Association pour la Recherche sur les Tumeurs de la Prostate

Session VI :
2022 ARTP Poster Prize Laureates

Despoina Pervizou (Centre d'Immunologie de Marseille-Luminy, Aix Marseille)

'Neutrophils: the immune cell population dominating murine prostate cancer'

Prostate cancer (PCa) is the most common diagnosed cancer among men of western societies, yet most immunotherapy trials were unsuccessful on PCa and the involvement of immune cells has been only recently addressed. The novelty of my PhD research lies on the deep characterization of the heterogeneity and function of immune infiltrates in healthy murine prostate and during PCa progression in PTEN (i)pe-/- mice. In this mouse model the PTEN gene is selectively ablated in prostatic luminal epithelial cells at adulthood, reproducing the occurrence and features of human PCa. The strict temporal control of PTEN depletion along with the slow tumour progression allows to characterize the immune cells in the tumour microenvironment and to test therapeutic strategies.By combining state-of-the art techniques, I established a high-resolution immune atlas of murine PCa from neoplasia to adenocarcinoma. I highlighted a massive neutrophil influx harboring immunosuppressive signature, infiltrating the cancerous epithelium and lumen, along with an increase of exhausted CD8+ T cells dominating the stromal area. Also, I noticed a heterogeneity in prostate macrophages infiltrating the prostatic epithelium and stroma, with one of the subsets increased upon PCa. Currently, I am testing immunotherapeutic approaches to control PCa by depleting the pro-tumoral neutrophils and reinvigorating the CD8+ T cells in vivo. Thus, my study elucidates the complexity of immune cell behavior in PCa and unravels potential immunotherapeutic targets to benefit the tumor immunology field.

Luce Dreno (Inserm U981, Institut Gustave Roussy, Villejuif)

'Functional, structural and binding studies of the atypical ER-Resident protein fkbp7, a potential target in chemoresistant prostate cancer'

Background: Prostate Cancer (PCa) is the second most common cancer among men worldwide. Chemoresistance still represents a major limitation in PCa latest stages such as metastatic castration resistant PCa. We previously identified FKBP7, a largely unknown FK506-Binding Protein family member, as a new potential therapeutic target in chemoresistant PCa. FKBP7 is overexpressed in chemoresistant PCa cell lines and its inhibition impacts both cell growth in vitro and response to docetaxel in vivo. We showed it interacts with the scaffolding subunit eIF4G of the translation initiation complex eIF4F, which could impact protein synthesis and cell survival.
Results: FKBP7 initially described as a luminal protein of the endoplasmic reticulum (ER) can be retro-translocated into the cytosol. This retro-translocation, that is increased in docetaxel-resistant cells, is potentiated by a panel of chemotherapies and by oxidative stress. Cytosolic FKBP7 is N-glycosylated confirming its ER origin and is not a target of proteasomal degradation confirming its functional state. Using immunoprecipitation, we identified the interacting domains between FKBP7 and the eIF4G1 isoform, including one structured HEAT domain. We next produced and purified 15N isotopically labeled recombinant catalytic domain of FKBP7 for interaction studies. NMR titration experiments showed that catalytic domain can interact with rapamycin and everolimus, two well-known FKBP ligands, but surprisingly not with the immunosuppressant FK506 that defines the FKBP family. At last, polysome profiling experiments identified a novel interaction partner for FKBP7 which is the eukaryotic small ribosomal subunit 40S.
Conclusions: Our results point out an atypical subcellular localization for the ER-resident protein FKBP7.
We propose a model in which FKBP7 could acquire new functions in the cytosol in response to several treatments, including chemotherapies, and to oxidative stress. We propose that the chemotherapy-induced oxidative stress could promote the observed FKBP7 retro-translocation in the cytosol. This model was identified in PCa but could be extended to other solid cancers. Our work indicates FKBP7 could contribute to translation regulation as a partner in a protein complex involving two actors of the translation initiation, the scaffolding subunit eIF4G1 and the small ribosomal subunit 40S.