Keynote Speaker – 01

Roles and Mechanisms of Sphingolipid Metabolism in the Regulation of Tumor Growth and Therapeutics: Implications in Personalized Cancer Chemotherapy and Tumor Immunology

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Sphingolipids, including the two central bioactive lipids ceramide and sphingosine 1-phosphate (S1P), have opposing roles regulating cancer cell death and survival, respectively, and there have been exciting developments in understanding how sphingolipid metabolism and signaling regulate these processes in response to anti-cancer therapy, including immunotherapy. Recent studies have provided mechanistic details of the roles of sphingolipids and their downstream targets in the regulation of tumor growth and response to chemotherapy, radiotherapy and/or immunotherapy using innovative molecular, genetic, and pharmacological tools to target sphingolipid signaling nodes in cancer cells. For example, structure–function-based studies have provided innovative opportunities to develop mechanism-based anti-cancer therapeutic strategies to restore anti-proliferative ceramide signaling and/or inhibit pro-survival S1P–S1P receptor (S1PR) signaling. This seminar will summarize how ceramide-induced cellular stress, including aging, mediates cancer cell death through various mechanisms involving the induction of apoptosis, necroptosis and/or mitophagy. Moreover, the metabolism of ceramide for S1P biosynthesis, which is mediated by sphingosine kinase 1 (SPHK1) and SPHK2, and its role in influencing cancer cell growth, drug resistance and tumor metastasis through S1PR-dependent or receptor-independent signaling will be highlighted. Moreover, mechanistic details of aging-mediated changes in mitochondrial bioenergetics and lipid metabolism that affect T cell function will be discussed. For example, ceramide, induced by aging stress, mediates mitophagy, and cell death; however, the aging-related roles of ceramide metabolism in regulating T cell function remain unknown. Here, we will discuss that activated T cells isolated from aging mice have elevated C14-/C16-ceramide accumulation in mitochondria, generated by ceramide synthase 6, leading to mitophagy/mitochondrial dysfunction. Mechanistically, aging-dependent mitochondrial ceramide inhibited protein kinase A, leading to mitophagy in activated T cells. This aging/ceramide-dependent mitophagy attenuated the anti-tumor functions of T cells in vitro and in vivo. Also, inhibition of ceramide metabolism or PKA activation by genetic and pharmacologic means prevented mitophagy and restored the central memory phenotype in aging T cells. Thus, these studies help explain the mechanisms behind stress-related dysregulation of T cells' anti-tumor activity that can be restored by inhibiting ceramide-dependent mitophagy. In addition, biological implications of alterations in ceramide-mediated mitophagy in cancer chemotherapy and immunotherapy regarding personalized therapy will be discussed.

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Potential Financial Conflict of Interests: Dr. Ogretmen is a Co-Founder of a small biotech company, Lipo-Immuno Tech, LLC, which has financial interests in therapeutics that are mentioned in these studies. Thus, there are potential financial conflict of interests that should be considered accordingly.

Keynote Speaker – 02

Metabolic Aspects of Cholangiocarcinoma Stem-Compartment

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Metabolic reprogramming is a hallmark of cancer and allows tumor cells to meet the increased energy demands required for rapid proliferation and metastasis. Several recent studies have explored the metabolic plasticity of cancer cells with the aim to identify new druggable targets, and therapeutic strategies aimed to limit the access to nutrients. Cholangiocarcinoma (CCA) is a deadly tumor without an effective therapy represents thus representing an unmet medical need. Cancer stem/initiating cells (CSCs) are highly drug- resistant but little is known regarding metabolic profiles of CSC and their functional role.

Our studies aim to explore the contribution of mitochondria-related metabolism with particular attention to the role of glucose and lipid metabolic pathways in the maintenance of stemness state.

We have recently demonstrated that the stem-subset of CCA cells, enriched by 3D sphere culture (SPH) revealed a more efficient respiratory phenotype than parental cells. Indeed, alteration of the integrity of the mitochondrial respiratory chain with metformin or downregulation of PGC1α (SR-18292) in the stem-subset of CCA cells severely impair tumor progression, demonstrating a crucial role of OXPHOS in CCA aggressiveness. These data indicate that, besides a general increase in glucose dependency, CCA displays a marked metabolic plasticity, and different pathways may be activated in various cell subtypes within the tumor mass, due to the different availability of nutrients. OXPHOS metabolism is crucial to sustain CCA stemness and the acquisition of a phenotype prone to metastatic dissemination.

Moreover, in CCA-SPH, expression levels of several key genes involved in fatty acid synthesis (i.e. FASN) and transport were upregulated. Notably FASN expression levels correlate with OS in iCCA patients. In vitro FASN depletion by orlistat or siRNA decreased sphere forming capability and expression of stem-like markers. Notably, in CCA xenograft model, growth of SPH derived tumors treated with orlistat was significantly lower than control.

The overall objective of our studies is to determine CSC-specific metabolic and mitochondrial-associated pathways regulating CCA initiation, progression and drug-response. The results of these studies are likely to expand the spectrum of therapeutic targets in CCA.

Keynote Speaker – 03

Polygenic Risk Score (PRS) for Cancer - Can It Deliver on the Promise of Precision Oncology?

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Public health strategies aimed at disease prevention or early detection and intervention have the potential to advance human health worldwide. However, their success depends on the identification of risk factors that underline disease burden in the general population. Acordingly, large-scale genotyping and phenotyping efforts, including biobanks, have revolutionized our understanding of the genetic architecture of human traits and diseases. Years of ever-larger genome-wide association studies (GWAS) have identified dozens or even hundreds of common single nucleotide polymorphisms (SNPs) associated with many complex diseases, including common cancers, e.g., breast cancer and prostate cancers. Combining genetic and clinical data and translating findings from GWAS to clinical utility in terms of informative risk prediction profile of complex traits is an important ambition of precision medicine that aims to improve human health. Against this backdrop, polygenic risk scores (PRS) that aggregate the effects of many genetic variants across the human genome into a single score can provide useful information for personalized risk stratification and disease risk assessment, especially when combined with non-genetic risk factors. This presentation aims to provide various perspectives on the application of PRS for different types of cancer, particularly, breast and prostate cancer.

Keynote Speaker – 04

Comprehensive Genomic Profiling for Precision Oncology

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Comprehensive genomic profiling assays have become a key cornerstone for today's clinical decision making in precision oncology. In this context, NGS sequencing results are often discussed at molecular tumor boards, where amongst other oncologists, pathologists, bioinformaticians, and geneticists discuss these results to decide on the best treatment options for a patient. However, with the increasing size and complexity of NGS cancer panels, NGS results have become challenging to interpret, especially if presented merely in the form of a written report. Manual analysis of several mutations from a comprehensive NGS cancer panel is time-consuming and often incomplete. Here I will describe the complexity on the example of the FoundationOneCDx assay and present the Molecular Tumor Profiling Pilot (MTPpilot) software, which provides automated annotation, linking and interactive visualization to support the interpretation of NGS results at molecular tumor boards.