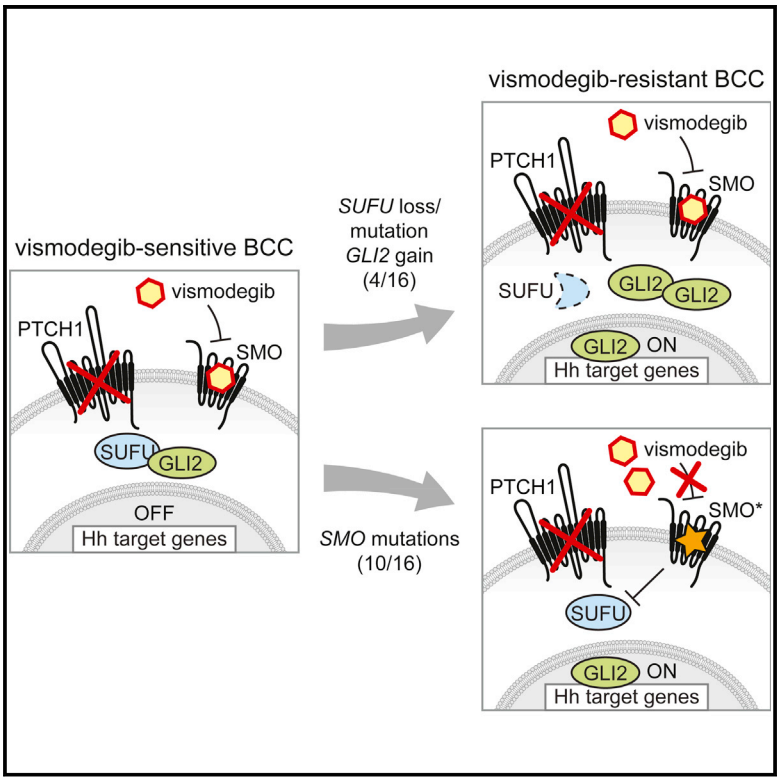
Article

Cancer Cell

Genomic Analysis of Smoothened Inhibitor Resistance in Basal Cell Carcinoma

Graphical Abstract



Highlights

- Recurrent mechanisms reactivate the Hh pathway in SMO inhibitor-resistant BCC
- Drug-binding pocket and activating SMO mutations reduce sensitivity to vismodegib
- Downstream *SUFU* variants co-occur with alterations predicted to increase *GLI2* levels
- A relapsed tumor can harbor multiple resistance mechanisms

Authors

Hayley J. Sharpe, Gregoire Pau, ...,
Robert L. Yauch,
Frederic J. de Sauvage

Correspondence

sauvage@gene.com

In Brief

Sharpe et al. identify SMO mutations in the binding pocket for SMO inhibitors or that constitutively activate SMO in vismodegib-resistant basal cell carcinoma. They demonstrate that a single relapsed tumor can harbor clones with different resistance mutations.

Sharpe et al., 2015, Cancer Cell *27*, 327–341
March 9, 2015
http://dx.doi.org/10.1016/j.ccell.2015.02.001

CellPress

Cancer Cell
Article

Genomic Analysis of Smoothened Inhibitor Resistance in Basal Cell Carcinoma

Hayley J. Sharpe,[1] Gregoire Pau,[2] Gerrit J. Dijkgraaf,[1] Nicole Basset-Seguin,[5] Zora Modrusan,[3] Thomas Januario,[1] Vickie Tsui,[4] Alison B. Durham,[6] Andrzej A. Dlugosz,[6] Peter M. Haverty,[2] Richard Bourgon,[2] Jean Y. Tang,[7] Kavita Y. Sarin,[7] Luc Dirix,[8] David C. Fisher,[9] Charles M. Rudin,[10] Howard Sofen,[11] Michael R. Migden,[12] Robert L. Yauch,[1] and Frederic J. de Sauvage[1,*]

[1]Department of Molecular Oncology
[2]Department of Bioinformatics and Computational Biology
[3]Department of Molecular Biology
[4]Department of Discovery Chemistry
Genentech, Inc., South San Francisco, CA 94080, USA
[5]Paris 7 Hôpital Saint-Louis, Paris 75010, France
[6]Department of Dermatology, University of Michigan, Ann Arbor, MI 48109, USA
[7]Stanford University School of Medicine, Stanford, CA 94305, USA
[8]Sint-Augustinus Cancer Center, Antwerp University Hospital, University of Antwerp, Antwerp 2610, Belgium
[9]Dana-Farber Cancer Institute, Boston, MA 02215, USA
[10]Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
[11]Department of Medicine/Dermatology, UCLA School of Medicine, Los Angeles, CA 90095, USA
[12]MD Anderson Cancer Center, Houston, TX 77030, USA
*Correspondence: sauvage@gene.com
http://dx.doi.org/10.1016/j.ccell.2015.02.001

SUMMARY

Smoothened (SMO) inhibitors are under clinical investigation for the treatment of several cancers. Vismodegib is approved for the treatment of locally advanced and metastatic basal cell carcinoma (BCC). Most BCC patients experience significant clinical benefit on vismodegib, but some develop resistance. Genomic analysis of tumor biopsies revealed that vismodegib resistance is associated with Hedgehog (Hh) pathway reactivation, predominantly through mutation of the drug target SMO and to a lesser extent through concurrent copy number changes in *SUFU* and *GLI2*. SMO mutations either directly impaired drug binding or activated SMO to varying levels. Furthermore, we found evidence for intra-tumor heterogeneity, suggesting that a combination of therapies targeting components at multiple levels of the Hh pathway is required to overcome resistance.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common human cancer and is driven predominantly by hyperactivation of the Hedgehog (Hh) pathway (Oro et al., 1997; Xie et al., 1998). The association between Hh signaling and cancer was first discovered in patients with Gorlin (or basal cell nevus) syndrome, who are highly susceptible to medulloblastoma (MB) and BCC. These patients generally possess heterozygous germline mutations in the Patched 1 gene (*PTCH1*), which encodes a receptor for Hh ligands (Hahn et al., 1996; Johnson et al., 1996). Hh ligand binding relieves PTCH1 suppression of the serpentine transmembrane (TM) signal transducer Smoothened (SMO; see Figure 1A for a schematic of the Hh pathway). The vast majority of sporadic BCCs are driven by inactivating mutations and loss of heterozygosity (LOH) in *PTCH1*, with most of the remainder harboring activating mutations in *SMO* (Reifenberger et al., 2005). SMO promotes the activation and nuclear localization of GLI

Significance

Acquired resistance represents a major challenge to the success of targeted cancer therapies. Therefore, understanding resistance mechanisms will help guide future therapeutic strategies. Vismodegib was approved for treatment of locally advanced and metastatic BCC and is under clinical investigation for several other cancers. We performed molecular analyses of tumor biopsies from BCC patients who initially responded but subsequently progressed on treatment. We found that vismodegib resistance is invariably linked to Hh pathway reactivation, indicating that BCC is addicted to Hh signaling. Variants occurred either in or downstream of the drug target SMO, with intra-tumor heterogeneity observed for both resistance mechanisms, suggesting that a combination of SMO and downstream targeting agents will be required to overcome vismodegib resistance in Hh-driven cancers.