

Editorial

Dissecting and targeting the heterogeneity and plasticity of the tumor ecosystem

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Primary tumors are abnormally developed and dysregulated organs that comprise a unique ecosystem. Disseminated and metastatic cancers represent a systemic disease that often reflects the macro- and microenvironments of the 'soil' organs. In both settings, in addition to malignant cells, there are myriad of non-cancer cells that are inter-mingled with and frequently overshadow the tumor parenchyma. These include stromal cells (different subtypes of fibroblasts, smooth muscle cells, myofibroblasts), immune and inflammatory cells (both innate and adaptive), vasculature cells (blood vessel endothelial cells, pericytes, lymphatic and glymphatic endothelial cells), neuronal and neural cells and nerves. These non-malignant cells constitute the so-called tumor micro-environment or TME, and they constantly cross-talk to cancer cells during progression and therapies and play intricate roles in developing treatment resistance and mediating cancer relapse. Strikingly, the tumor ecosystem also exhibits sex- and aging-associated differences and dynamics. Technical advances in the past decade, especially single-cell multi-Omics (e.g., scRNA-seq, scATAC-seq, snRNA-/ATAC-seq), spatial Omics (spatial transcriptomics and spatial proteomics), and multi-spectral imaging platforms (e.g., IMC, Vectra, Phenocycler), have generated unprecedented details about the cellular (and extracellular) compositions of the tumor ecosystem, and have identified numerous novel therapeutic targets. In this Special Issue with a broad theme "**Dissecting and Targeting the Heterogeneity and Plasticity of the Tumor Ecosystem**", we have collected manuscripts (Reviews, Perspectives, Research Articles) that:

- **Report** the heterogeneity and plasticity of cancer cell subpopulations as well as non-cancer cell types including stromal, neural and immune/inflammatory cells
- **Elucidate** evolutionary dynamics of and interactions/relationships between cancer cell and stromal/immune cell subpopulations
- **Dissect** molecular, transcriptomic, epigenetic/epigenomic, and cellular mechanisms driving the cellular plasticity and cell state transitions in both cancer and non-cancer cell compartments

- **Report** and **dissect** the heterogeneity of extracellular and systemic factors in cancer patients including (but not limited to) CTCs, cfDNAs, ctDNAs, and EVs
- **Demonstrate** how the cellular heterogeneity and plasticity impact and promote cancer progression, therapeutic resistance, and metastasis
- **Expound on** sex and aging as important biological variables associated with and driving the evolution of cancer ecosystem
- **Develop and summarize** novel therapeutic strategies, particularly immunotherapeutic approaches (e.g., BsAb, ADC, BiTE, CAR-T), that aim to target the cancer ecosystem including the tumor immune microenvironment.

We hope that you will be as excited as we are reading through these timely papers!

Declarations

Competing Interests

Dean G. Tang is the Editor-in-Chief, and Justin D Lathia is a member of the Editorial Board of the journal *Cancer Heterogeneity and Plasticity*. The authors were not involved in the journal's review of or decisions related to this manuscript. The authors have declared that no other competing interests exist.