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Breast Cancer

Major finding: The secreted protein TINAGL1 inhibits TNBC progression and metastasis.

Mechanism: TINAGL1 binds to EGFR and ITGB1 and respectively blocks the formation of EGFR:EGFR and ITGB1:FN complexes.

Impact: TINAGL1 is a potential prognostic biomarker and therapeutic agent for patients with TNBC.

TINAGL1 REPRESSES BREAST CANCER TUMORIGENESIS AND METASTASIS

Few therapeutic options are available for patients with triple-negative breast cancer (TNBC) due to the lack of expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (encoded by *ERBB2*), all of which are currently clinically targetable. Further, TNBC, which is highly aggressive and metastatic, frequently exhibits both innate and adaptive drug resistance. Having previously shown that ablation of the secreted extracellular matrix (ECM) protein tubulointerstitial nephritis antigen-like 1 (TINAGL1) in breast cancer cells increased metastatic lung colonization, Shen and colleagues sought to further elucidate the mechanism underlying the role of TINAGL1 in breast cancer tumorigenesis. High *TINAGL1* expression was found to be correlated with good prognosis in patients with TNBC, and weakly metastatic breast cancer cell lines exhibited higher *TINAGL1* expression than highly metastatic cell lines. Further, constitutive and inducible overexpression of *TINAGL1* or treatment with recombinant TINAGL1 (r-TINAGL1) reduced the growth and lung colonization of the LM2 cell line, a highly metastatic variant of MDA-MB-231. Immunoprecipitation–mass spectrometry profiling identified proteins involved in PI3K/AKT signaling, focal adhesion, and ECM-receptor interactions as potential TINAGL1 binding partners; coimmunoprecipitation confirmed the interactions of TINAGL1 with EGFR and integrin β1 subunit (ITGB1) and further showed that TINAGL1 interacts with integrins α5β1 and αvβ1, the two major receptors for fibronectin. Consistent with these findings, expression of *TINAGL1* or treatment with r-TINAGL1 repressed EGFR and integrin/FAK signaling in LM2 cells. Mechanistically, TINAGL1 binds to EGFR to prevent ligand-induced EGFR dimerization and binds to ITGB1 to prevent the interaction between integrins α5β1 and αvβ1 with fibronectin. Pharmacologic inhibition of FAK/integrin signaling and/or EGFR revealed that suppression of both pathways was necessary to recapitulate the level of r-TINAGL1–mediated suppression of tumor growth and metastasis. These results characterize the role of TINAGL1 in TNBC tumorigenesis and metastasis and suggest potential therapeutic approaches. ■

Shen M, Jiang Y-Z, Wei Y, Ell B, Sheng X, Esposito M, et al. Tinagl1 suppresses triple-negative breast cancer progression and metastasis by simultaneously inhibiting integrin/FAK and EGFR signaling. Cancer Cell 2019;35:64–80.e7.

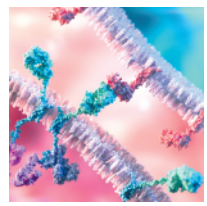
Immunotherapy

Major finding: The number and position of CD3ζ ITAMs in CD19 CAR 19-28ζ T cells controls T-cell fate.

Concept: Redundant CD28 and CD3ζ signaling drives both CD19 CAR 19-28ζ T-cell activation and exhaustion.

Impact: Optimizing the balance between T-cell effector function and memory functions is critical for CAR design.

REDUCING ACTIVATION POTENTIAL ENHANCES CAR T-CELL PERSISTENCE



CD19-targeting chimeric antigen receptor (CAR) T cells have been highly efficacious in patients with hematologic cancers; recently, it has been shown that the CD19 CAR 19-28ζ construct, which encodes for a single CD28 signaling domain and 3 CD3ζ immunoreceptor tyrosine-based activation motifs (ITAM), results in strong effector functions and limited life span of T cells. To ascertain whether modulating the redundancy of CD28- and CD3ζ-mediated signaling enhances T-cell life span without affecting potency, Feucht, Sun, and colleagues performed mutagenesis to inactivate 1 or 2 of the CD3ζ ITAMs (X) from the membrane-proximal to membrane-distal CD3ζ ITAM1/2/3 and generate the mutant CD19 CAR 19-28ζ constructs termed 1XX, X2X, XX3, and X23. Compared to parental CAR T cells, mutant 1XX T cells were more efficacious and induced long-term remission in a xenograft model of pre-B acute lymphoblastic leukemia whereas mutant X2X and X23 T cells exhibited similar antitumor efficacy, and mutant XX3 T cells were the least efficacious of all CARs evaluated. *In vitro*, XX3 CAR T cells exhibited diminished effector function compared with the other mutant and parental CAR T cells, but all single ITAM mutants exhibited increased persistence and delayed T-cell differentiation *in vivo*. CAR constructs encoding for ITAM1 or ITAM3 in the ITAM1 position exhibited similar cytotoxicity activity, decreased T-cell differentiation, and increased antitumor efficacy. 1XX-engineered naïve T cells acquired a persistent stem-like state, whereas those engineered with the parental CAR rapidly exhibited a gene signature associated with exhausted T cells, while 1XX T cells exhibited a gene signature associated with a less-differentiated T-cell state, and XX3 T cells preserved expression of naïve/memory–associated genes but failed to activate sufficient effector programs. These results suggest that defined mutations in the CD3ζ chain of the 19-28ζ CAR construct control the balance between T-cell differentiation and effector activity and suggest potential approaches to improve the efficacy of CD28-based CAR constructs. ■

Feucht J, Sun J, Eyquem J, Ho Y-J, Zhao Z, Leibold J, et al. Calibration of CAR activation potential directs alternative T cell fates and therapeutic potency. Nat Med 2019;25:82–8.

AACR American Association for Cancer Research

CANCER DISCOVERY

Reducing Activation Potential Enhances CAR T-cell Persistence

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