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Single-Nucleus Chromatin Accessibility Profiling Reveals Distinct Epigenetic Landscapes and Transcription Factor Regulation Across Thyroid Cancer Subtypes

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Thyroid cancer is a highly heterogeneous disease, with its characteristics varying depending on various mutations. To understand this complexity, numerous studies have been conducted at the transcriptome level, yet the epigenetic landscape remains poorly understood. In this study, single-nucleus ATAC-seq (snATAC-seq) was obtained from 9 samples of three different subtypes including follicular thyroid cancer (FTC), papillary thyroid cancer (PTC), and anaplastic thyroid cancer (ATC). Malignant epithelial cells were classified based on established thyroid cancer–related gene sets, revealing heterogeneous subtype distributions. Cancer cells were classified using well-established thyroid cancer-related gene sets, revealing heterogeneous distributions across cancer subtypes and patient samples. Identification of cell type-specific transcription factors revealed unique regulatory mechanisms shaping cellular identity and tumor behavior. Enhancer-driven regulation varied by cell type, and promoter-enhancer interactions supported by predicted Hi-C data indicated changes in 3D genome structure. Integration of external methylation datasets demonstrated associations between chromatin accessibility at CpG sites and DNA methylation status. This study provides an understanding of the distinct epigenetic regulation of thyroid cancer subtypes and is expected to contribute to the development of subtype-specific therapeutic strategies.