Review Article

Hedgehog Signaling: An Emerging Targeting Therapy in Cancer

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Abstract

Stem cell biology has come of an age. During the past few years, CSCs have been increasingly found in many malignancies. Tumor relapse and metastasis remains major hurdle for improving overall cancer survival. CSCs basically have slow growth rates and are resistant to chemotherapy and/or radiotherapy. Thus, new treatment strategies targeting CSCs can be developed. Various stem cell maintenance pathways such as Notch, Wnt and Hedgehog are found to be activated in the various cancers stem cells. Hedgehog signaling is most active during the embryonic development and aberrant reactivation of the pathway in adult tissue can lead to development of cancer. A variety of cancers such as brain, gastrointestinal, lung, breast and prostate cancer shows possible signs of activation of Hedgehog pathway. Targeted inhibition of Hedgehog signaling can be found effective in the treatment and prevention of many types of human cancers. Hence, the discovery and synthesis of specific Hedgehog pathway inhibitors may have significant clinical implications in novel cancer therapeutics. In this review, we have discussed Hedgehog signaling and its activation in different types of cancers and the development of its targeted therapies.

Keywords: Hedgehog signaling, signal transduction, cancer.

Introduction

Stem cells are defined as cells that have the ability to sustain themselves through the self-renewal and to generate mature cells of a particular tissue through differentiation. Stem Cells have three distinct properties:- self-renewal, the capacity to develop into multiple new lineages, and the potential to proliferate extensively. The amalgamation of these three properties makes stem cells unique. The property of self-renewal is especially notable, because its role is very important in relevance to oncogenesis and malignancy (Reya et al., 2001). Many studies have been conducted since last few years, that the characteristics of stem cells, are found relevant to some types of human cancers. The increased ability of self-renewal by stem cells, in combination to growth potential of stem cells, results in a cell with a phenotype similar to that of a cancer cell (Jordan et al., 2006; Al-Hajj and Clarke, 2004). Rare types of "tumor-initiating cells" have been identified in cancers of the hematopoietic system, brain and breast (Jordan et al., 2006). It is found that these properties of tumor-initiating cells closely resemble to the features of normal stem cells. Such types of cells are termed as "cancer stem cells"(Jordan et al., 2006). As normal and cancer stem cells has the ability to self-renew, it is believed that newly arising cancer cells could be implying the

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same self-renewing cell division that is observed in stem cells. CSCs have been found to involve activation of many signaling pathways such as Notch, Wnt and Hedgehog for development and tissue homeostasis (Kaur et al., 2018). The Notch signaling has been found to have a major role in stem cell fate, differentiation and cell cycle progression. It is over-activated in cancer and thus helps CSCs in their maintenance (Bandhavkar, 2016). The Wnt family of signaling molecules triggers a signaling cascade resulting in activation of genes involved in stem cell maintenance, cell survival, proliferation, motility, migration and fate development during development, whereas Wnt abberant overexpression is responsible for activation of Wnt-signaling activity in transforming cells, favoring stemness and chemotherapy resistance (Gomez-Orte et al., 2013). Hedgehog signaling pathway plays a major role in embryonic growth development and in regulation of stem cell in skin and intestine. The abberant activation of Hedgehog pathway contributes to tumorigenesis in many of the human cancers (Bandhavkar, 2016; Taipale and Beachy, 2001).

There are evidences which show that pathways associated with cancer also regulates normal stem cell development (Reye et al., 2001; Valent et al., 2012). Although there are many features of stem cells that are preserved to greater or lesser extent in cancer stem cells, the key issue for consideration is the presence of the cancer cells for its normal growth. The concept of stem cells, as discussed can differ in many contexts i.e acquisition of features related to tumor progression, such as genetic instability and drug resistance, associated with cancer stem cells. It is becoming clear that a cancer treatment that fails to eliminate cancer stem cells helps in possible relapse of tumor, in which it is thought that disease is eradicated by chemotherapy, though there are chances of regrowth of tumor, with a believable justification that cancer stem cells might not have been completely destroyed (Jordan et al., 2006).

