Deciphering the role of fatty acid metabolizing CYP4F11 in lung cancer and its potential as drug target

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Lung cancer is the leading cause of cancer deaths worldwide with tobacco smoke as a major driver for oncogenesis. The lipid mediator 20-hydroxyeicosatetraenoic acid (20-HETE) is known to regulate the blood pressure and promotes angiogenesis in healthy individuals. However, in cancer 20-HETE promotes cell proliferation, invasion, and migration. 20-HETE is generated by members of the cytochrome P450 family 4A/F by a selective ω-hydroxylation of arachidonic acid. Intriguingly, the unselective inhibition of 20-HETE-producing CYP4 enzymes reduces the lung cancer tumor growth in xenograft mouse models. We conducted a bioinformatic analysis and found that the isoform CYP4F11 is the only ω-hydroxylase which is significantly overexpressed in patients with lung squamous carcinoma. However, the exact role of CYP4F11 in lung cancer and its potential as drug target has not been established yet.

We hypothesize that CYP4F11-mediated 20-HETE production contributes to lung cancer cell proliferation and invasion. Thus, CYP4F11 could be an exciting new drug target for lung cancer therapy. To test our hypothesis, we pursue two strategies. First, we conduct cell culture studies to examine the role of CYP4F11 in lung cancer. For this, we performed a transient knockdown of CYP4F11 in lung cancer cell lines to assess the impact of CYP4F11 on cell proliferation, invasion, and migration. We found that lung cancer cell proliferation of the CYP4F11 knockdown cells was significantly decreased compared to wild type cells indicating a pivotal role of CYP4F11 in lung cancer. Excitingly, the addition of exogenous 20-HETE to the CYP4F11 knock down cells could rescue cell proliferation indicating that CYP4F11 mediated 20-HETE production impacts cancer cell proliferation. We then conducted cell migration and invasion assays and observed that a CYP4F11 knockdown attenuates the migration and invasion of lung cancer cells which emphasizes the high potential of CYP4F11 as drug target.

Second, we perform a preliminary screening for compounds inhibiting CYP4F11 which provides valuable information for lung cancer drug design. For this, we use a three-step strategy. Using recombinant human CYP4F11, we conduct spectroscopic ligand binding assays to determine compounds with a high affinity to CYP4F11. Subsequently, the half-maximal inhibitory efficiency (IC50) of compounds with a nanomolar dissociation constant (Kd) will be determined. Lead compounds will then be cross evaluated in lung cancer cell lines to test their impact on cell proliferation. Using this strategy, we could successfully evaluate the CYP4A/F inhibitor HET0016 which non-selectively inhibits 20-HETE production. In spectroscopic ligand binding studies, HET0016 shows high affinity to recombinant CYP4F11. We then examined the impact of HET0016 on lung cancer cell proliferation and found that it attenuates cell proliferation in a dose dependent manner. Using this strategy, additional compounds, such as azoles and fatty acid amides, are currently evaluated.

We aim to further establish the role of CYP4F11 in lung cancer and the underlying mechanism. Furthermore, we are invested to promote the exploitation of CYP4F11 as therapeutic target for a transformative lung cancer treatment option.

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