Targeting Trop-2 as a Cancer Driver

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The Trop-2–targeting antibody-drug conjugate (ADC) sacituzumab govitecan (SG) has been approved by the US Food and Drug Administration and European Medicines Agency for therapy of patients with breast[1] and urothelial carcinomas,[2] paving the way for Trop-2 targeting for cancer therapy. To our knowledge, Shimizu et al[3] have presented the first in-human, phase I TROPION-PanTumor01 dose-escalation study of the Trop-2–targeting ADC datopotamab deruxtecan (Dato-DXd) in non–small-cell lung cancer. In this trial, 210 patients received up to 8 mg/kg intravenously on day 1 of each 21-day cycle (once every 3 weeks) Dato-DXd. The objective response rate was 26%, with a median progression-free survival and overall survival of 6.9 months and 11.4 months, respectively. Any-grade treatment-emergent adverse events and treatment-related AEs occurred in 54% and 26% of patients, respectively. The mode of action of Dato-DXd, as well as that of SG, is inhibition of topoisomerase I in replicating cells on internalization and payload release.[4] An improved understanding of Trop-2 biological functions and signaling pathways may lead to better management of drug-related toxicities and to an increased impact of Trop-2–targeted therapies.

Trop-2 is a type-I transmembrane protein encoded by the tumor-associated calcium signal transducer 2 (*TACSTD2*/*TROP2*) gene.[5-7] The extracellular domain of human Trop-2 (ECD, residues 27-274) encompasses a cysteine-rich N-terminal domain (residues 27-148), followed by a C-terminal region devoid of cysteines (residues 149-274).[5] A single transmembrane helix connects the ECD to the intracellular domain (ICD), which encompasses a 26-amino acid cytoplasmic tail. The cytoplasmic tail contains a HIKE motif,[8] as a regulatory site for protein-protein and protein-phospholipid interactions,[9,10] and two PKCα phosphorylation sites at Ser303 and Ser322.[11,12]

Upregulation of wild-type Trop-2 induces tumor and cancer stem cell growth[13-17] and has been associated with poor prognosis of lung,[18] breast,[19] pancreatic,[20] stomach,[21] head and neck,[22] ovary,[23] and colon-rectum cancers,[24] supporting a key role of this molecule in malignant tumor progression.[13,15-17,24]

Activation of the protumor, prometastatic program requires Trop-2 proteolysis by ADAM10[17,24] or matriptase[25,26] between R87 and T88. Trop-2 is subsequently activated by intramembrane proteolysis by the ADAM17/TNF-α–converting enzyme (TACE) at A187-V188, followed by γ-secretase processing at G285-V286,[14] within the transmembrane domain. This results in ECD shedding and ICD transport into the nucleus of cancer cells (Fig 1A).

This proteolytic cascade leads to the inhibition of E-cadherin–mediated cell-cell adhesion via cleavage of its cytoplasmic tail,[24] thus inducing a functional, rather than transcriptional EMT.[24] This causes the release of E-cadherin–sequestered β-catenin and nuclear signaling of Trop-2 ICD/β-catenin[14,24] (Fig 1B). Src prompts Trop-2 ICD nuclear accumulation through cyclin D1. Cyclin D1 additionally induces the accumulation of Trop-2 proteolytic cleavage effectors (γ-secretase, TACE) and restrains the expression of inhibitory components (Numb),[27] thus sustaining the Trop-2 activation loop.

ADAM10 cleavage of Trop-2 does not occur in normal human tissues,[17,24] suggesting a distinct function of Trop-2 in normal cells. Consistently, Trop-2 is expressed in terminally differentiated cells and in multistratified epithelia, but not in proliferating cells.[28] Genomic loss of the murine *TROP2* (*mTrop2*) gene does not lead to alterations in development. However, this was shown to promote carcinogenesis in squamous cell carcinomas through modulation of Arf, Src, and mutated Ras pathways,[29] suggesting a tumor suppressor role of nonactivated Trop-2 in normal cells.

