ION CHANNEL ACTIVITY PROMOTES MITOTIC ENTRY AND TUMOR CELL GROWTH

Medulloblastomas are classified into 4 distinct subgroups—SHH, WNT, group 3, and group 4—based on their clinical, biologic, and genetic profiles. Actionable targets have not yet been identified for WNT, group 3, and group 4 tumors, which represent approximately three quarters of all medulloblastomas. Overexpression or amplification of ion channels, which are abundant in the central nervous system, has been observed in several cancers, but the contributions of ion channels to tumorigenesis are unclear. Huang and colleagues performed a genome-wide expression analysis on mouse medulloblastomas and observed that ether-a-go-go-related potassium channel 2 (EAG2) was the most highly upregulated ion channel gene in medulloblastomas relative to normal cerebellum. An analysis of 4 independent cohorts of human medulloblastomas further revealed that EAG2 was overexpressed in a sizable subset of tumors representing multiple clinical subgroups. Knockdown of EAG2 in primary medulloblastoma cells inhibited cell growth in vitro and significantly improved the survival of tumor-bearing mice. The authors noted that EAG2 shuttles to the plasma membrane in late G2 phase and remains there throughout mitosis, suggesting that the impaired cell growth caused by EAG2 loss might be due to defects in mitotic entry. Indeed, EAG2 knockdown in medulloblastoma cells led to G2 arrest and mitotic catastrophe associated with aberrant premitotic cytoplasmic condensation. EAG2 depletion led to a striking increase in cell volume in late G2 that activated a p38 MAP kinase-mediated hypotonic stress response required for cell-cycle arrest, providing a potential explanation for the reduced tumorigenicity of EAG2-deficient medulloblastoma cells. These findings thus suggest that EAG2 overexpression in medulloblastoma may accommodate the frequent changes in cell volume required for rapid cell proliferation and implicate the EAG2 voltage-gated potassium channel as a potentially druggable therapeutic target in a subset of medulloblastomas.


PES1 MODULATES THE BALANCE BETWEEN ERα AND ERβ IN BREAST CANCER

Estrogen-mediated regulation of breast cancer is dependent on signaling through estrogen receptors (ER) α and β, which have been shown to function antagonistically. Increased ERα expression promotes tumor growth, whereas ERβ inhibits ERα-stimulated proliferation and is downregulated in breast tumors. Cheng and colleagues investigated the mechanisms that control the balance of these 2 proteins and identified Pescadillo (PES1), an estrogen-induced protein that is overexpressed in breast cancer, as a critical mediator of ERα-driven tumorigenesis. Microarray analysis demonstrated that PES1 regulated the expression of estrogen-responsive genes involved in DNA replication and cell-cycle progression, many of which are activated by ERα and repressed by ERβ. In addition, PES1 specifically enhanced ERα homodimerization and recruitment to estrogen-responsive promoters while decreasing these activities of ERβ, indicating that PES1 differentially regulates ERα and ERβ transcriptional activity in breast cancer. This effect was mediated via modulation of ER protein levels through the E3 ubiquitin ligase carboxyl terminus of Hsc70-interacting protein (CHIP). PES1 expression stabilized ERα protein but promoted CHIP-driven ubiquitination and proteasomal degradation of ERβ, suggesting that PES1 may facilitate breast cancer growth via increased ERα signaling and decreased ERβ signaling. Consistent with this idea, PES1 depletion impaired estrogen-stimulated breast cancer cell proliferation and anchorage-independent growth in vitro and diminished estrogen-dependent tumor growth in vivo. Conversely, PES1 expression was sufficient to transform normal human mammary epithelial cells in soft agar assays. Furthermore, PES1 expression was positively correlated with ERα and negatively correlated with ERβ expression in human breast cancer samples. These results support a critical role for PES1 in breast cancer pathogenesis and suggest that current endocrine therapy might be improved by targeted inhibition of this protein.

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Cancer Discovery 2012;2:763. Published OnlineFirst August 9, 2012.

Updated version

Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-RW2012-124

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