

Hedgehog pathway key in tamoxifen-resistant breast CA

November 6 2012



Noncanonical Hedgehog signaling is activated in tamoxifen-resistant tumors, and the phosphoinositide 3-kinase inhibitor/protein kinase B pathway plays a key role protecting Hedgehog signaling molecules, according to a study published in the Oct. 1 issue of *Cancer Research*.

(HealthDay)—Noncanonical Hedgehog (Hh) signaling is activated in tamoxifen-resistant tumors, and the phosphoinositide 3-kinase inhibitor/protein kinase B (PI3K/AKT) pathway plays a key role protecting Hh signaling molecules, according to a study published in the Oct. 1 issue of *Cancer Research*.

Noting that patients with resistance to endocrine therapy have poor outcomes, Bhuvanewari Ramaswamy, M.D., from The Ohio State University in Columbus, and colleagues examined the role of Hh signaling in tamoxifen-resistant tumors.

The researchers found that the Hh signaling pathway was activated in

tamoxifen-resistant tumors and that the [PI3K/AKT pathway](#) protected key components of the Hh signaling pathway from proteasomal degradation. In tamoxifen-resistant MCF-7 and T47D cells, the levels of Hh signaling molecules SMO and GLI1 and their targets were found to be significantly elevated. Serial passage of the [resistant cells](#) in mice led to [aggressive tumors](#), which spread to distant organs, and simultaneous increases in Hh marker expression. SMO or GLI1 depletion mediated by RNAi correlated with reduced proliferation, clonogenic survival, and delayed transition from G₁ to S. Treatment of resistant cells with PI3K inhibitors resulted in reduced SMO and GLI1 protein levels and activity, while blocking GSK3 β and proteasomal degradation rescued these levels and activity. Anti-Hh compound GDC-0449 treatment of tamoxifen-resistant xenografts correlated with blocked tumor growth in mice. In a cohort of 315 patients with breast cancer, high GLI1 expression was inversely associated with disease-free and overall survival.

"In summary, our results describe a signaling event linking PI3K/AKT pathway with Hh signaling that promotes tamoxifen resistance," the authors write. "Targeting Hh pathway alone or in combination with PI3K/AKT pathway could therefore be a novel therapeutic option in treating endocrine-resistant breast cancer."

More information: [Abstract](#)
[Full Text \(subscription or payment may be required\)](#)

Copyright © 2012 [HealthDay](#). All rights reserved.

Citation: Hedgehog pathway key in tamoxifen-resistant breast CA (2012, November 6) retrieved 11 May 2024 from <https://medicalxpress.com/news/2012-11-hedgehog-pathway-key-tamoxifen-resistant-breast.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private

study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.