CANCER SCIENCE
INSTITUTE OF SINGAPORE

RESEARCH MEETINGS

16 June 2017, Friday I 12pm – 1pm

LT36, Level 3, Centre for Translational Medicine (MD6)

14 Medical Drive, Singapore 117599

Shreya Kar I PhD Student, Dr Alan Prem Kumar's Group (L11)

PPARγ-Annexin A1 Axis in the Dynamics of Macrophage Polarization in Breast Cancer

Tumor-associated macrophages (TAMs) choreograph various aspects of the tumor microenvironment. Macrophages exhibit cellular plasticity and can be polarized to M1/M2 subtypes in presence of different microenvironment "signals". Peroxisome proliferator-activated receptor gamma (PPARγ), a ligand-activated transcription factor expressed in macrophages, has been shown to polarize macrophages towards the M2 phenotype. Annexin A1 (ANXA1), an anti-inflammatory protein is highly expressed in metastatic breast cancer. Clinically, we found that M2 TAMs were highly enriched in Claudin-low breast cancer subtype and was strongly associated with PPARγ and ANXA1 expression. In the MMTV mouse model, TAMs were higher in the breast tumors compared to the mammary tissues. Additionally, BMDMs from ANXA1+/+ mice skewed to a M2 TAM-like phenotype upon co-culture with invasive breast cancer cells. Interestingly, BMDMs from ANXA1-/- mice failed to polarize in the same experimental set-up. Surprisingly, in presence of breast cancer conditioned media, PPARγ expression was greatly reduced in ANXAI-/- BMDMs. Our study show for the first time a role ANXA1 in promoting PPARγ expression and therefore its activity which is critical for macrophage polarization. Further studies are underway to explore the signaling mechanism involved in governing this dynamic process.

Fernando Bellido Molias I Research Fellow, Dr Polly Chen's Group (L12)

The Impact of Antisense RNAs on Hepatocellular Cancer Development

The term '*Antisense (AS) RNA*' includes all those RNAs transcribed from the opposite DNA strand of a gene. Some of these AS RNAs have been found to modulate the expression of protein-coding genes both in a transcriptional and in a post-transcriptional manner. As of today, the detailed expression profile of the AS RNAs and their functions in hepatocellular cancer (HCC) remains unclear. In order to shed light on this question, we conducted a strand-specific high-throughput RNA sequencing (RNA-Seq) for 6 matched pairs of tumor and non-tumor liver tissues. Those AS RNAs showing the most dramatic expression changes from non-tumor to tumor tissue were considered for validation. Subsequently, taking into account the function and relevance of the overlapping sense gene, a final set of three AS RNAs (HNF4A-AS, TMEM220-AS and DLG5-AS) was selected for further study. Due to the scarcity of AS RNA annotation data obtained from the Ensembl browser, we performed the Rapid Amplification of cDNA Ends (RACE) assay to identify the full-length sequence and the most enriched isoform for each of the three selected AS. Once the sequence of the prevalent isoform was known, silencing (shRNA) and overexpression constructs were generated to investigate the role of these AS RNAs in HCC by means of liver cell lines. Currently we are carrying out these modulating expression assays.

Toh Tan Boon I Research Fellow, Dr Edward Chow's Group (L13)

The Role of G9a in Myc-driven Liver Cancer

Liver cancer is the second most common cause of cancer-related death in the world with the highest incidence in Asia. Current treatments have limited efficacy in patients with advanced HCC, and the clinically-approved neoplastic agents for the treatment of advanced HCC are Sorafenib and Regorafenib. We use the hydrodynamic transfection Myc liver tumor model to investigate the epigenetic regulation of HCC. We showed that Myc-driven liver tumors have a unique H3K9 methylation pattern with corresponding upregulation of G9a. This phenomenon was further observed in our Myc-positive HCC patient-derived xenografts (PDXs), demonstrating the clinical relevance of studying Myc and G9a. In addition, using both potent and specific pharmacological inhibitors and genetic knockdown of G9a, we were able to reduce Myc levels significantly, with concomitant increased in tumor suppressor genes important for metastasis. More importantly, we showed that HCC patients with higher Myc and G9a expression levels portend a poorer survival with lower mean survival months. Our work suggests that targeting G9a could prove to be a potential therapeutic avenue for Myc-driven liver cancer. This will increase our understanding of the underlying epigenetic mechanisms of aggressive tumor initiation as well as improving therapeutic and diagnostic options for Myc-driven hepatic tumors.