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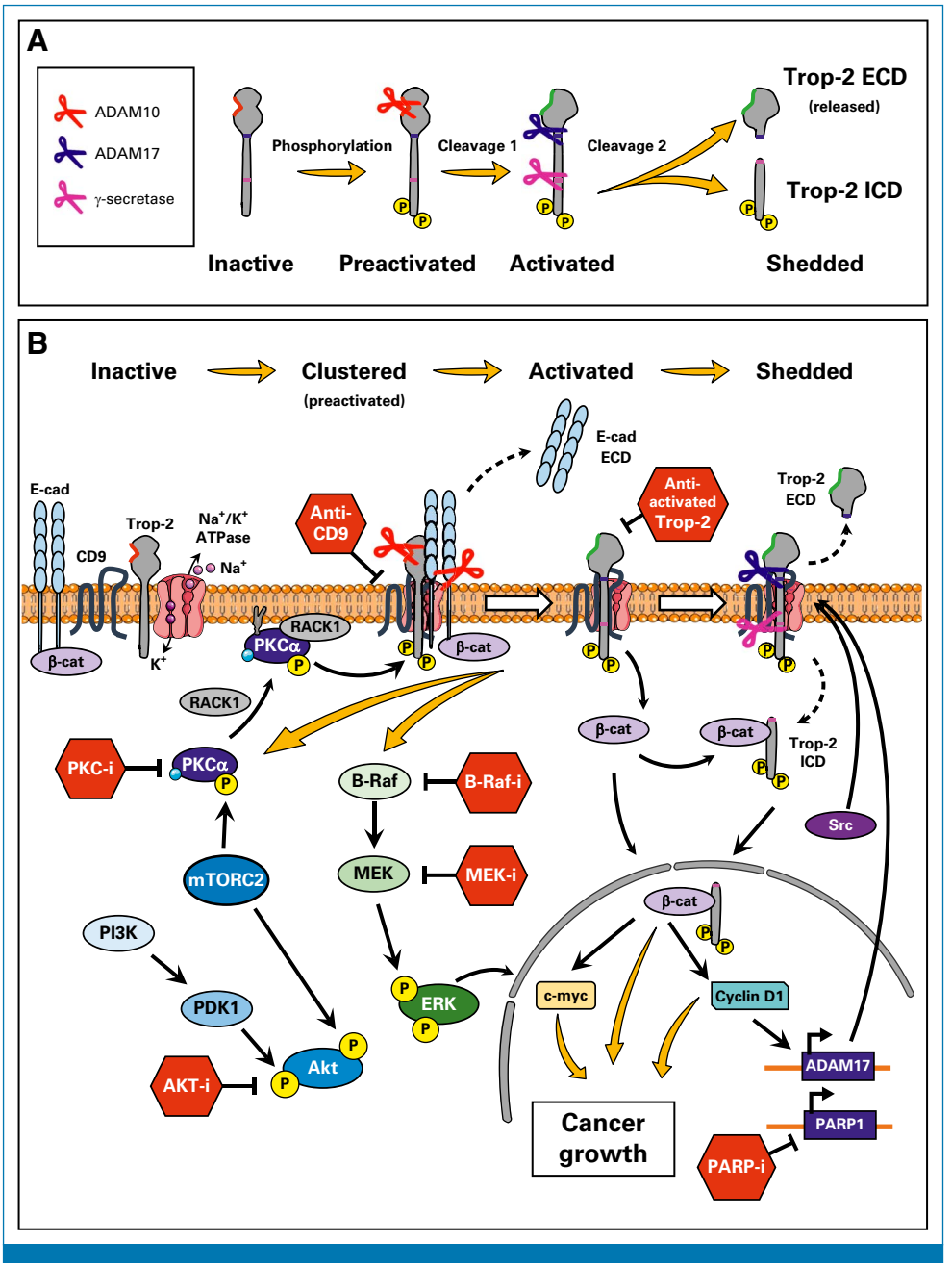

FIG 1. (A) Sequential activation of Trop-2 by proteolysis. ADAM10 or matriptase (red scissors) can cleave Trop-2 between R87 and T88 (in red) in cancer cells. This cleavage opens the structure of the targeted GA733 type-I domain and exposes an activation cleft (in green). Then, Trop-2 becomes further activated by ADAM17/TACE processing (blue scissors) at A187-V188, followed by γ-secretase intramembrane proteolysis (purple scissors) at G285-V286. Full Trop-2 activation results in shedding of the ECD and translocation of the ICD to the nucleus. (B) The major Trop-2–driven signaling pathways. Trop-2 cancer growth stimulation is initiated by the clustering of Trop-2 with NA^+/K^+-ATPase, CD9, and PKCα into a membrane signaling super-complex. ADAM10 cleaves Trop-2 and Trop-2–associated E-cadherin and leads to the release of E-cadherin–sequestered β-catenin and nuclear signaling of Trop-2 ICD/β-catenin. Src prompts Trop-2 ICD nuclear accumulation through cyclin D1, and cyclin D1 induces the accumulation of ADAM17/TACE, thus sustaining the Trop-2 activation loop. Trop-2 upregulates PARP1 and activates PKCα and Akt signaling through mTORC2. ERK signaling is induced through the MAPK cascade, thus providing potential targets for selective inhibition in Trop-2–expressing cells (red hexagons), using small molecules (PKCα, B-Raf, MEK, Akt, and PARP inhibitors) and antibody-based therapeutics (activated Trop-2, CD9). ECD, extracellular domain; ICD, intracellular domain.

