

LETTER TO THE EDITOR

Open Access

Hedgehog pathway inhibitors – current status and future prospects

Asfandyar Sheikh*, Arsalan Ahmad Alvi, Hafiz Muhammad Aslam and Abdul Haseeb

Abstract

The Hedgehog (Hh) proteins comprise a group of secreted proteins that regulate cell growth, differentiation and survival. Inappropriate activation of the Hh signaling pathway has been implicated in the development of a variety of cancers. Hedgehog pathway inhibitors are a relatively new class of therapeutic agents that act by targeting the proteins involved in the regulation of Hh pathway (PTCH, SMO and Gli). Together, they serve as exciting new prospects, with a bright future, both alone or as an adjuvant to the more traditional anti-cancer drugs.

Letter

The Hedgehog (Hh) proteins comprise a group of secreted proteins that regulate cell growth, differentiation and survival [1]. They are involved in organogenesis, and have been shown to promote adult stem cell proliferation [2,3]. Inappropriate activation of the Hh signaling pathway has been implicated in the development of several types of cancers including prostate, lung, pancreas, breast, brain and skin [4-9].

Sonic Hedgehog (Shh) is the best studied ligand of Hh pathway in vertebrates. In the absence of the ligand, the Patched (PTCH) receptor inhibits Smoothed (SMO), a downstream protein in the pathway. Binding of Shh to PTCH alleviates this inhibition, thus regulating the expression of Gli transcription factors [10]. Loss-of-function mutations of PTCH, gain-of-function mutations of SMO and misexpression of the Gli2 and Gli3 have been associated with tumor formation and maintenance in animal models of medulloblastoma and basal cell carcinoma of the skin [11-14]. Other studies have pointed towards Hedgehog signaling having an important role in angiogenesis (by increasing angiopoietin-1 and angiopoietin-2), metastasis (by increasing Snail expression) and suppression of apoptosis (by increasing Cyclins and anti-apoptotic factors and decreasing pro-apoptotic genes such as Fas) [15-18].

Hedgehog pathway inhibitors are a relatively new class of therapeutic agents that act by targeting the proteins

involved in the regulation of Hh pathway. Cyclopamine is the prototype inhibitor of the Shh pathway that inactivates SMO by binding to its hepta-helical bundle [19]. It is currently undergoing preclinical and clinical studies as an anticancer agent in basal cell carcinoma, medulloblastoma and rhabdomyosarcoma [20,21]. Saridegib (IPI-926), a synthetic analog of cyclopamine, has shown positive results in Phase I clinical trial of advanced solid tumors [22]. Similarly, itraconazole, an antifungal drug, has also been shown to suppress growth of medulloblastoma in mice allograft models [23]. This compound acts as an SMO antagonist, in a manner distinct from its anti-lanosterol activity in fungi (otherazole drugs have not been found to have this effect). Other candidates for future trials include Novartis' LDE-225, Millennium Pharmaceuticals' TAK-441, Exelixis/Bristol-Myers Squibb's BMS-833923 (XL139) and Pfizer's PF-04449913 [24,25].

Vismodegib (IPI-926; Erivedge: Genentech, South St Francisco, CA, USA) has been recently approved by the FDA for treatment of advanced basal cell carcinoma [26]. However, like other drugs in the category, it also has an adverse effect profile. Due to its mechanism of action, it is contraindicated during pregnancy, as it is teratogenic, embryotoxic and fetotoxic [27]. Other adverse reactions include alopecia, muscle spasms, weight loss, fatigue, GIT disturbances and arthralgias [27].

The approval of Vismodegib by the FDA can prove to be the beginning of a new era in anti-cancer therapeutics. Other drugs targeting the Hh pathway are likely to follow. Together, they serve as exciting new prospects,

* Correspondence: asfandyarshikh@gmail.com

Dow Medical College, Dow University of Health Sciences, Baba-e-Urdu Road, Karachi 74200, Pakistan

with a bright future, both alone or as an adjuvant to the more traditional anti-cancer drugs.

Competing interests

The authors declare that they have no conflict of interests.

Authors' contributions

AS was involved in choosing the topic and drafting the initial manuscript. HMA, AAA and AH were involved in critically revising the manuscript, listed in decreasing order of their contributions. The authors have read and approved the manuscript. The authors did not receive any financial support/grant.

