CANCER RESEARCH

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Abstract 367: Trop-2 activates a dormant Na^+/K^+-ATPase/PKCα/CD9/ezrin signaling axis to override the basal growth program of cancer cells

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Abstract

Trop-2 is overexpressed in most human cancers, suggesting selective pressure for a key, conserved function. Here we show that Trop-2 stimulates cancer cell growth through the activation of a constitutively expressed, yet otherwise dormant, growth-control module. We discovered that crosslinking of membrane Trop-2 with specific Abs leads to a cytoplasmic Ca^{2+} raise through interaction with the Na^+/K^+-ATPase α_1 subunit and mobilization of the intracellular stores. This triggers a feed-forward loop through Trop-2-dependent activation and membrane recruitment of PKCα;, which in turn phosphorylates the Trop-2 cytoplasmic tail at two target sites, activating the molecule to stimulate its downstream signaling targets Akt and ERK. Our findings indicate that the Trop-2-triggered cell growth operates through binding and extensive crosstalk with CD9, CD81, CD82 and CD151 through PKCα. Detailed analysis of CD9 and CD81 indicates that they bind to the HIKE region of the Trop-2 intracellular tail. Correspondingly, we found that the HIKE region of Trop-2 mediates its anchoring to the β-actin cytoskeleton through direct interaction with the ERM protein ezrin. Consistently, the Trop-2-dependent dynamic remodeling of the cell cytoskeleton is discovered to occur through activation of myosin II and binding of annexins A1/A11, α-actinin and gelsolin. Systematic drug screening, gene expression silencing and site-directed mutagenesis revealed that cytoskeleton disassembly, HIKE deletion and CD9 inhibition revert the growth of Trop-2-expressing cancer cells to that of their Trop-2-null counterparts. On the other hand, these inhibitors have no effects on basal cell growth. This indicates that Trop-2-centered protein interactions and activations are an essential step for the Trop-2-dependent cancer growth. Tight co-expression of the key components of the Trop-2

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growth-stimulatory complex is found in a large breast cancer case series, thus indicating strong clinical relevance. Hence, Trop-2 triggers a universal, but otherwise dormant, layer of cancer growth, that overrides basal cell growth regulatory mechanisms and sensitizes tumors to targeted anticancer therapies.

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