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A TIAM double hit to oppose YAP/TAZ

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Abstract

In this issue of Cancer Cell, Diamantopoulou et al. uncover dual mechanisms of inhibiting YAP/TZ by TIAM1 that oppose invasiveness of colorectal cancer cells: TIAM1 interacts with TAZ in the cytoplasm to promote TAZ degradation by the destruction complex, whereas it antagonizes binding of TAZ/YAP to TEAD in the nucleus.

In this issue of Cancer Cell, Diamantopoulou et al. describe how acquisition of migratory properties by colorectal cancer (CRC) cells is inhibited by previously unnoticed functions of TIAM1. TIAM1 is a Guanine nucleotide exchange factor (GEF) mainly known as positive regulator of Rac. In light of the critical functions of Rac as effector of oncogenic signaling, TIAM1 should also favor tumor development. Consistently, genetic inactivation of TIAM1 significantly reduces the formation and growth of benign tumors in mouse models of human familial adenomatous polyposis (e.g., Apc^{Min} mice). Surprisingly, however, TIAM1-deficient tumors progress more frequently, suggestive that TIAM1 also entails enigmatic functions as suppressor of tumor progression and cancer cell invasion (Porter et al., 2016). Consistently, TIAM1 protein expression in human CRC negatively correlates with tumor progression and positively with patients' overall survival. Searching for the molecular programs controlled by TIAM1, Diamantopoulou et al. now identify YAP and TAZ as the factors inhibited by TIAM1 and whose activity is unleashed in TIAM1-deficient tumors for intestinal cancer cell invasion (Diamantopoulou et al., 2017).

YAP and TAZ are mainly understood as effectors of the Hippo and mechanotransduction pathways, but have been recently reported to also serve as transcriptional mediators of Wnt signaling (Azzolin et al., 2012) (Azzolin et al., 2014). The central engine of the Wnt pathway is the activity of a "destruction complex", best known for its role in β-catenin degradation. In addition to β-catenin, the destruction complex also blunts YAP and TAZ, inducing their degradation and/or sequestration on the cytoplasm. Mutation of destruction complex components, such as in APC or AXIN, is a relevant oncogenic event in cancer biology, and most notably in intestinal tumors, leading to constitutive activation of the Wnt cascade. As such, APC mutations trigger nuclear accumulation of both β-catenin and YAP/TAZ; crucially, proliferation and progenitor cell expansion that epitomize aberrant Wnt signaling in APC mutants cell lines and mouse models depend on aberrant YAP/TAZ-

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dependent transcription, as YAP/TAZ inactivation blocks the effects of APC deficiency (Azzolin et al., 2014) (Cai et al., 2015).

Diamantopoulou et al. show that the activation of YAP/TAZ after APC inactivation is further increased by inactivation of TIAM1. TIAM1 protein is localized at the base of intestinal crypts but it is almost undetectable in more differentiated cells. In cells carrying a functional destruction complex, cytoplasmic TIAM1 binds AXIN, β-catenin, β-TrCP and YAP/TAZ. TIAM1 blunts YAP/TAZ by stabilizing the interaction between TAZ and β-TrCP, thus restraining TAZ overall levels and/or favoring YAP/TAZ sequestration within the complex. Treatments with Wnt ligands or GSK3 inhibitors or knockdown of APC all cause the disassembly of the destruction complex and ensuing nuclear translocation of TIAM1. In the nucleus, TIAM1 competes YAP/TAZ away from TEAD, the main DNA-binding platform for YAP/TAZ. In other words, TIAM1 is a double assurance to prevent unscheduled activation of YAP/TAZ, chasing them in both the cytoplasm and the nucleus, and blunting their activity at both sites. This is elegantly achieved by linking TIAM1 localization to the same destruction complex that controls YAP/TAZ in the cytoplasm. Thus, TIAM1 is a Wnt-responsive protein buffering the Wnt-TAZ/YAP cascade.

The association of TAZ/YAP and TIAM1 expands the repertoire of regulations of TAZ/YAP that take place in the destruction complex and are influenced by physiological or pathological activation of the classic Wnt cascade; yet, Diamantopoulou et al. have left unaddressed whether any connection exists between TIAM1 and these other layers of control. For example, YAP interaction with AXIN is mediated by SETD7-dependent methylation of YAP (Oudhoff et al., 2016); the actin regulator WIP increased YAP/TAZ stability by detaching them from the complex and targeting it to the multi-vescicular body (Gargini et al., 2016); and PKCζ phosphorylates YAP inside the complex to prevent its nuclear localization and intestinal tumorigenesis (Llado et al., 2015).

