

**Seminar abstract**

The primary function of the thyroid gland is the synthesis and release of thyroid hormones, which are essential for health from embryogenesis to adulthood. Thyroid disorders occur frequently and include congenital hypothyroidism, which occurs due to aberrant thyroid development (thyroid dysgenesis) or impaired hormone synthesis and is particularly prevalent in trisomy 21 (T21). In contrast, thyroid carcinoma, an acquired disorder, is the most common endocrine malignancy in both paediatric and adult populations. Understanding the molecular basis of thyroid dysgenesis and paediatric thyroid carcinoma remains challenging, and requires an improved understanding of fetal thyroid development. To address this, we generated a comprehensive spatiotemporal atlas of the human thyroid during the first and second trimesters of pregnancy. Profiling over 200,000 cells with single-cell sequencing revealed key cell types involved in thyroid gland development, including the hormone-producing thyrocytes. We discovered that fetal thyroid follicular cells are heterogeneous epithelial populations consisting of two main functional subtypes (fTFC1, fTFC2), with fTFC2 expressing increased levels of PAX8, and spatial transcriptomics revealed subtype co-occurrence within individual follicles. While both fTFC1 and fTFC2 persist in adult thyroid, fTFC2 is a minor population amongst additional PAX8-positive follicular cell subsets. We observed thyroid dysgenesis in T21 age-matched specimens, and T21 thyrocytes showed transcriptional signatures of cytoskeletal disorganisation and altered interactions with the extracellular matrix, as well as compensatory activation of metabolic stress gene programs and upregulation of thyroid biosynthetic genes. In line with the altered proportions of fTFC2 in healthy fetal and adult thyroid, papillary thyroid cancer in children is transcriptionally enriched for the fTFC2 signature compared to that in adults. All together, these findings reveal thyrocyte heterogeneity across the lifespan and provide insights into thyroid development in health and disease, informing potential therapeutic interventions.