Hedgehog

The Hedgehog (Hh) gene was initially discovered by ChrsitianeNusslein-Volhard and Eric F. Weischaus in 1980 during the screening of mutation for Drosophila larval body plane (Nusslein-Volhard and Wieschaus., 1980). The name Hedgehog is given due to the similarity between the spikes of the hedgehog (Varjosalo and Taipale, 2008; Ingham and McMahon, 2001). It is found that, the things known for this pathway has been derived from the studies on Drosophila, and as a result many of the key elements have been conserved from flies to humans (Hahn et al., 1996; Goodrich et al., 1996). The general signaling mechanism for the Hedgehog pathway is preserved from fly to mammal although more and distinct components are discovered in mammalian cells (Jia et al., 2015).

The Hedgehog signaling pathway is one of the most fundamental signal transduction pathways in embryonic development, being responsible for patterning the developing neural tube, axial skeleton, limbs, lungs, skin, hair and teeth (Bellusci et al., 1997; Hardcastle et al., 1998; Marigo et al., 1996). The Hedgehog signaling pathway plays critical role in the growth and patterning during the embryonic development (Kubo et al., 2004). The Hh signaling pathway is responsible for tissue polarity, patterning maintenance, and stem cell maintenance during embryonic development (Takebe et al., 2011). Hedgehog signaling is conserved in vertebrates and highly active during mammalian development, however, some postnatal organs, such as the central nervous system and the lung, depends on continued Hh signaling for tissue homeostasis and repair following injury (Merchant and Matsui, 2010).

Signal Transduction of Hedgehog

The mechanism of Hh protein processing, secretion and signaling appears to be more or less conserved in evolutions between Drosophila and higher organisms, except certain difficulties. Drosophila has only one Hh gene, whereas vertebrates have three homologues within different spatial and temporal distribution patterns:- Sonic Hedgehog (SHh), Indian Hedgehog (IHh) and Desert Hedgehog (DHh). In-vitro studies of these protein suggests that each of these goes through the same signal transduction pathway, and that the different hedgehog gene regulates patterning of different organ systems on basis of their expression of their unique pattern (Gupta et al., 2010; Wicking et al., 1999; Porter et al., 1995; Varjosalo and Taipale, 2007). The most widely studied among the three is SHh which is expressed widely throughout the developing central nervous system, gut, limb, teeth and hair follicle (Goodrich et al., Bellusci et al., 1997; Wicking et al., 1999), whereas DHh and IHh plays an important role in the development of germline and skeletal system respectively (Bitgood et al., 1996; Vortkamp et al., 1996).

The Hh gene is found to be a secreted molecule, which is a precursor of N-terminal signaling unit and C-terminal protease domain. The precursor Hh molecule is cleaved to release the active signaling domain called HhNp. Now, the C-terminal domain of the Hh polypeptide helps in catalyzing an intramolecular cholesteroyl transfer resulting in formation of C-terminal cholesterol modified N-terminal Hh signaling domain. The eventual cholesterol modifications results in alliance of Hh with the membranes, thus opening the way for the final processing step, in which the palmitoyl group is added to the N-terminal of Hh, thus generating the active form of HhN. The gene Rasp plays a crucial role in encoding the enzyme, required for Hh

acylation and production of active Hh (Gupta et al., 2010; Varjosalo and Taipale, 2007; Porter et al., 1996).

Hh is released from the cell through the transmembrane transporter Dispatched after the acylation of Hh N-terminus with the help of the enzyme Rasp located in the endoplasmic reticulum (Micchelli et al., 2002). The Hh signaling cascade is initiated in the target cell with the Hh ligand binding to the Patched1 protein (PTCH). In the absence of Hh ligand , PTCH catalytically inhibits the activity of the seven transmembrane - span receptor protein called Smoothened (SMO), potentially by affecting its localization to the cell surface. Now, upon binding of the Hh to PTCH, the Hh-PTCH complex is internalized, resulting in the loss of PTCH activity, thus consequent activation of the SMO, which helps in transduction of the Hh signal to cytoplasm (Taipale et al., 2002). Localization of SMO helps in the initiation of the signaling cascade in the mammals, which leads to the activation of the GLI family of the zinc-finger transcription factors. There are total three GLI proteins act as three separate zinc-finger proteins - GLI1 and GLI2 as transcriptional activators and GLI3 as a transcriptional repressor (Altaba et al., 2007; Corbit et al., 2005; Rubin and De Sauvage, 2006). The expression of GLI1 is considered to be actively dependent upon the Hh signaling and is thus often used as a marker of pathway activation (Gupta et al., 2010).

