Spatial Pseudotiming and Adaptive Gradient Encoding: A Novel Framework for Early Metastatic Trajectory Inference and RNA-Based Therapeutic Intervention

Yadalam, Nidhi (School: Jesuit High School)

Lung cancer remains the leading cause of cancer-related mortality, primarily due to its high metastatic potential and difficulty of early detection. Current clinical approaches rely on low-sensitivity assessments for early-stage metastases, often detecting spread only after it occurs. Building on prior work predicting metastatic risk, this system conceptualizes metastasis as a gradual spatial progression rather than a sudden transition. Leveraging spatial transcriptomics, the model captures cellular interactions missed by traditional methods, identifying high-risk tumor regions and metastatic drivers. A semi-supervised graph-based pipeline was developed, integrating spatial adjacency modeling, variational autoencoders, clustering, and pseudotime reconstruction. This approach generated (1) a Metastasis Risk Score (MRS) and (2) a continuous Metastatic Progression Gradient (MPG) that quantifies localized metastatic trajectory prior to critical transition points, pinpointing crucial genetic targets. In-silico validation demonstrated strong predictive performance, with spatial concordance to invasive tumor boundaries and stability across datasets. An ML-guided lipid nanoparticle optimization pipeline using combinatorial chemistry and a custom variational autoencoder was enhanced from earlier research, designing RNA-loaded formulations targeting prioritized pathways. The deep-learning model improved the stability and efficiency of siRNA delivery candidates. Subsequent in-vitro validation demonstrated high stability and biocompatibility in cell lines, supporting scalable, personalized therapeutic suppression. By shifting treatment from late-stage intervention to proactive, gene-targeted suppression, this work presents a novel precision nanomedicine framework.

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