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DISSERTATION

"Identification of the multifaceted tumor suppressive functions of miR-708-5p in lung cancer cells"

by

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Molecular Biology, Genetics, & Cancer Track

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ABSTRACT

Many cancers maintain an inflammatory microenvironment to promote their growth. Lung cancer is of particular importance, as it is the deadliest cancer. One inflammatory pathway commonly dysregulated in cancer is the metabolism of arachidonic acid (AA) by Cyclooxygenase-2 (COX-2) and microsomal Prostaglandin E Synthase (mPGES-1) into Prostaglandin E2 (PGE_2). While researchers have identified PGE_2's pro-tumorigenic functions, the mechanisms governing overexpression of COX-2 and mPGES-1 are incompletely understood. MicroRNAs (miRNAs) are important post-transcriptional regulators commonly dysregulated in cancer. Interestingly, miR-708-5p is predicted to target both COX-2 and mPGES-1. In this thesis, we explore the various tumor suppressive functions of miR-708-5p in lung cancer cells.

First, we show that miR-708-5p is underexpressed in lung cancer cells and associated with survival rates in lung squamous cell carcinoma patients. miR-708-5p also represses PGE_2 production by suppressing both COX-2 and mPGES-1 expression through targeting of their 3′ untranslated regions (UTRs). Moreover, miR-708-5p decreases lung cancer cell proliferation, survival, and migration, which can be partially attributed to miR-708-5p's inhibition of AA signaling. We also discovered that combinatory treatment of miR-708-5p and paclitaxel/erlotinib enhanced anti-tumor phenotypic effects greater than either treatment alone. Lastly, we created erlotinib and paclitaxel resistant lung cancer cells and found miR-708-5p was underexpressed in these cells compared to the parent sensitive cells. miR-708-5p treatment resensitized resistant cells to erlotinib and paclitaxel. Together, these data suggest miR-708-5p has pivotal functions in regulating pro-tumorigenic AA signaling, lung cancer cell phenotype, and chemoresistance.