In the absence of a Hh ligand, PTCH blocks SMO activity and full-length GLI proteins are cleaved to create the repressor GLI^R, largely derived from GLI 3, which represses Hh target genes. Hh binding to PTCH alleviates the SMO inhibition, which helps in promoting the generation of the activator GLI^A, largely contributed by the GLI 2 and the subsequent expression of the target genes (Varjosalo and Taipale, 2007; Ferretti et al., 2005). Suppressor of fused (SUFU) acts as another negative regulator of the pathway by binding to Gli, both in the cytoplasm and in the nucleus, to prevent it from activating Hh target genes (Geng et al., 2007).

Hedgehog Signaling in Cancer

Abberant activation of the Hh pathway in cancers is due to two reasons: mutations in the pathway (ligand independent) or through the over expression of Hh ligand (ligand dependent) (Evangelista et al., 2006). Among the two reasons, three basic models have been proposed for Hh activity in cancer. The first to be discovered were Type I Hh-pathway-activating mutations, are considered to be ligand independent such as Basal Cell Carcinoma (BCC) and medullablastomas. Type II models are ligand dependent and have autocrine way of signaling, explaining that Hh is both produced and responded by the same tumor cells. Type III models are also ligand dependent but are found to have paracrine signaling, which suggests that Hh is produced by tumor epithelium which is received by the cells present in stroma, which feeds other signals back to the tumor to promote its growth and survival (Rubin and De Sauvage, 2006; Scales and De Sauvage, 2009).

Type I Hedgehog Signaling: Ligand Independent, Mutation driven

Hh signaling was initially linked to cancers, when identification of somatic PTCH mutations were found in patients of Gorlins syndrome (Hahn et al., 1996; Johnson et al., 1996). Patients diagnosed with Gorlins syndrome have a higher incidence ratio of developing BCC, medulloblastoma and rhabdomyosarcoma. Further testament to the fact was provided by abnormal Hh activity observed due to the presence of PTCH or SMO mutations found in sporadic BCCs and medulloblastomas (Johnson et al., 1996; Xie et al., 1998; Pietsch et al., 1997). About 85% of the tumors had inactivating mutations in PTCH or 10% of the activating mutations in SMO were found. Other than PTCH and SMO mutations, many components of Hh pathway can be also found in cancers such as SUFU mutations observed in medulloblastoma, GLI1 and GLI3 mutations related to adenocarcinoma, as well as GLI1 mutation in glioblastoma (Merchant and Matsui, 2010; Taylor et al., 2002; Parsons et al., 2008). Deregulated Hh signaling has led to increased cell proliferation and tumor formation. These observations have been confirmed in the mouse models also. Similar to patients observed with Gorlin's syndrome, mice with PTCH mutations were seen with medulloblastoma and were with a higher risk to develop UV-induced BCC (Gupta et al., 2010; Azterbaum et al., 1999).

Type II Hedgehog Signaling: Ligand Dependent, Over-Expression of Hh ligand

Several ligand-dependent cancers caused due to over-expression of Hh ligands have been identified in various type of cancers, including lung (Watkins et al., 2003; Yuan et al., 2007), pancreatic (Thayer et al., 2003), upper gastrointestinal tract (Berman et al., 2003; Ma et al ., 2006), colorectal (Qualtrough et al., 2004), prostate (Karhadkar et al., 2004; Sanchez et al., 2004), breast (Mukherjee et al., 2006) and melanoma (Stecca et al., 2007) tumors. In all of these malignancies, it was proposed that Hh was secreted in autocrine signaling, as Hh secreted from the tumor cell acted upon itself to stimulate proliferation or survival, leading to tumor growth (Scales and De Sauvage, 2009).The tumors observed with these type of signaling are found dissimilar to BCCs or medulloblastomas as they do not have any mutations in Hh signaling pathway. Increased Hh activity has been observed either due to mutational activation or due to autocrine signaling, which have been

seen to induce the expression of genes affecting proliferation, cell-survival, angiogenesis and instability (Ingram et al., 2008; Pola et al., 2001; Regl et al., 2004).

