Cancer-associated fibroblast-derived periostin promotes papillary thyroid tumor growth through integrin-FAK-STAT3 signaling

Theranostics 2024; 14(7):3014-3028

Presenter : Yi-Hsuan Hsu Date /Time:2025/10/23,16:20-17:10

Commentator: Shih-Chieh Lin, Ph.D. Location: Room 601, Med College Building

Background: Thyroid cancer is the most common endocrine malignancy, accounting for approximately 3% of all cancer cases worldwide. Among its subtypes, papillary thyroid cancer (PTC) represents nearly 80% of all cases. Although the overall prognosis for most PTC patients is favorable, with a 5-year survival rate exceeding 90%, a small subset of patients develops aggressive disease characterized by local invasion, distant metastasis, or recurrence, resulting in poor outcomes. The tumor microenvironment (TME) is a complex system composed of tumor cells surrounded by cancer-associated fibroblasts (CAFs), immune cells, endothelial cells, extracellular matrix (ECM), and soluble factors. Within the TME of thyroid cancer, CAFs remodel the ECM and create a tumor-supportive niche, playing a crucial role in cancer progression. Periostin (POSTN) is an important ECM protein frequently upregulated in various tumor microenvironments, but its specific role in thyroid cancer progression remains unclear.

Objective: To demonstrate the mechanisms through which POSTN promotes papillary thyroid tumor growth.

Result: The authors used Postn and Rag1 knock-out mice and orthotopic mouse models to determine the role of POSTN on papillary thyroid tumor progression and examined how POSTN affects papillary thyroid tumor growth. They used immunofluorescence, cell co-culture, fluorescence in situ hybridization (FISH), chromatin immunoprecipitation (ChIP), recombinant proteins, and inhibitor treatments to explore the underlying molecular mechanisms. First, they found POSTN was up-regulated in papillary thyroid tumors and negatively correlates with the overall survival of patients with thyroid cancer. And they proved that CAF-derived POSTN promotes papillary thyroid tumor growth in vivo and in vitro, while the loss of POSTN in CAFs significantly reduces tumor growth ability. Mechanistically, POSTN enhanced tumor cell proliferation and IL-4 expression through the integrin-FAK-STAT3 signaling pathway. In turn, tumor cell-derived IL-4 activated CAFs and stimulated POSTN expression by activating STAT6, thereby forming a positive feedback loop. The results showed the development of papillary thyroid tumors could through the pathway: POSTN-integrin-FAK-STAT3-IL-4 pathway in tumor cells and IL-4-STAT6-POSTN signaling in CAFs.

Conclusion: These findings show the significance of POSTN and IL-4 as critical molecular mediators in the dynamic interplay between CAFs and tumor cells, driving papillary thyroid tumor progression through a POSTN – integrin – FAK – STAT3 → IL-4 → STAT6 → POSTN feedback loop.