**Lung Adenocarcinoma (LADC)** is a form of Non-Small lung cancer in which tumor cell growth is aggressive and invasive, often leading to death. As a result, treating this disease in its early stages are especially important. As an alternative to chemotherapy, targeting oncogenes that motivate cell proliferation in epithelial tissue in the lung can enhance treatment. Tyrosine Kinase Inhibitors (TKIs) that repress tumor growth in cells expressing mutated Epidermal Growth Factor Receptor (EGFR) genes have been found to have a significant response rate4. Although these anticancer agents have been used clinically, most patients eventually developed resistance towards TKIs. For example, many patients with LADC, even those who initially responded to the treatment, showed rapidly acquired resistance towards Osimertinib, Erlotinib and Gefitinib, which are commonly used inhibitors of EGFR3. Somehow working around acquired resistance could optimize TKI treatment for LADC. One promising lead is that levels of cells undergoing epithelial–mesenchymal transition (EMT) in LADC patients are related to sensitivity to TKIs2. EMT is a process by which epithelial cells lose their cell polarity and cell-cell adhesion and gain invasive tendencies to become mesenchymal stem cells. For example, the T790M, a deletion in exon 19 of EGFR has been suspected as a driver of EMT and TKI resistance4. Deletions in the exon 19 portion of EGFR as well as L858R mutations are common in many LADC patients, but TKI sensitivity hasn’t been thoroughly in vivo4,2. *It’s still unclear how different mutations of EGFR influence this invasive phenotype and thereby their sensitivity to TKIs in tumor microenvironments.*

**My objective** is to whether TKI sensitivity is dependent on various EGFR mutants corresponding to different levels of EMT or *invasive phenotype*. The **long-term goal** of this study is to find better means to treat LADC cases that would eventually become resistant to TKI treatments. I **hypothesize** that sensitivity to TKIs is dependent on the invasive phenotype associated with known EGFR mutations or combinations thereof.

**Aim 1: To identify EMT-motivated mutations in conserved regions of EGFR amongst model organisms.**

**Approach:** Ensemble and NCBI Homologene will provide known homologs of the EGFR gene. Following that, ClustalOmega will be used to align protein sequences. Any amino acid that is conserved among organisms could display different EGFR mutations, like L858R or TM790M1. Model organisms determined from the preceding method; namely EGFR-Induced Lung Tumor Drosophila will be studied to determine the invasive phenotype characteristics of EMT. Comparing EMT markers, like E-adherin2, between wildtype flies and transgenic Drosophila (as well as transgenic Drosophila non-tumor tissue) with tumor motivating EGFR mutations can determine the progression of the mesenchymal transition. The mobility of these cells against non-EGFR could be visualized with epitope tags to further quantify EMT progression. This will verify which combinations of EGFR mutations could characterize early LADC tumor development in humans.

**Hypothesis:** Mesenchymal versus Epithelial cell characteristics exhibiting combinations of both rate and common mutations found in Humans and Zebrafish show different levels of EMT progression in Drosophila.

**Rationale:** EMT may might contribute to tumor sensitivity to TKIs2. However, there doesn’t seem to be a consensus on how common mutations of EGFR actually motivate the invasive phenotype. An observational experiment of cell proliferation and migration may demonstrate the combinatorial or isolated effects of EGFR mutations. Furthermore, constitutively expressed EGFR have been used to induce an effective LADC models in Drosophila, which could be combined with CRISP/Cas9 knockouts of other known mutation positions in the Drosophila genome5. This could yield a better understanding of the important parts of EGFR that may contribute to EMT and thereby TKIs.

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