Hedgehog signaling in basal cell carcinoma

Otsuka, Atsushi; Levesque, Mitchell P; Dummer, Reinhard; Kabashima, Kenji

Abstract: Basal cell carcinoma (BCC), the most common type of skin cancer, is occasionally aggressive with deep invasion, destruction of adjacent structures, recurrence and, on very rare occasions, regional and distant metastases. Mutations that occur in BCC in hedgehog (Hh) pathway genes primarily involve the genes encoding patched homolog (PTCH) and smoothened homolog (SMO). Several animal models have demonstrated the functional relevance of genetic alterations in the Hh pathway during tumorigenesis. Recently, targeted therapy has become available both commercially and in the context of human clinical trials. Interestingly, Hh pathway inhibitors not only suppress BCC progression but also promote acquired immune responses. Since immune responses are crucial for long-term tumor control, new clinical trials, such as those involving a combination of Hh inhibitors with immune modifiers, are needed to supplement standard methods of tumor control.

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Figure 1

A

Primary cilium
PTCH

SMO
SUFU
PKA
Gli

Proteasomal cleavage

Hh target gene off
GLI target genes

B

Primary cilium
PTCH

SMO
SUFU
PKA
Gli

Hh target gene on
GLI target genes

Lysosomal degradation
Figure 2

A

- Primary cilia
- PTCH
- Mutations
- Basal body
- SMO
- SUFU
- PKA
- GlI

B

- Primary cilia
- PTCH
- SMO
- SUFU
- PKA
- GlI
- PI3K
- mTOR
- PDK1
- aPKC
- S6K1
- Proliferation BCCs
- GLI1* target genes
- Hh target gene on
SMO antagonists: Visomodegib Sonidegib PF-04449913 Erismodegib LEQ506 Saridegib Itraconazole

mTOR inhibitor: Sirolimus

Gli inhibitor: ATO

Proliferation BCCs

Hh target gene on