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Review

Piceatannol mediated regulation of deregulated signaling pathways in different cancers: Tumbling of the ninepins of molecular oncology

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Abstract: With the recent technological advancements, a new golden era of natural products drug discovery has dawned. Increasingly it is being realized that structural modularity of many pharmacologically active products derived natural sources allows a building-block approach which can be exploited for analysis of regulation of deregulated oncogenic protein networks in different cancers. Piceatannol has been shown to effectively modulate JAK/STAT, Wnt/β-catenin, mTOR pathway in different cancers. In addition, certain hints have emerged which shed light on the regulation of microRNAs by piceatannol in some cancers. Regulation of deregulated oncogenic pathways by Piceatannol is gradually capturing attention and might be helpful in the multi-targeting of deregulated oncogenic networks in cancers.

Key words: Cancer; Piceatannol; Apoptosis; Molecular oncology; Signaling.

Introduction

Nobel Prize in Physiology or Medicine 2015 was awarded by the Nobel Assembly at Karolinska Institutet (Stockholm, Sweden) to honour the discovery of high-quality pharmacologically active natural products. These ground-breaking discoveries have re-iterated pinnacle significance of bioactive molecules derived from natural sources for treatment of different cancers (1,2). Excitingly, tremendous advancements have been made in the past five decades and we have witnessed waves of transformative innovation in the R&D which paradigmatically shifted the visions in molecular pharmacology: the appraisal of 'rational drug discovery' methodology in the 1970s, followed by the development of recombinant proteins as effective therapeutic options in 1980s (3). Medicinal role of biologically active products derived from natural sources has urged researchers to uncover wide-ranging biological effects (4). Essentially, natural products have the potential to re-emerge as a key start-point in discovery of pharmacologically active chemopreventive agents (5). While significant research continues to focus on strategies to prevent/inhibit cancer, sophisticated knowledge has helped us in developing a better understanding of the heterogenous nature of cancer. There has been an explosion in the field related to molecular analysis of pharmacological properties of natural products. Piceatannol is a bioactive molecule reportedly involved in regulation of diverse protein networks in different cancers. In this review, we will exclusively focus on the available literature related to piceatannol-mediated targeting of oncogenic protein networks in wide variety of cancers.

Regulation of JAK/STAT Signaling

Binding of the extracellular proteins to cell-surface receptors ignites intracellular signaling and spatio-temporally changes nuclear gene expression patterns. STAT (signal transducer and activator of transcription) proteins are transcriptional factors reportedly involved in regulation of target gene network in different cancers. Kinases of the Janus kinase family and members of the STAT family mechanistically constitute a membrane-to-nucleus signaling module which regulates wide-ranging cellular processes.

In this section we will exclusively focus on Piceatannol mediated regulation of STAT proteins in different cancers. However, before critical evaluation of STAT-targeting activity of Piceatannol, we will summarize some of the STAT proteins reportedly involved in regulation of cancer.

STAT1 behaved as a double-edge sword in cancer. Available evidence highlighted diametrically opposed roles of STAT1. The inhibition of JAK1/STAT1 cascade sensitized ovarian cancer cells to bortezomib-mediated

apoptosis (6). Interestingly, STAT1β interacted with STAT1α and reduced degradation of STAT1α by the proteasome. Furthermore, STAT1β potently enhanced DNA binding and transcriptional activity of STAT1. STAT1β also sensitized esophageal squamous cell carcinoma cells to chemotherapeutic drugs (7)

STAT2 inhibition suppressed colony forming ability and cell proliferation of melanoma cells (8). STAT2 fueled cancer progression and glioblastoma tumorigenicity (9).

EZH2 (Enhancer of Zeste Homolog 2) is a histone methyltransferase (10). However, studies have shown that contextually, EZH2 can switch from histone to a non-histone methyltransferase. EZH2 has been shown to methylate STAT3 in prostate cancer cells. Therefore, inhibition of STAT3 methylation is necessary to inhibit prostate cancer (10). JAK-STAT signaling is also tightly regulated by non-coding RNAs. MiR-26a, a tumor suppressor miRNA negative regulated JAK1. However, circular RNA-9119 interfered with miR-26a-mediated targeting of JAK1 and promoted JAK1-STAT3-induced signaling (11).

STAT3-transcriptionally upregulated a long non-coding RNA, DLGAP1-AS1 and protected IL-6 from targeting by miR-26a-5p and miR-26b-5p in hepatocellular carcinoma cells (12).

Recent studies have also shown that STAT3 stimulated the expression of another oncogenic lncRNA, BlackMamba which worked synchronously with DNA helicase HELLS and played central role in the maintenance of the neoplastic phenotype of ALK$^-$ALCL (13).