Type III Hedgehog Signaling: Ligand Dependent, Paracrine Signaling

There have been reports that tumor Hh signaling may occur via paracrine way of signaling, and has emphasized the significance of Hh signaling in promoting the tumor microenvironment (Yauch et al., 2008; Jiang and Hui, 2008). Hh signaling is critical to the development and maintenance of the various epithelial structures such as small intestine (Ingham and McMahon, 2001; Theunissen and De Sauvage, 2009, Varjosalo and Taipale, 2008). In such type of signaling, Hh ligand is secreted by the epithelium and is received by the mesenchymal stroma, which plays an important role in affecting and stimulating the proliferation. As soon as the Hh target genes are activated, the mesenchyme produces additional molecules that feed back to the epithelium (Pola et al., 2001; Hegde et al., 2008; Becher et al., 2008)

Recently, there has been an alternate type of paracrine signaling found in Hh signaling, known as "Reverse - Paracrine Signaling". In this type of signaling, Hh is received from the stroma and is received by the tumor cells (Theunissen and De Sauvage, 2009). In reverse paracrine signaling model, stromal Hh is considered to provide the appropriate tumor microenvironment for supporting tumor growth (Dierks et al., 2007). Until now, this has been observed in malignancies such as multiple myeloma, lymphoma and leukemia (Scales and De Sauvage, 2009; Becher et al., 2008; Epstein, 2008).

Hh signaling: A Modernistic Approach for Cancer

Many recent findings have revealed various roles of the Hh signaling pathway in the development and progression of various cancers. Many key molecules of Hh pathway such as SHh, IHh, DHh, PTCH1, SMO, SUFU and GLI factors plays an important role in the development of cancer.

The first hint, that showed the involvement of Hh pathway in contributing to cancer development, came with the studies, which described mutations in PTCH1 gene in BCC. This was supported by the discovery of mutations in PTCH1, SMO and SUFU at a higher incidence in spontaneous BCCs or medulloblastomas (Geng et al., 2007; Kool et al., 2008; Didiasova et al., 2018).

Abberant pathway activity has also been associated with response to increased levels of Hh ligand, found in many malignancies such as multiple myelomas, gastric, breast, prostate and pancreatic signaling. Autocrine signaling has been observed in many cases of multiple myelomas and gastric cancer. Paracrine signaling is also observed in prostate, pancreatic and lung cancer (Berman et al., 2002; Li et al., 2014; Bermudez et al., 2013). Over expression of Hh pathway components has also been found to be the reason for the pathway over activation in lung, gastric, ovarian and skin cancer (Huang et al., 2011; Wang et al., 2014).

The expression of GLIs is also induced in glioblastomas and breast cancer. Though several mechanism of Hh pathway activation plays a major role in cancer development and progression, it all comes to the level of transcription factors - GLIs, which performs transcriptional response to Hh signaling. GLI induces expression of genes which were involved in (i) proliferation: Cyclin D1, Cyclin D2, insulin-like growth factor 2 (IGF2), (ii) cell survival: B-cell lymphoma, (iii) angiogenesis: VEGF, (iv) genetic instability: p53 and (v) epithelial to mesenchymal transition and (vi) stem cell and self-renewal (Katoh and Katoh, 2009; Duman-Scheel et al., 2002; Laurendeau et al., 2010).

The clear link between the Hh pathways and human cancers, such as BCC and medulloblastoma, has garnered interest in identifying small molecule Hh antagonist to block the pathway (Chen et al., 2002). Initial evidences have been observed that Hh signaling can be pharmacologically inhibited by cyclopamine, a steroidal alkaloid derived from *Veratrum californicum,* as an active compound (Binns et al., 1972). Using cyclopamine or many small molecule antagonists, experiments have shown the prospective use of the compound by targeting the pathway in tumors when the pathway is mutated or in tumors where the Hh ligand is over-expressed (Chen et al., 2002; Frank-Kamenetsky., 2002). Cyclopamine has been observed in mouse xenograft models to inhibit tumor growth and proliferation in human orthotopic glioma, melanoma, colon, pancreatic and prostate cancers (Varnat et al., 2009; Feldmann et al., 2007; Sanchez and Altaba, 2005, Stecca et al., 2007, Karhadkar et al., 2004).

Initially, cyclopamine was found as a first Hh inhibitor which could target SMO. As a result of that Gli activation was inhibited. However, cyclopamine exhibited several undesired side effects such as skin toxicity in mouse model along with poor solubility and acid sensitivity, which halted its clinical trials for treating the patients with Hh tumors. Such unacceptable results of cyclopamine led to identify highly soluble, acid stable and potentially more suited compound for Hh tumors. Eventually Vismodegib (GDC-0449) was found with high solubility and acid stability as a standard therapy in patients with locally advanced, recurrent and metastatic BCC which was approved by the US Food and Drug Administration (FDA) in 2012 - a SMO antagonist (Chahal et al., 2018; Sekulic et al., 2012). Vismodegib binds to the SMO which is a downstrem activator of the pathway and suppresses its activity. It has shown the positive results in phase I and phase II clinical