TROP2 mutations were shown to cause the rare genetic disease gelatinous drop–like corneal dystrophy.[30] Instances of *TROP2* gene amplification were revealed,[13,31] but no cancer driver mutations of *TROP2* have been identified,[13] indicating that upregulation of wild-type Trop-2 quantitatively stimulates human cancer growth.[13,15]

THE TROP-2 SIGNALING PATHWAYS

The expression of the *TROP2* gene was shown to be under epigenetic control in choriocarcinomas,[31,32] prostate cancer,[33] lung adenocarcinomas,[34] and cholangiocarcinomas.[35] *TROP2* was shown to be further modulated at a post-transcriptional and post-translational level,[13,36] for example, by miR-125b.[37] An oncogenic bicistronic *CYCLIN D1-TROP2* mRNA chimera is generated post-transcriptionally in human gastrointestinal, ovarian, and endometrial tumors.[38] The *CYCLIN D1-TROP2* mRNA chimera transforms primary normal cells, through oncogenic synergy between Trop-2 and cyclin D1. Silencing of the chimeric mRNA was shown to inhibit breast cancer growth.[38]

Cancer cleaved/activated Trop-2 triggers a dormant, ubiquitously expressed signaling super-complex that comprises the NA^+/K^+-ATPase ion pump, CD9, PKCα, and cofilin[12] (Fig 1B). CD9 binding is abolished by deletion of the Trop-2 HIKE region, suggesting HIKE as the tetraspanin docking site on Trop-2. CD9 shRNA-mediated knockdown or anti-CD9 antibodies[39] abrogate Trop-2–dependent stimulation of cell growth, indicating CD9 as a unique transducer of Trop-2 function.[12]

Trop-2 induces an intracellular Ca^{2+} rise, and this is required for membrane translocation of PKCα.[12] Correspondingly required are the corecruitment of PKCα by CD9 and its functional enabling by the Trop-2–driven β1 integrin-RACK1-Src-FAK signaling axis.[40] Deletion of the HIKE region (ΔHIKE_Trop-2) or S303A mutagenesis prevent Trop-2 from recruiting PKCα to the cell membrane. ΔHIKE_Trop-2, S303A, or S322A mutants or PKCα inhibition all prevent Trop-2–driven cell growth, indicating PKCα as a required mediator of Trop-2 growth induction.[12]

mTORC2 is a pivotal mediator of the Trop-2/PKCα feed-forward activation loop,[12] through phosphorylation/activation of PKCα[41] and Akt.[42] Proteomic profiling identified Akt as a required hub of Trop-2–activated networks,[43] and Akt allosteric inhibitors selectively abolish the growth of Trop-2–expressing tumors.[43] mTORC2 upregulates NFkB[44] as a required Trop-2 downstream effector,[45] and this leads to the activation of the cyclin D1 and ERK pathways for tumor cell growth and metastatic diffusion[17] (Fig 1B).

OPEN ISSUES AND FUTURE DIRECTIONS

High Trop-2 levels were expected to identify cancers that are sensitive to Trop-2–targeting therapies.[12,17,46] However, therapeutic responses to anti–Trop-2 ADC have been detected also in low-to-nil Trop-2 cases.[3,47] Notably, though, Trop-2 expression was revealed in approximately 75% of breast cancers,[17] ≥77% TNBC,[47] and in up to 94% of lung adenocarcinomas.[3] As the immunohistochemistry zero-to-low class routinely corresponds to expression in up to 10% of cancer cells,[48] we argue that Trop-2 may be more broadly expressed than currently recognized. Bulk analysis by Western blotting revealed, indeed, sizable levels of Trop-2 in all breast cancer cases analyzed.[17]

Still, high levels of Trop-2 appear to predict the largest responses to anti–Trop-2 ADCs.[3,47] Thus, it will be important to develop standardized IHC assays for Trop-2 quantification in cancer samples. Randomized studies with patient stratification according to validated Trop-2 expression levels may rigorously assess predictive impacts versus ADC therapy.

Selective pressure for Trop-2 expression applies during tumor growth[15] and malignant progression,[17,24] suggesting that this may contribute to preserving its expression as a target during cytotoxic therapy. Suggestive of this scenario, Trop-2 remains expressed in most cases of advanced prostate cancer resistant to androgen receptor (AR) signaling inhibitors.[49] A main mechanism of resistance such as AR gene amplification does not decrease the expression of Trop-2, and the AR-V7 splice variant actually increases it.[49]

An additional issue that requires attention is the expression of Trop-2 in normal tissues.[12,15,17,24,28,50] As anti–Trop-2 ADC evolve toward carrying more active payloads,[1,3] determinants of toxicity events may shift from payload-release alone, toward on-target/off-tumor effects.[4,51] As Trop-2 is not cleaved in normal human tissues,[17,24] specific targeting of cancer cleaved/activated Trop-2[52] may pave the way for tackling this issue.

Downregulation of Trop-2–driven PARP1[46] or Akt,[43] was shown to inhibit the growth of Trop-2–expressing cancer cells (Fig 1B). Thus, the inhibition of signaling pathways triggered by Trop-2, among them PKCα,[53] B-Raf, MEK,[54] Cyclin D1,[38] Akt,[43] PARP1,[46] and CD9,[39] using small molecules (PKCα, B-Raf, MEK, Akt, and PARP inhibitors) or antibody-based therapeutics (activated Trop-2 and CD9) can be proposed as a strategy for reaching a selective, additive therapeutic impact in Trop-2–expressing cancers.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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