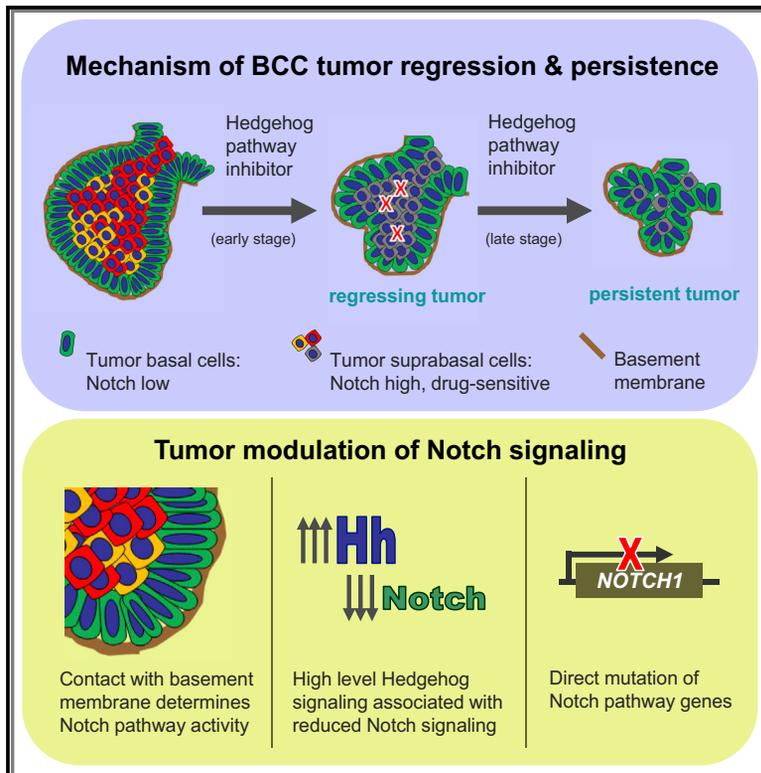


Tumor Architecture and Notch Signaling Modulate Drug Response in Basal Cell Carcinoma

Graphical Abstract



Authors

Markus Eberl, Doris Mangelberger, Jacob B. Swanson, ..., Marcus L. Frohm, Andrzej A. Dlugosz, Sunny Y. Wong

Correspondence

sunnyw@umich.edu

In Brief

Eberl et al. show that in mouse basal cell carcinoma models, interior $Hh^+/Notch^+$ suprabasal cells undergo apoptosis in response to vismodegib, whereas peripheral $Hh^{+++}/Notch^-$ basal cells survive throughout treatment. Modulating Notch overcomes the drug response hierarchy established by tumor architecture.

Highlights

- Hedgehog pathway inhibitors are effective against BCC, but tumor cells often persist
- Tumor basal and suprabasal cells differ in gene expression and drug response
- Inhibiting Notch promotes tumor persistence, but not drug resistance, upon treatment
- Latently activating Notch is sufficient to regress already established tumors

Tumor Architecture and Notch Signaling Modulate Drug Response in Basal Cell Carcinoma

Markus Eberl,¹ Doris Mangelberger,^{1,3} Jacob B. Swanson,¹ Monique E. Verhaegen,¹ Paul W. Harms,² Marcus L. Frohm,^{1,4} Andrzej A. Dlugosz,¹ and Sunny Y. Wong^{1,5,*}

¹Departments of Dermatology, and Cell and Developmental Biology, University of Michigan, Ann Arbor, MI 48109, USA

²Departments of Pathology and Dermatology, University of Michigan, Ann Arbor, MI 48109, USA

³Present address: Department of Chemistry and Pharmacy, Ludwig-Maximilians-University Munich, Munich 81377, Germany

⁴Present address: Sanford Health, Sioux Falls, SD 57105, USA

⁵Lead Contact

*Correspondence: sunnyw@umich.edu

<https://doi.org/10.1016/j.ccell.2017.12.015>

SUMMARY

Hedgehog (Hh) pathway inhibitors such as vismodegib are highly effective for treating basal cell carcinoma (BCC); however, residual tumor cells frequently persist and regenerate the primary tumor upon drug discontinuation. Here, we show that BCCs are organized into two molecularly and functionally distinct compartments. Whereas interior Hh⁺/Notch⁺ suprabasal cells undergo apoptosis in response to vismodegib, peripheral Hh⁺⁺⁺/Notch⁻ basal cells survive throughout treatment. Inhibiting Notch specifically promotes tumor persistence without causing drug resistance, while activating Notch is sufficient to regress already established lesions. Altogether, these findings suggest that the three-dimensional architecture of BCCs establishes a natural hierarchy of drug response in the tumor and that this hierarchy can be overcome, for better or worse, by modulating Notch.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common cancer in North America, with >1 million new cases diagnosed each year. Although these tumors rarely metastasize, the ubiquity of this disease imposes a significant economic burden on our health-care system. At an individual level, BCCs often cause local tissue damage, which is especially problematic for Gorlin syndrome patients who are genetically predisposed to BCC. These individuals can develop hundreds of lesions throughout the skin, potentially spending a lifetime having their tumors excised, only for new ones to invariably appear.

The singular defining feature of all BCCs is dysregulation of Hedgehog (Hh) signaling, a key developmental pathway that is also critical for adult tissue homeostasis and regeneration (Briscoe and Thérond, 2013; Epstein, 2008; Lum and Beachy, 2004). In the absence of ligand, Hh signaling is normally silenced by Patched1 (PTCH1), which inhibits Smoothened (SMO), the major upstream activator of the pathway. Upon binding Hh ligands,

PTCH1 is itself inhibited, enabling SMO to transduce downstream signals via GLI transcription factors. In BCCs, it is this delicate balance of PTCH1-mediated silencing, and SMO-mediated activation, that is perturbed: roughly 80%–90% of tumors are caused by loss-of-function mutations in *PTCH1*, while the remainder are largely driven by gain-of-function mutations in *SMO* (Gailani et al., 1996; Hahn et al., 1996; Johnson et al., 1996; Reifenberger et al., 2005; Xie et al., 1998).

As SMO is the central upstream activator of canonical Hh signaling, small-molecule inhibitors targeting this protein represent a promising new class of therapeutics for combating Hh-dependent tumors such as BCC and medulloblastoma (Metcalfe and de Sauvage, 2011). Vismodegib (vismo), a US FDA-approved SMO inhibitor for treating advanced BCC, has been reported to induce therapeutic responses in roughly half of sporadic BCCs and in nearly all Gorlin BCCs (Axelson et al., 2013; von Hoff et al., 2009; Sekulic et al., 2012; Tang et al., 2012). These successes, however, have been tempered by the fact that a significant fraction of sporadic tumors either do not

Significance

Although therapeutics targeting the Hedgehog signaling pathway are highly effective at treating basal cell carcinoma (BCC), cancer cells frequently persist and regenerate the primary tumor once treatment is stopped. Our findings suggest that persistent cancer cells likely originate from the tumor periphery and display low Notch pathway activity. In contrast, cancer cells located at the interior of the tumor mass activate Notch and are efficiently eliminated by drug treatment. These findings suggest that the cellular architecture of BCC, likely determined by contact with the surrounding basement membrane, may influence whether tumor cells persist or are destroyed in response to therapy.

متن کامل مقاله

دریافت فوری ←

ISIArticles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات