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Tumor suppressor REIC/Dkk-3 and its co-chaperone SGTA: Their interaction and role to control castration-resistant prostate cancer by the release from androgen independence and malignancy

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Sadahira T. , Maruyama Y. , Mitsui Y. , Wada K. , Edamura K. , Kobayashi Y. , Araki M. , Watanabe M. , Watanabe T. , Nasu Y.

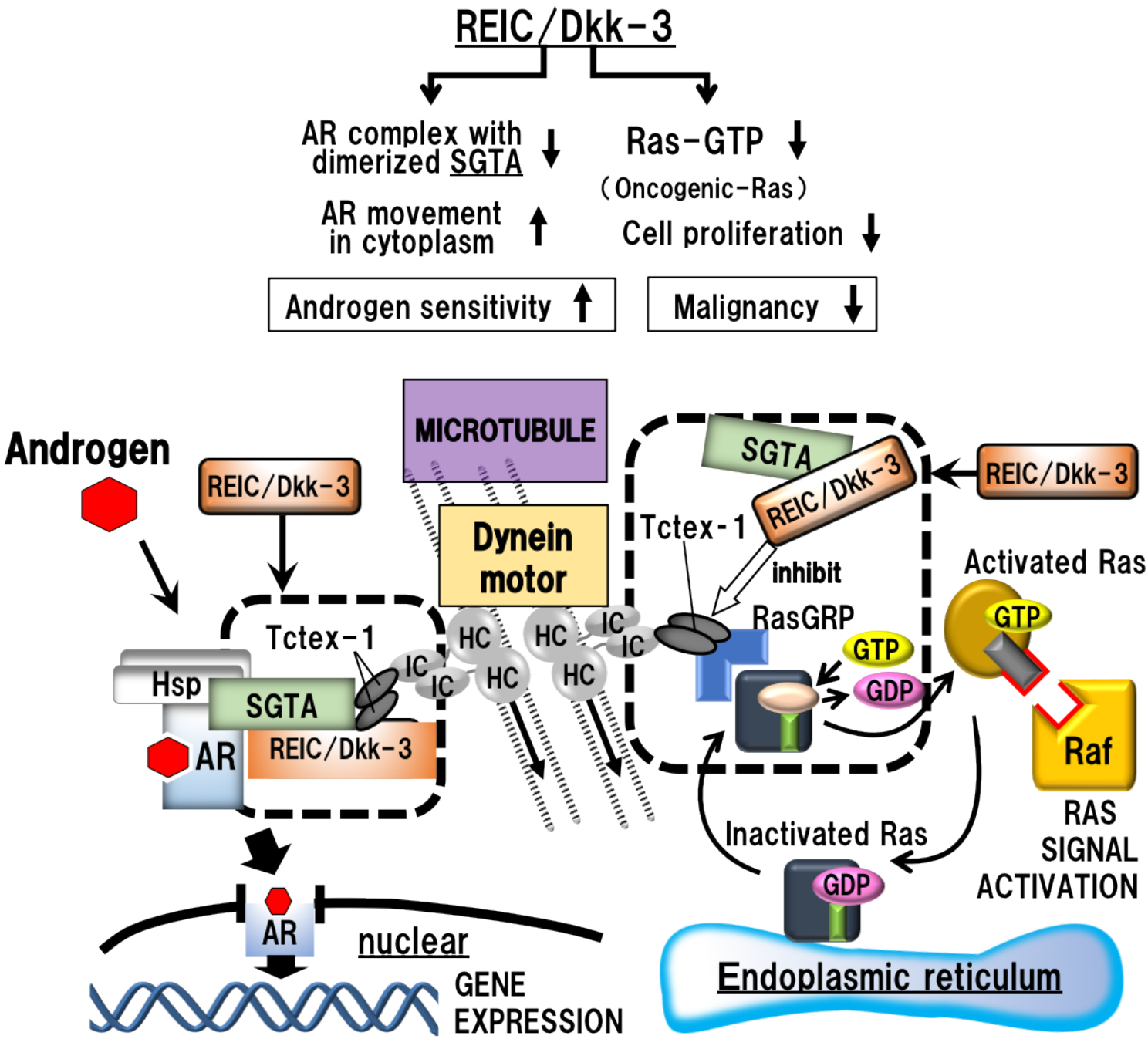
Okayama University Graduate School of Medicine, Dept. of Urology, Okayama, Japan

Introduction & Objectives: RIEC/Dkk-3 is a member of the Dickkopf (Dkk) family protein known as a tumor suppressor, and its expression is significantly downregulated in human castration-resistant prostate cancer (CRPC). However, its intracellular physiological functions and interaction molecules have not been fully understood.

Materials & Methods: To confirm the novel interacting partners for REIC/Dkk-3 protein, a yeast two-hybrid screen was conducted using cDNA libraries derived from a normal prostate and a prostate adenocarcinoma. We expressed and co-expressed these proteins in human CRPC cells under additional AR co-expression to examine the role of intracellular REIC/Dkk-3 and its co-chaperone and their interaction in androgen receptor (AR) signal transduction. Next, we attempted to elucidate the effect of REIC/Dkk-3 on malignancy. Tumors was established by using benzo(a)pyrene in WT and REIC/Dkk-3 KO mice, and oncogenic pathway was examined.

Results: We identify that the small glutamine-rich tetratricopeptide repeat-containing protein (SGTA), known as a negative modulator of cytoplasmic AR signaling, is a novel interacting modulator of REIC/Dkk-3. We also indicate that the REIC/Dkk-3 protein interferes with the dimerization of SGTA and then upregulates the AR transport and signaling in human CRPC cells. The tumor volume was suppressed in WT mice compared to REIC/Dkk-3 KO mice. REIC/Dkk-3 led to regulate the expression of Ras-GTP (oncogenic-Ras), and hence suppressed tumor progression.

Conclusions: The present study indicates that REIC/Dkk-3 interacts with SGTA and interferes with the dimerization of SGTA. The expression of REIC/Dkk-3 regulates oncogenic-Ras signal activation and abolishes the function of SGTA, resulting in enhanced AR sensitivity in CRPC cells.


REIC/Dkk-3
AR complex with dimerized SGTA
Ras-GTP
(Oncogenic-Ras)
AR movement in cytoplasm
Cell proliferation
Androgen sensitivity
Malignancy
Androgen
REIC/Dkk-3
MICROTUBULE
Dynein motor
Tctex-1
Hsp
SGTA
AR
REIC/Dkk-3
HC
IC
SGTA
REIC/Dkk-3
Tctex-1
inhibit
RasGRP
GTP
GDP
Activated Ras
Raf
RAS SIGNAL ACTIVATION
Inactivated Ras
AR
nuclear
GENE EXPRESSION
Endoplasmic reticulum