STAT5A induced upregulation of an oncogenic lncRNA, SNHG17 in prostate cancer cells (14). miR-339-5p directly targeted STAT5A but SNHG17 sequestered miR-339-5p away and potentiated the expression of STAT5A in prostate cancer cells. Tumor growth was considerably reduced in mice xenografted with SHNG17-silenced prostate cancer cells (14).

Ever-increasing list of studies suggested linchpin role of JAK/STAT signaling in different cancers.

Tyrosine phosphorylation of STAT3 and STAT5 was selectively inhibited by piceatannol (15).

Piceatannol exerted suppressive effect on lung metastasis in BALB/c mice injected with 4T1 breast cancer cells (16). Piceatannol also reduced infiltration of macrophages in 4T1 tumor tissues. Piceatannol suppressed p-STAT3 in 4T1 tumor tissues (16). Piceatannol was also found to effectively inhibit IL-6/STAT3 signaling in prostate cancer cells (17).

Rituximab, a monoclonal anti-CD20 antibody was found to be effective against human diffuse large B-cell lymphoma (18). HMGB1 (High mobility group protein B 1) caused bending of DNA and facilitated the binding of multiple regulatory protein complexes to DNA. Rituximab induced exit of both STAT3/HMGB1 to the cytoplasm and disassembly of STAT3 and HMGB1. Additionally, rituximab reduced phosphorylated levels of STAT3 (18).

Anti-IL-10 antibody and rituximab treatment reduced STAT3 binding to promoter region of target genes (19). Moreover, reduction in STAT3 activation by these treatments correlated with a decrease in expression of Bcl-2. Piceatannol reduced p-STAT3 levels and downregulated the expression of Bcl-2 (19).

Targeted inhibition of STAT3 and STAT5 activity has been reported to be advantageous in cell culture and animal models using siRNA-mediated knockdown of STAT proteins. Result-oriented approaches which can robustly disrupt STAT phosphorylation or inhibit nuclear accumulation of STATs will be highly effective. In addition, inhibition of physical association of STAT proteins and DNA can also yield encouraging results. These strategies have been shown to exert inhibitory effects on cancer cell proliferation and tumor growth in xenografted mice.

Regulation of TRAIL/TRAIL-R and FasL/Fas Signaling

Apoptosis is a highly intricate mechanism and substantial fraction of high-impact research-work has enabled us to develop a better knowledge of the underlying mechanisms which make cells resistant to drug-induced apoptosis. Apoptosis is classically divided into categories. Extrinsic pathway is activated through death receptor pathway (FasL/Fas, TRAIL/TRAIL-R and TNF/TNFR). While intrinsic pathway is routed through mitochondria. Our rapidly expanding knowledge about the role of mitochondria in molecular biology has revealed that mitochondria is a key platform for a plethora of cell signaling cascades. Research on this paradigmatic TRAIL-driven pathway has undergone substantial broadening. We have witnessed exponential growth particularly in the past two decades which has generated wealth of knowledge that profoundly influenced modern understanding of loss of TRAIL-mediated apoptosis and cancer progression.

Piceatannol induced significant increase in mRNA and protein levels of DR5 (20). Furthermore, piceatannol enhanced promoter activity of DR5 via activation of Sp1 (shown in figure 1). Piceatannol increased binding of Sp1 to the promoter region of DR5 (20).

Piceatannol although inhibited ERK-mediated phosphorylation of c-Fos but simultaneously promoted p38MAPK-induced c-Jun and ATF2 phosphorylation (21). Downregulation of c-Jun or/and ATF2 by siRNA repressed upregulation of Fas/FasL in piceatannol-treated cells. Collectively, these findings provided clear evidence that c-Fos suppressed functional activity of ATF2/c-Jun heterodimer (21).

Higher expression of NOXA was noted to be critical in the induction of apoptosis (22). Therefore, piceatannol not only stimulated p53-triggered expression of NOXA and simultaneously enhanced degradation of XIAP via the ubiquitin–proteasomal pathway and activated caspase-3 to induce apoptosis (shown in figure 1). Co-treatment with piceatannol and cisplatin significantly induced regression of tumors in mice subcutaneously implanted with OV2008 cancer cells (22).

Piceatannol was also found to enhance the cytotoxic effects of gemcitabine by enhancing expression of the proapoptotic protein Bak (23).

Piceatannol induced an increase in the levels of truncated Bid and Bax but lowered the levels of Bcl-xL and Mcl-1 in prostate cancer cells (shown in figure 1) (24).

As highlighted above, scientists have dismantled the complexity of the layered regulatory roles that diverse

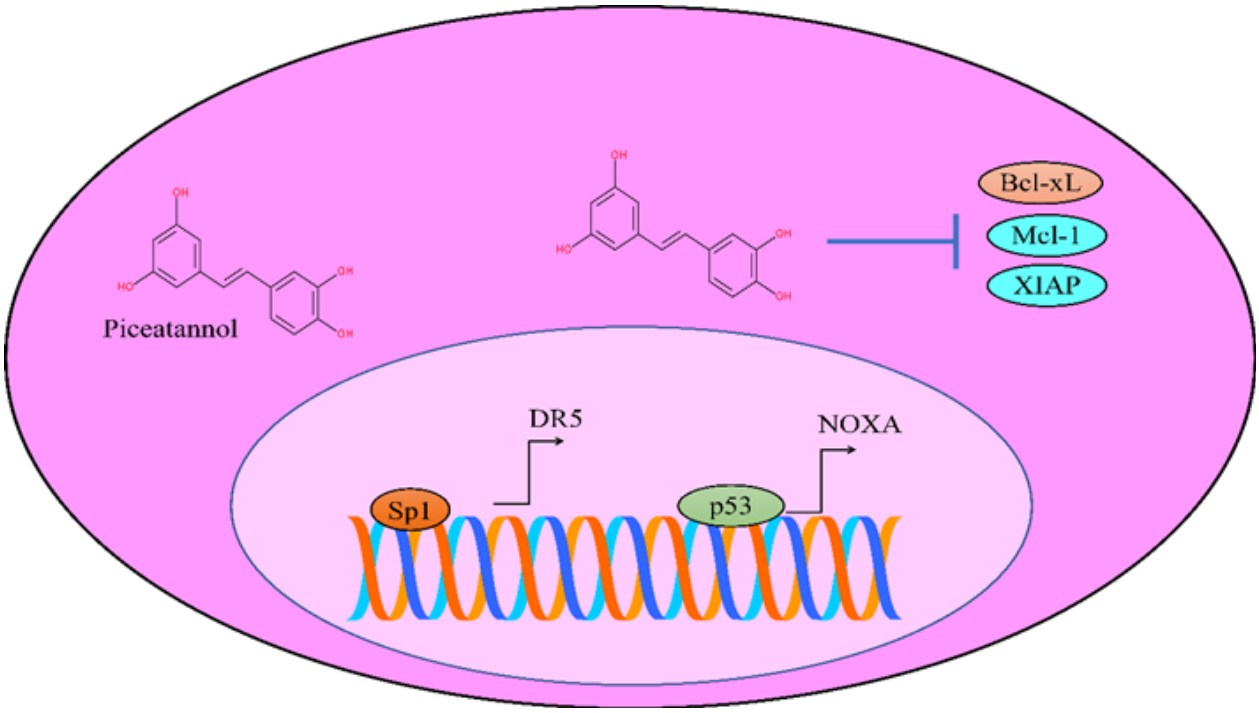

Figure 1. Piceatannol mediated regulation of apoptotic pathway. Piceatannol stimulated the expression of pro-apoptotic genes (NOXA). Whereas, piceatannol inhibited anti-apoptotic proteins.

pathways play in the modulation and stability of key constituents of the TRAIL-induced signaling cascade. In the past few years, we have witnessed significant developments in our understanding related to regulation of TRAIL-driven pathway by oncogenic cell signaling pathways and non-coding RNAs.

mTOR-driven Pathway

Intriguingly, biochemical effects of mTOR signaling are multifaceted and context specific. Different natural and synthetic agents have been shown to reduce mTOR-driven downstream signaling. They efficiently blocked phosphorylation of S6K1 and 4E-BP1 by mTORC1, which altered the translation of wide variety of mRNAs.

Piceatannol exerted inhibitory effects on mTOR and 4E-BP1 in prostate cancer cells (25). More precisely, piceatannol cell-type specifically reduced mTOR levels and p-4E-BP1 in prostate cancer cells (25).

In breast cancer cells, piceatannol reduced p-mTOR levels (26).

Likewise, piceatannol reduced p-Akt and p-mTOR in osteosarcoma cells (27). Intraperitoneally injected piceatannol induced regression of tumors in mice xenografted with osteosarcoma cells. Levels of p-Akt and p-mTOR were also found to be reduced in tumor tissues of piceatannol-treated xenografted mice (27).

Wnt/β-catenin Signaling

Genome sequencing and gene expression studies have helped researchers in the identification of novel Wnt pathway constituents and their functionalities. Wnt pathway is characterized into β-catenin dependent and independent signaling.