Received: 2 September 2012 Accepted: 31 October 2012

Published: 1 November 2012

References

1. Varjosalo M, Taipale J: **Hedgehog: functions and mechanisms.** *Genes Dev* 2008, **22**(18):2454–2472.
2. Ingham PW, McMahon AP: **Hedgehog signaling in animal development: paradigms and principles.** *Genes Dev* 2001, **15**(23):3059.
3. Bhardwaj G, Murdoch B, Wu D, Baker D, Williams K, Chadwick K, Ling L, Karanu F, Bhatia M: **Sonic hedgehog induces the proliferation of primitive human hematopoietic cells via BMP regulation.** *Nat Immunol* 2001, **2**(2):172–180.
4. Sheng T, Li C, Zhang X, Chi S, He N, Chen K, McCormick F, Gatalica Z, Xie J: **Activation of the hedgehog pathway in advanced prostate cancer.** *Mol Cancer* 2004, **3**(1):29.
5. Watkins DN, Berman DM, Burkholder SG, Wang B, Beachy PA, Baylin SB: **Hedgehog signalling within airway epithelial progenitors and in small-cell lung cancer.** *Nature* 2003, **422**(6929):313–317.
6. Thayer SP, Di Magliano MP, Heiser PW, Nielsen CM, Roberts DJ, Lauwers GY, Qi YP, Gysin S, Fernández-del Castillo C, Yajnik V: **Hedgehog is an early and late mediator of pancreatic cancer tumorigenesis.** *Nature* 2003, **425**(6960):851–856.
7. Liu S, Dontu G, Mantle ID, Patel S, Ahn N, Jackson KW, Suri P, Wicha MS: **Hedgehog signaling and Bmi-1 regulate self-renewal of normal and malignant human mammary stem cells.** *Cancer Res* 2006, **66**(12):6063.
8. Dellovade T, Romer JT, Curran T, Rubin LL: **The hedgehog pathway and neurological disorders.** *Annu Rev Neurosci* 2006, **29**:539–563.
9. Bale AE, Yu K: **The hedgehog pathway and basal cell carcinomas.** *Hum Mol Genet* 2001, **10**(7):757–762.
10. Michaud EJ, Yoder BK: **The primary cilium in cell signaling and cancer.** *Cancer Res* 2006, **66**(13):6463.
11. Oro AE, Higgins KM, Hu Z, Bonifas JM, Epstein EH Jr, Scott MP: **Basal cell carcinomas in mice overexpressing sonic hedgehog.** *Science* 1997, **276**(5313):817–821.
12. Xie J, Murone M, Luoh S-M, Ryan A, Gu Q, Zhang C, Bonifas JM, Lam C-W, Hynes M, Goddard A, *et al*: **Activating Smoothened mutations in sporadic basal-cell carcinoma.** *Nature* 1998, **391**(6662):90–92.
13. Nilsson M, Undén AB, Krause D, Malmqwist U, Raza K, Zaphiropoulos PG, Toftgård R: **Induction of basal cell carcinomas and trichoepitheliomas in mice overexpressing GLI-1.** *Proc Natl Acad Sci* 2000, **97**(7):3438–3443.
14. Grachtchouk M, Mo R, Yu S, Zhang X, Sasaki H, Hui C, Dlugosz AA: **Basal cell carcinomas in mice overexpressing Gli2 in skin.** *Nat Genet* 2000, **24**(3):216–217.
15. Lee SW, Moskowitz MA, Sims JR: **Sonic hedgehog inversely regulates the expression of angiopoietin-1 and angiopoietin-2 in fibroblasts.** *Int J Mol Med* 2007, **19**(3):445.
16. Li X, Deng W, Nail CD, Bailey SK, Kraus MH, Ruppert JM, Lobo-Ruppert SM: **Snail induction is an early response to Gli1 that determines the efficiency of epithelial transformation.** *Oncogene* 2005, **25**(4):609–621.
17. Adolphe C, Hetherington R, Ellis T, Wainwright B: **Patched1 functions as a gatekeeper by promoting cell cycle progression.** *Cancer Res* 2006, **66**(4):2081–2088.
18. Athar M, Li C, Tang X, Chi S, Zhang X, Kim AL, Tying SK, Kopelovich L, Hebert J, Epstein EH, *et al*: **Inhibition of smoothened signaling prevents ultraviolet B-induced basal cell carcinomas through regulation of fas expression and apoptosis.** *Cancer Res* 2004, **64**(20):7545–7552.
19. Chen JK, Taipale J, Cooper MK, Beachy PA: **Inhibition of hedgehog signaling by direct binding of cyclopamine to Smoothened.** *Genes Dev* 2002, **16**(21):2743–2748.
20. Kolterud Å, Toftgård R: **Strategies for Hedgehog inhibition and its potential role in cancer treatment.** *Drug Discovery Today: Therapeutic Strategies* 2007, **4**(4):229–235.
21. Taipale J, Chen JK, Cooper MK, Wang B, Mann RK, Milenkovic L, Scott MP, Beachy PA: **Effects of oncogenic mutations in smoothened and patched can be reversed by cyclopamine.** *Nature* 2000, **406**(6799):1005–1009.
22. Rudin C, Jimeno A, Miller W Jr, Eigel B, Gettinger S, Chang A, Faia K, Sweeney J, Loewen G, Ross R: **A phase 1 study of IPI-926, a novel hedgehog pathway inhibitor, in patients with advanced or metastatic solid tumors.** *Surgery* 2011, **32**:94.
23. Kim J, Tang JY, Gong R, Kim J, Lee JJ, Clemons KV, Chong CR, Chang KS, Fereshteh M, Gardner D, *et al*: **Itraconazole, a commonly used antifungal that inhibits hedgehog pathway activity and cancer growth.** *Cancer Cell* 2010, **17**(4):388–399.
24. Tremblay MR, McGovern K, Read MA, Castro AC: **New developments in the discovery of small molecule Hedgehog pathway antagonists.** *Curr Opin Chem Biol* 2010, **14**(3):428–435.
25. McMillan R, Matsui W: **Molecular Pathways: The Hedgehog Signaling Pathway in Cancer.** *Clinical Cancer Research* 2012, **18**(18):4883–4888.
26. Dlugosz A, Agrawal S, Kirkpatrick P: **Vismodegib.** *Nat Rev Drug Discov* 2012, **11**(6):437–438.
27. Genentech: *Erivedge [vismodegib; prescribing information]*. South San Francisco, CA: Genentech, Inc; 2012.

doi:10.1186/1750-9378-7-29

Cite this article as: Sheikh *et al*: Hedgehog pathway inhibitors – current status and future prospects. *Infectious Agents and Cancer* 2012 **7**:29.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

