Genetics Day Poster Submission

Presenter: Juliana Cazarin de Menezes

Category: Postdoc

Authors: JULIANA CAZARIN, Siti Noor Ain Binti Ahmad Shahidan, Rachel E. DeRollo, Brian Altman

Title: THE MYC ONCOPROTEIN DRIVES CIRCADIAN CLOCK DISRUPTION IN THE LUNG: IMPLICATIONS EARLY IN LUNG CARCINOGENESIS.

Abstract: Circadian rhythms are 24-hour cycles that coordinate biological processes such as metabolism and cell division. In many human cancers, circadian rhythms are disrupted, supporting cancer growth. Non-small cell lung cancers (NSCLCs) exhibit a disrupted molecular circadian clock, and associated alterations in circadian gene expression indicate a poor prognosis. However, it remains unclear how clock disruption occurs in NSCLCs and what NSCLCs gain from this disturbance. The oncogene MYC has been functionally implicated in circadian disruption in a variety of cancer cell lines. In NSCLCs, the MYC family of oncoproteins is a key driver of carcinogenesis and is found mutated or amplified in more than 50% of the cases. However, it is unknown if MYC drives clock disruption in lung carcinogenesis and whether clock disruption is functionally required for MYC oncogenic effects. Using an organoid model generated from isolated alveolar type II cells (ATII), the cell of origin of NSCLC, we showed that MYC suppresses the expression of the core clock genes BMAL1 and Clock. In parallel, MYC decreased the expression of specific cell-lineage markers, suggesting the activation of a dedifferentiation program. Using an in vivo mouse model of NSCLC with MYC-inducible expression in ATII cells, we further demonstrated that MYC overexpression for 3 days is enough to induce an overall suppression of molecular clock genes, including BMAL1. Corroborating the in vitro data, we also observed a loss of cell-lineage markers in ATII cells and increased expression of proliferative markers such as Ki67 within the same time frame. Circadian clock pharmacological restoration in vivo, using the RORα agonist SR1078, attenuated the expression of the proliferation marker Ki67 induced by MYC in the lung, suggesting that clock disruption potentially mediates MYC oncogenic effects to some extent. Additionally, we performed CUT&TAG in a mouse lung epithelial cell line (MLE12) and identified that BMAL1 binds to the promoter of ATII identity genes (Sftpb, Abca3) and cell cycle genes (Cdk4), suggesting that the molecular clock potentially regulates lung epithelial cell identity and proliferation. Overall, our data suggest that MYC disrupts the clock of lung alveolar cells in vitro and in vivo, which might be a potential mechanism involved in MYC-driven proliferation and dedifferentiation in lung cancer. We anticipate our data to be a starting point to characterize if the MYC-driven lung tumorigenesis is dependent on clock disruption and whether targeting the molecular clock can be a therapeutic strategy to target these tumors. provides an opportunity to explore potentially conserved mechanisms by which genetic sex can regulate neuronal and behavioral responses to nutritional status.