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Investigating potential drugs against the acquired resistance to EGFR Inhibitors based on Single-Cell Analysis

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Lung cancer, particularly non-small cell lung cancer (NSCLC), is a leading cause of cancer-related deaths globally. A major challenge in its treatment is the acquired resistance to targeted therapies, such as Epidermal Growth Factor Receptor (EGFR) inhibitors. Single-cell analysis, a breakthrough in cancer research, shedding light on tumor heterogeneity and pinpointing cell subpopulations responsible for drug resistance, including dormant drug-resistant persistent cells (DTPs) and proliferating drug-resistant extended persistent cells (DTEPs). In this study, we utilized single-cell transcriptomics to investigate potential drugs that could counteract resistance development in NSCLC cells treated with erlotinib, an EGFR inhibitor. This analysis revealed dynamic shifts in cell population composition and their associated transcriptome signatures. By employing a Connectivity Map (cMap)-based drug repositioning strategy, we identified drugs capable of reversing these signatures. We found that topoisomerase inhibitors (mitoxantrone, idarubicin, camptothecin, and epirubicin) serve as potent early-stage treatments for DTPs, while inhibitors targeting RSKs (BI-D1870 and LJI-308) and CDKs (AZD-5438 and CINK-4) show promise in later stages for DTEPs. These distinct patterns highlight the need for different strategies to counteract resistance mechanisms. Our findings pave the way for personalized treatment strategies based on a patient's resistance profile and tumor characteristics.