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Research Paper

SOX13/TRIM11/YAP axis promotes the proliferation, migration and chemoresistance of anaplastic thyroid cancer

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Abstract

Anaplastic thyroid cancer (ATC) is one of the most aggressive and virulent solid tumors. The ubiquitin proteasome system presents in all eukaryotic cells and is essential for cellular homeostasis. While its underlying role in ATC remains largely unclear. TRIM11 is an E3 ubiquitin ligase and has been reported to act as an oncogene in several human cancers. The present study aims to reveal the oncogenic function of TRIM11 in ATC. Western blot was used to measure the protein expression of TRIM11 and YAP, while the YAP target genes were measured by real-time PCR. CCK8 assay was used to detect cell viability; wound-healing assay and transwell assay were used to measure the migration ability of ATC. The xeno-graft tumor model was used for *in vivo* study. Immuno-precipitation assay was used to detect the interaction domain between YAP and TRIM11. And the ubiquitin-based Immuno-precipitation assays were used to detect the specific ubiquitination manner happened on YAP. TRIM11 depletion significantly decreases cell proliferation and migration capabilities of ATC cells, and elevates cell sensitivity to chemotherapy, which effect could be further rescued by YAP overexpression. TRIM11 depletion decreases YAP protein level and YAP/TEAD target genes, such as CTGF, ANKRD1 and CYR61 in ATC. Indicating that TRIM11 is a regulator of Hippo signaling pathway. Immuno-precipitation assay shows that the RING domain of TRIM11 is essential for the interaction with WW domain of YAP. Further mechanistic analysis suggests that TRIM11 promotes the mono-ubiquitination of YAP, thus prolongs its protein half. Furthermore, TRIM11 promoter analysis revealed that SOX13 activates TRIM11 transcription by binding to the promoter of TRIM11. In summary, our study describes the oncogenic function of TRIM11 in ATC, which acts as a post-translational modulating factor of Hippo pathway. Targeting TRIM11 may be a potential therapeutic method for ATC treatment.

Key words: anaplastic thyroid cancer; TRIM11; YAP; stabilization; mono-ubiquitination

Introduction

Thyroid cancer ranks in ninth place in malignancy worldwide. It is the most commonly diagnosed endocrine malignancy, accounting for more than 90% of all endocrine cancer cases [1, 2]. Based on the histopathological features and the degree of differentiation, thyroid cancer has been divided into three major categories: well-differentiated thyroid cancer (WDTC) which includes papillary thyroid cancer and follicular thyroid cancer; poorly-differentiated thyroid cancer (PDTC) and undifferentiated/anaplastic thyroid cancer (ATC) [3]. Well differentiated thyroid cancer is the most common thyroid cancer, accounting for approximately 90% of all cases. It is one of the most indolent tumors, which exhibits excellent prognosis with > 98% 5-year survival [4-6]. ATC is a small subset of thyroid cancer. It accounts for only 2-5% of thyroid cancer [7-9]. Due to the high proliferation rate and invasive behavior of ATC, it is responsible for 40-50% of total thyroid cancer-related deaths. Median survival of ATC patients is 3 to 5 months. 1-year survival rate is estimated at 10-20% [10-12]. ATCs rarely respond to the conventional treatment such as radioactive iodine and chemotherapy, and treatment options of ATC remain limited and largely ineffective [13].