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RECONCILING MOLECULAR AND HISTOLOGICAL TUMOR HETEROGENEITY TO PREDICT CANCER EVOLUTION

Intra-tumor heterogeneity (ITH) leads to a rapidly evolving disease, often preventing durable therapeutic responses. Multi-regional analyses of the same tumor have allowed exploring tumor evolution and its clinical impact in individual patients and tumor types. However, these approaches often relied on randomly sampled regions, which lacked distinctive phenotypes, and focused on genetic variants. Hence, the interplay between genetic and epigenetic modifications in cancer evolution is largely unexplored and given the high ratio of passenger vs. driver mutations, genetic heterogeneity might not reflect functional heterogeneity. In parallel, histopathology analyses have discovered in several tumor types intra-tumor regions where cancer cells exhibit heterogenous morphology and growth patterns (cell patterns or CPs). However, their molecular features and dynamic emergence are unknown. Here, we hypothesize that CPs are identifiable milestones of tumor evolution and the key to design a novel experimental and computational strategy to capture and decipher functional ITH. CPs can be traced over time and space, compared among patients, and have been associated with tumor stage and aggressiveness. Using lung cancer as a model, we will generate and integrate multi-omics profiles of intra-tumor CPs and single cells with the design of algorithms and machine learning models to: 1) determine the genetic and epigenetic evolution of human tumors and predict when they converge; 2) define the biological pathways and evolutionary trajectories giving rise to distinct CPs; and 3) map ITH to the tumor spatial architecture and microenvironment, to estimate the contribution of Darwinian selection and adaptive response to CP emergence and expansion. The success of this project will provide critical insight into lung cancer functional and prognostic heterogeneity, and, beyond that, a new paradigm to explore cancer evolution.