trials in a variety of carcinomas. It is a compound of high permeability with low aqueous solubility. Vismodegib gets metabolized by CYP2C9, P glycoproteins and CYP3A4/5 and excreted from body by haepatic route. In patients with advanced stage of BCC, a daily dose of 150 mg of Vismodegib for 6 months and longer period of time showed various side effects such as alopecia, muscle spasms, weight loss, vomiting, diarrhoea, decreased appetite and fatigue in 20-40% of the patients (Abidi, 2014). Hh antagonists have also shown promises for treatment of medulloblastoma though human medulloblastoma tumors have seemed to be more responsive (Berman et al., 2002). In subsequent clinical trials for metastatic BCCs, Vismodegib treatment resulted in tumor regression which lead to the discovery of a novel SMO mutation in the tumor tissue (Rudin et al., 2009; Yauch et al., 2009). Although Vismodegib has shown fruitful results in the initial phases of the clinical trials, its long term efficiency and sensitivity needs to be determined in phase III clinical trials. Additionally, these trials have not been conducted in Indian population for efficacy and safety purpose which needs be determined before application in the wider range of the population and other tumors also (Abidi, 2014). Recently, phosphotidylinositol 4 phosphate (PI4P) – a new player of the Hh has found to play role as a pathway activator. The cellular level of PI4P increases upon the activation of the Hh pathway (Jiang et al., 2016). Additionally, PI4P was found essential for the normal Hh signaling because knockout of the inositol 5 phosphatase resulted in decrease in cellular response to Hh pathway (Chavez et al., 2015; Garcia-Gonzalo et al., 2015). A change in local ciliary membrane could make as a target to control the elevated levels of PI4P and thus, may regulate the Hh signaling. However, further *in-vivo* experiments are needed to understand the mode of action for development of more efficient therapies for Hh pathway dependent tumors (Wu et al., 2017).

Several other SMO antagonists such as PF-04449913 (Pfizer), LEQ-506 (Novartis Pharmaceuticals), Itraconazole (John Hopkins University) - all in Phase 1 clinical trials and Vitamin D3 (Mastricht University Medical Centre) and BMS-833923 (Bristol-Myers Squibb) - in Phase 2 Clinical trials , are currently undergoing development (Chahal et al., 2018).

Hh Signaling inhibitors have been also found which blocks the signaling by interaction between Hh ligand and PTCH receptor. 5E1, a monoclonal antibody blocks the binding of Hh to PTCH and reduces the growth of breast, and GI tumors. It has also been used to inhibit growth of medulloblastoma in mouse models. However, animal models have shown a reduced tumor proliferation, increased tumor cell apoptosis and are found to have a better survival compared to cyclopamine-treated mice (Maun et al., 2010; Coon et al., 2010; Chang et al., 2013). Yet, it has not reached human trials. Robotnikinin is also found to have positive results on blocking Hh pathway by binding to Shh ligand (Stanton et al., 2009; Laukkanen and Domenica, 2016).

Considering, development of resistance for Vismodegib via SMO mutation, efforts were put to target the GLI which identified compounds (GANT 58 & GANT 56) to inhibit the transcription mediated by GLI (Akyla & Peppelenbosch, 2018). Additionally, arsenic trioxide (ATO) is an approved FDA inhibitor of GLI1 and GLI2 transcription factors. ATO has also been found playing a major role in increasing apoptosis, reducing tumor cell growth and decreasing SHh target genes in osteosarcoma, acute promyelocytic leukemia, malignant pleural mesothelioma, malignant rhabdosarcoma, prostate, and colon cancer cell lines and xenograft models (Bansal et al., 2015; Cai et al., 2015; Kerl et al., 2014; Nakamura et al., 2013; Yang et al., 2013; You et al., 2014). It has been shown to inhibit GLI-dependent growth in medulloblastomas mouse models and block GLI2 accumulation in primary cilia (Beauchamp et al., 2011). These drugs may become a boon in the future for the patients carrying chemoresistant tumors and poor prognosis. However, it is necessary to keep in mind while designing a novel compounds that such compounds must not disturb the Patched-dependent Smoothened-independent non-canonical signaling.