The paper also raises additional unanswered questions: How do aggressive CRCs lose expression of TIAM1? Does the recruitment of TIAM1 to the destruction complex impact on the stability of the complex itself? Could TIAM1 influence other functions of the destruction complex, for example for β-catenin degradation? Interestingly, TIAM1 depletion does not unleash an overt oncogenic transcriptional program, but it rather induces EMT, a profound change in cell shape in turn associated to acquisition of stem cell-like traits. This suggests that loss of TIAM1 might raise the tumor's cancer stem cell content, per se a potent inducer of malignancy in other tumor types. Connected to this, it is worth noting that EMT increases TAZ nuclear levels in breast cancer (Cordenonsi et al., 2011), where YAP/TAZ are instrumental for EMT-induced tumor stemness and metastasis.

APC mutations are typical of CRCs; yet, in other tumor types, *APC* may also be inactivated epigenetically, as it is the case for some form of aggressive mammary tumors displaying loss of *APC* expression by promoter methylation. It remains ground for future investigations whether TIAM1 can be considered a general modifier of tumor progression in a number of tumors displaying reduced destruction complex activity irrespectively of overt mutational events. Perhaps in support to this view, TIAM1 inactivation favors progression of otherwise-benign lesions to squamous cell carcinoma in a mouse model of skin carcinogenesis (Porter

et al., 2016). That said, TIAM1 could exhibit different roles in different cell types or oncogenic contexts: in the MMTV-NeuN-derived mammary tumors, TIAM1 inactivation in fact inhibits metastatic dissemination inviting cautions in generalizations beyond the scopes of the present study (Strumane et al., 2009).

As for CRCs, what this work leaves open for future studies is whether the classic role of TIAM1 as Rac-GEF is independent from its role as YAP/TAZ inhibitors. Should this be the case, then TIAM1 may be the subject of a dual therapeutic targeting in CRC: first inhibited to prevent Rac-driven tumor growth and then fostered to prevent YAP/TAZ-driven dissemination of CRC cells.

More immediately, the definition of molecular markers distinguishing CRCs cured after surgical resection from those that will relapse as metastatic nodules in the liver or other sites remains an unmet medical need. The correlation between TIAM-TAZ/YAP interaction and outcome in CRC identified by Diamantopoulou et al. suggest the potential for the use of these molecules as markers in prognostic stratification of CRC patients in addition to conventional clinical and histopathological staging markers.

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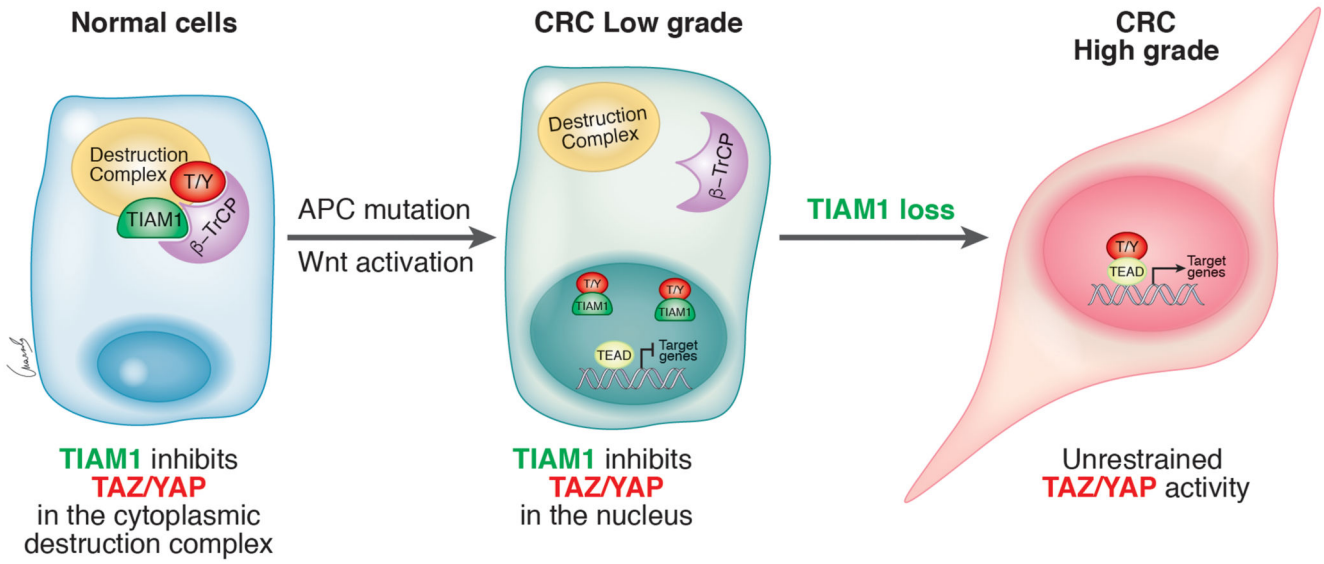

Figure 1. TIAM1 displays tumor suppressive behaviours in the colon by inhibiting YAP/TAZ both in the cytoplasm and in the nucleus.

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