Two Novel Single-cell Algorithms Elucidate the Therapeutic Potential of Clinically-relevant Small-molecule Inhibitors for Targeting Cancer Metastasis

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Cancer metastasis poses a significant threat to global public health, accounting for an estimated 90% of cancer-related deaths, due to a lack of effective anti-metastatic agents. The overexpression of coactivator-associated arginine methyltransferase 1 (CARM1), a coregulator of transcription, has been implicated in metastatic breast cancer, and is thus a target for selective inhibition. Three promising small-molecule CARM1 inhibitors are EZM2302, TP-064, and SKI-73. The effect of EZM2302 and TP-064 on metastatic breast cancer subpopulations is unknown. This study found that the only published algorithm that can fill this gap unexpectedly fails to identify subpopulations depleted by two CARM1 inhibitors. Consequently, this study introduces two novel single-cell algorithms to classify the perturbation of cancer subpopulations to small-molecule inhibitors. These algorithms are applicable to any cancer type with demonstrated epigenetic plasticity. Single-cell RNA sequencing data of breast cancer cells treated with CARM1 inhibitors, and their corresponding control compounds, was used. While EZM2302 and TP-064 failed to target identified metastatic subpopulations, SKI-73 exhibited a noticeable anti-metastasis effect, supporting published literature, and should be considered for animal testing. Related ancillary findings were the novel identification of potential off-target effects for control compounds EPZ029751 and TP-064N, and differences in clustering between versions of the Seurat R package. Overall, this study provides two single-cell algorithms that can categorize the perturbation of cancer subpopulations to small-molecule inhibitors, identify the specific effect on metastatic subpopulations, and thus recommend well-performing inhibitors for future clinical research.

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