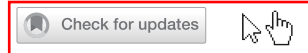


ARTICLE OPEN




USP26 promotes anaplastic thyroid cancer progression by stabilizing TAZ

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Anaplastic thyroid cancer (ATC) is one of the most lethal and aggressive human malignancies, with no effective treatment currently available. The Hippo tumor suppressor pathway is highly conserved in mammals and plays an important role in carcinogenesis. TAZ is one of major key effectors of the Hippo pathway. However, the mechanism supporting abnormal TAZ expression in ATC remains to be characterized. In the present study, we identified USP26, a DUB enzyme in the ubiquitin-specific proteases family, as a bona fide deubiquitylase of TAZ in ATC. USP26 was shown to interact with, deubiquitylate, and stabilize TAZ in a deubiquitylation activity-dependent manner. USP26 depletion significantly decreased ATC cell proliferation, migration, and invasion. The effects induced by USP26 depletion could be rescued by further TAZ overexpression. Depletion of USP26 decreased the TAZ protein level and the expression of TAZ/TEAD target genes in ATC, including CTGF, ANKRD1, and CYR61. In general, our findings establish a previously undocumented catalytic role for USP26 as a deubiquitinating enzyme of TAZ and provides a possible target for the therapy of ATC.

Cell Death and Disease (2022)13:326; <https://doi.org/10.1038/s41419-022-04781-1> 

INTRODUCTION

Thyroid cancer is the most commonly diagnosed endocrine-related malignancy. Depending on the degree of differentiation, thyroid cancer has been traditionally categorized as either differentiated thyroid carcinoma (DTC) or undifferentiated/anaplastic thyroid carcinoma (ATC) [1]. DTC comprises of more than 90% of all thyroid cancers, including papillary and follicular carcinoma. This group of thyroid cancer exhibits good prognosis with >98% five-year survival [2]. ATC is a small subset of thyroid cancer. It is rare but extremely aggressive. Although ATC accounts for approximately 1–2% of thyroid cancers, it is responsible for half of thyroid cancer related deaths [3, 4]. Unlike normal follicular cells, ATC cells do not retain the biological functions such as iodine uptake and thyroglobulin synthesis, it is inherently resistant to both conventional chemotherapy and radioactive iodine. To date, there exist no effective therapies to cure or to prolong the survival of patients with ATC [5].


The Hippo pathway is an evolutionarily conserved pathway which was initially identified from *Drosophila* [6]. WW domain-containing transcription factor (WWTR1 or TAZ) and Yes-associated protein (YAP) are the two major downstream effectors. As transcriptional co-activators, YAP and TAZ mediate the biological functions of the Hippo pathway by regulating gene transcription [7]. The activity of YAP and TAZ can also be regulated in a Hippo-independent manner, which is composed of a kinase cascade: the upstream kinase MST1/2 promotes LATS1/2 phosphorylation and activation, leading to YAP/TAZ phosphorylation and inducing its cytoplasmic retention and subsequent β -TrCP-mediated proteasomal degradation. When Hippo signaling is off,

YAP/TAZ enter the nucleus, and recruit other factors, such as TEAD and RUNX to activate genes involved in cell proliferation, migration, survival, and metabolism [8–10]. The dysregulation of Hippo pathway is thought to play a crucial role during tumor invasion and metastasis. YAP and TAZ are frequently activated in a variety of human malignancies. The activation of YAP/TAZ can promote cancer cell proliferation, metastasis, chemoresistance, and cancer stem cell-features, making them promising therapeutic targets in cancer [11]. While the underlying mechanisms regarding YAP/TAZ activation or overexpression in malignant tumors have not been well defined.

Accumulating studies indicate that the Hippo pathway is tightly modulated by the ubiquitin–proteasome system. A number of E3 ligases, such as PRAJA, ITCH, SIAH2, FBW7, and WWP1 are shown to play an essential role in controlling the abundance of several Hippo pathway components [12–14]. Deubiquitinases (DUBs) can reverse the ubiquitination of proteins by removing ubiquitin from the substrates. The DUBs in the human genome can be categorized into six families: ubiquitin COOH-terminal hydrolases (UCH), ubiquitin-specific proteases (USP), the JAB1/MPN/MOV34 family (JAMM), Josephins, ovarian tumor proteases (OTU), and motif interacting with ubiquitin-containing novel DUB family (MINDY) [15]. YOD1 was reported to induce LATS degradation and YAP/TAZ activation though de-ubiquitinating ITCH. The YOD1–ITCH–YAP/TAZ signaling axis would be a therapeutic target for liver cancer [16]. However, how DUBs regulate the Hippo signaling in ATC remains less well understood.

To investigate the involvement of DUBs in the Hippo pathway, we randomly selected 39 DUBs from a DUB siRNA library and

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Edited by Professor Gennaro Ciliberto

Received: 10 April 2021 Revised: 7 September 2021 Accepted: 22 September 2021

Published online: 09 April 2022