There have been other combination therapies also, which is suggestive of providing a more effective treatment strategy than a monotherapy. There have been many cross-talks between various pathways such as Wnt and Notch and combination therapies along with radiotherapy are under preclinical trials or clinical studies (Filbin et al., 2013; Ma et al., 2013).

In addition to this, the different levels of Hh signaling pathway can be blocked via developing anti SHh-antibody could be an area to explore the research (Merchant et al., 2017).

Summary and Conclusion

Deregulated Hh signaling is associated with tumor growth and proliferation. It increases tumor aggressiveness and raises the frequency of metastasis. Targeting CSC via modification of the Hh pathway – an embryonic developmental signaling pathway holds the promise of preventing disease relapses. From the studies till now, it is very clear that there are various issues still to be solved out regarding the role of Hh signaling pathway in human cancers, including the precise mechanisms of signal transduction, the exact mode of signaling between tumor cells and the microenvironment, and the role of signaling cascade in the regulation of CSCs. However, the study of this pathway is in

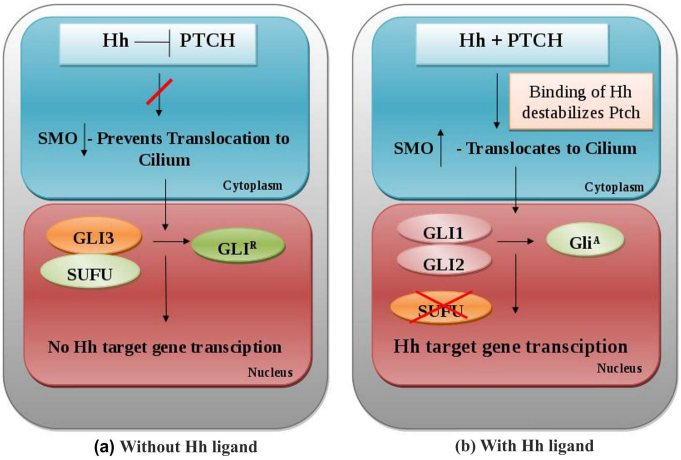

Figure 1. Hedgehog Signaling Pathway: In the absence of Hh ligand,Figure 1(a), PTCH1 binds to SMO, thus preventing its translocation to cilium. This leads to sequestration of GLI in cytoplasm, their association with negative regulator, resulting into subsequent cleavage into GLI repressor form, which blocks Hh gene transcription. Whereas in the presence of Hh ligand Figure 1(b), SMO inhibition by PTCH1 does not takes place, and SMO translocates to cilium, preventing GLI cleavage. GLI proteins get dissociated from SUFU, resulting into activation of GLI activator form, which then transports to nucleus, and helps in expressing target Hh gene.

Table 1. Various Hh signaling pathway molecules as targets in various cancers

Hh Pathway Targets	Malignancies	References
PTCH	Basal Cell Carcinomas, Medulloblastoma, Rhabdomyosarcoma	Geng et al., 2007; Kool et al., 2008; Tostar et al., 2006
SMO	Basal Cell Carcinomas, Medulloblastoma, Triple negative breast cancer	Geng et al., 2007; Kool et al., 2008; Tao et al., 2011
SUFU	Medulloblastoma, Rhabdomyosarcoma	Taylor et al., 2002; Tostar et al., 2006
GLI1	Pancreatic Adenocarcinoma, Glioblastoma, Triple Negative Breast Cancer	Parsons et al., 2008; Tao et al., 2011
GLI3	Pancreatic Adenocarcinoma	Parsons et al., 2008
Hh ligand	Lung Cancer, Pancreatic Cancer, Upper GI tract cancer, Colorectal Cancer, Prostate Cancer, Breast Cancer, Melanoma Cancer	Watkins et al., 2003; Thayer et al., 2003; Berman et al; 2003; Ma et al., 2006; Qualtrough et al., 2004; Karhadkar et al., 2004; Sanchez et al., 2004; Mukherjee et al., 2006; Stecca et al., 2007

its infancy, informative molecular biomarkers that interrogate pathway activity and predict efficacy are necessary to yield mature products for cancer patients.

Conflicts of interest: Nil

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Abbreviations

ATO : Arsenic Trioxide
BCC : Basal Cell Carcinoma
CSCs : Cancer Stem Cells
DHh : Desert Hedgehog
FDA : Food and Drug Administration
Hh : Hedgehog
IHh : Indian Hedgehog
PTCH1: Patched 1 protein
SHh : Sonic Hedgehog
SMO1 : Smoothened1 protein