PCa progression and underline the need for personalized therapies.

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Michel Kahi (C3M, Nice)

'Metabolic Reprogramming In Prostate Cancer: New Perspective From The Polyamines/Hypusination Pathway'

Tumor development and metastatic spread require substantial metabolic plasticity. Cancer cells adapt their metabolism to meet their increased bioenergetic needs, to survive, proliferate and boost their aggressiveness. Our team is working on innovating therapeutic approaches for prostate cancer by targeting mitochondrial metabolism. Prostate cancer cells rely on mitochondria to control their bioenergy. They increase the activity of their Krebs cycle to produce ATP. We have come up with a new strategic way to inhibit mitochondrial activity by targeting the polyamines/hypusination pathway. Hypusination is a unique post-translational modification of the eukaryotic translation initiation factor 5A (eIF5A) and it is required for its activity. This reaction is dependent on the polyamine spermidine and it is regulated by two enzymes, the deoxyhypusine synthetase (DHPS) and the deoxyhypusine hydroxylase (DOHH).Hypusination alleviate translational stalling of the ribosome at hard-to-translate motifs. It is involved in several cellular processes. However, the mechanism by which it is implicated in metabolism, tumor growth and metastasis is still unclear. To elucidate its role in PCa, we inhibited the enzymes that catalyze this reaction and investigated the effects on PCa cells aggressiveness and metabolism.

We have shown that inhibition of hypusination decreases PCa cell growth, cell migration and invasion. Furthermore, it decreases mitochondrial respiration and disrupts the mitochondrial network. Our metabolomic and proteomic analysis revealed a reprogramming of cancer cell metabolism and an alteration of the mitochondrial respiratory chain. We identified several proteins implicated in mitochondrial metabolism and containing ribosomal motif stalling regulated by eif5a hypusination. Interestingly, we also developed a protocol to monitor mitochondrial respiration in patient-derived tumoroids and found that the inhibition of eIF5A hypusination decreases oxygen consumption in 3D models.

Conclusions

Metabolic plasticity is important to induce and maintain PCa aggressiveness. We show that eIF5A plays a major role in reprogramming PCa metabolism. In particular, by regulating mitochondrial metabolism, which is responsible for maintaining this aggressiveness. Our results highlight a potential therapeutic opportunity for PCa that target hypusination and could be used for clinical applications.