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Metastasis

Major finding: TRAF4 mediates TGFβ-driven EMT and metastasis via activation of SMAD and non-SMAD signaling.

Mechanism: Recruitment of TRAF4 stabilizes membrane-bound TβRI, and ubiquitination of TRAF4 induces TAK1.

Impact: TRAF4 is associated with poor prognosis and may be a therapeutic target in breast cancer.

TRAF4 POTENTIATES TGFβ ONCOGENIC SIGNALING IN BREAST CANCER

TGFβ has been shown to function as a tumor suppressor, but can also promote invasion, epithelial–mesenchymal transition, and metastasis in advanced cancers. However, the mechanisms that specifically regulate the pro-oncogenic activity of TGFβ are poorly understood. Zhang and colleagues identified TNF receptor–associated factor 4 (TRAF4), an E3 ubiquitin ligase implicated in regulation of cell migration, as an activator of TGFβ receptor signaling. In response to TGFβ stimulation, TRAF4 transiently interacted with activated TGFβ receptor complexes and stabilized TGFβ receptor I (TβRI) at the plasma membrane. This effect was dependent on recruitment of ubiquitin specific peptidase 15 (USP15), a TβRI deubiquitinase, and TRAF4-mediated polyubiquitination and degradation of SMAD specific E3 ubiquitin protein ligase 2 (SMURF2), an E3 ligase that downregulates TGFβ/SMAD activity. In addition to this regulation of SMAD signaling, association of TRAF4 with activated TβRI induced lysine 63-linked ubiquitination of TRAF4, resulting in its interaction with TGFβ-activated kinase 1 (TAK1) and activation of downstream TAK1-regulated pathways including p38 MAPK and NF-κB, indicating that TRAF4 also potentiates non-SMAD signaling. Depletion of TRAF4 impaired TGFβ-driven cell migration and invasion and prevented induction of EMT markers and prometastatic genes by TGFβ in breast cancer cells *in vitro*, suggesting that TRAF4 is required for breast cancer progression and metastasis. In support of this idea, TRAF4 knockdown inhibited breast cancer metastasis in zebrafish and mouse xenograft models. Furthermore, *TRAF4* was amplified in human breast and ovarian tumors, and elevated TRAF4 expression was positively correlated with activated SMAD2 and TAK1 signaling and associated with decreased relapse-free survival and poor prognosis in breast cancer. These results establish TRAF4 as a critical regulator of the pro-oncogenic activity of TGFβ and suggest TRAF4 as a potential therapeutic target in breast cancer. ■

Zhang L, Zhou F, García de Vinuesa A, de Kruijff EM, Mesker WE, Hui L, et al. TRAF4 promotes TGF-β receptor signaling and drives breast cancer metastasis. Mol Cell 2013;51:559–72.

Melanoma

Major finding: MC1R binds PTEN and protects it from ubiquitination upon UV exposure in melanocytes.

Concept: MC1R variants associated with red hair, fair skin, and poor tanning do not interact with PTEN.

Impact: Some MC1R variants may increase melanoma risk because they cannot stabilize PTEN after UV exposure.

MC1R STABILIZES PTEN AFTER UV EXPOSURE

Melancortin-1 receptor (MC1R) is a melanocyte-specific G protein-coupled receptor that is activated and stimulates pigment production upon UV exposure. Naturally occurring polymorphisms in the *MC1R* gene lead to reduced pigment production in response to UV and are associated with red hair color (RHC), fair skin, and poor tanning ability. Individuals carrying such variants also have an increased risk of melanoma, but how MC1R-RHC variants might promote melanomagenesis is unclear. Cao and colleagues compared UV-irradiated human melanocytes expressing wild-type MC1R or MC1R-RHC variants and found that PTEN levels were reduced and AKT was activated specifically in cells expressing the MC1R-RHC variants. Upon UV exposure, wild-type MC1R physically interacted with the nonphosphorylated, active form of PTEN and protected it from WWP2-mediated ubiquitination and subsequent proteasomal degradation, thus preventing downstream AKT activation. In contrast, RHC-associated MC1R variants failed to bind and stabilize PTEN and inhibit AKT activation in response to UV exposure. Inactivation of MC1R and subsequent AKT hyperactivation in primary human melanocytes led to a premature senescence phenotype much like the oncogene-induced senescence caused by the oncogenic $BRAF^{V600E}$ mutation found in over half of human melanomas. However, combined inactivation of MC1R and expression of $BRAF^{V600E}$ in immortalized melanocytes led to robust proliferation, anchorage-independent growth, and *in vivo* tumor formation. Notably, the transformed phenotype could only be reversed by wild-type MC1R, but not RHC-associated MC1R variants defective in PTEN binding. In patient-derived melanoma cell lines, *PTEN* mutations and RHC-associated *MC1R* polymorphisms were largely mutually exclusive, providing further evidence that these genetic changes are functionally equivalent in melanoma. The finding that RHC-associated MC1R variants fail to inhibit AKT in UV-exposed melanocytes and can cooperate with $BRAF^{V600E}$ to drive melanocytic transformation provides a mechanistic explanation for the elevated risk of melanoma in individuals with decreased pigmentation. ■

Cao J, Wan L, Hacker E, Dai X, Lenna S, Jimenez-Cervantes C, et al. MC1R is a potent regulator of PTEN after UV exposure in melanocytes. Mol Cell 2013;51:409–22.

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AACR American Association for Cancer Research

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