Previous studies had shown that β-catenin interacted with the DNA-binding TCF (T cell factor) family proteins and transcriptionally controlled the expression of target gene networks. Piceatannol reduced the levels of β-catenin and TCF4 in multiple myeloma cells (28).

p-Tyrosine-142- β-catenin is present in centrosomes in glioblastoma (U251MG and U87MG) cells (29). Spleen tyrosine kinase (SYK), a non-receptor tyrosine kinase phosphorylated β-catenin at Tyrosine residues. p-Tyr142-β-catenin contributed to the maintenance of centrosome cohesion. Upon mitotic entry, absence of p-Tyr142-β-catenin and Syk at the centrosomes allowed their separation, corrected bipolar spindle formation and chromosomal segregation. Piceatannol reduced centrosomal p-Tyr142- β-catenin levels (29).

Regulation of Protein Network in Different Cancers

PD-L1 (Programmed cell death ligand 1) is present on cancer cells. PD-L1 interacted with its receptor PD-1 (programmed cell death 1) and initialized an immunological response (30).

Series of published studies have shown that key step in NFκB activation is the IKK (IκB kinase) complex-mediated phosphorylation of IκB proteins, which leads to IκB protein ubiquitylation and consequent degradation. Loss of IκB resulted in the release of cytoplasmic NFκB complexes, which moved into the nucleus and stimulated the expression of target genes. Thus, different signaling pathways which converge on the activation of the IKK complex are vital in activation of NFκB. BMS-345541 (IKK inhibitor) blocked IκB phosphorylation and efficiently inhibited accumulation of NFκB in the nucleus. BMS-345541 treatment interfered with piceatannol and resveratrol-induced PD-L1 upregulation in SW620 cells. However, in the absence of BMS-345541, piceatannol and resveratrol strongly induced the expression of PD-L1 by promoting nuclear translocation and accumulation of NFκB (30).

Cbl proteins are a highly conserved family of ubiquitin ligases tightly involved in regulation of signaling pathways (31). Catechol ring of piceatannol was oxida-

tively converted into a highly reactive O-benzoquinone which triggered piceatannol-induced Cbl loss (31).

Regulation of TGF/SMAD and Notch pathway by Piceatannol: Outstanding Questions

It will not be wrong to say that we have scattered pieces of information in context of the ability of piceatannol to modulate cell signaling pathways. Therefore, in this section, we have highlighted different cascades which not only have critical involvement in carcinogenesis but they have been pharmaceutically targeted in different cancers by wide range of bioactive natural products.

TGF/SMAD signaling has emerged as a versatile transduction cascade reportedly involved in regulation of different cancers. SMAD proteins are phosphorylated and accumulate in the nucleus to transcriptionally control expression of target gene-network. Whether or not piceatannol modulates TGF/SMAD pathway in various cancers is an intriguing query which needs detailed research. It will be exciting to analyze if piceatannol inhibited SMAD-driven signaling and blocked proliferation and metastasis.

Emerging evidence highlights that Notch signaling depends basically on contextual cues such as interaction with the tumor microenvironment and crosstalks with different signaling cascades. Crosstalk between Notch and other signaling pathways may provide opportunities for combinatorial treatments, particularly in specific cancers where targeting several pathways simultaneously may offer significant advantages and fewer side-effects.

Regulation of microRNAs by piceatannol

The discovery of non-coding RNAs has opened new horizons for an ever-widening understanding of cellular processes that are controlled or influenced by non-coding RNAs.

FOXP3 acted as a central transcription hub for multiple cellular stimuli in variety of cancers. FOXP3 has also been reported to transcriptionally control expression of non-coding RNAs (32,33). Likewise, binding sites for FOXP3 had also been identified in promoter of miR-183. Series of experiments provided important information and uncovered the underlying mechanism of regulation of miR-183 by FOXP3. Molecular insights revealed that binding of FOXP3 to promoter region of miR-183 stimulated its expression.

Inhibition of miR-183 function or mutation of the miR-183-binding sites stabilized mRNA of β-TrCP and elevated the levels of β-TrCP (34). FOXP3-induced miR-183 expression markedly interfered with β-TrCP-induced degradation of Sp1. Stable Sp1-mediated upregulation of ADAM17 (A disintegrin and metalloproteinase 17) in cancer cells. Piceatannol exerted repressive effects on FOXP3 and downregulated miR-183 in leukemia cells. miR-183 suppression induced an increase in the stability of β-TrCP (35). Collectively, these findings suggested that piceatannol interfered with FOXP3-triggered stimulation of miR-183. Additionally, β-TrCP negatively regulated Sp1 and inhibited expression of ADAM17 in piceatannol-treated leukemia cells (shown in figure 2).

Recently emerging insights into the dynamic interactions between BCL-2 family proteins and regulatory role of these proteins in apoptotic cell death in different cancers had unveiled previously unexplored opportunities for pharmaceutical targeting of anti-apoptotic proteins. BCL-2 is frequently overexpressed in different apoptosis-resistant cancers.

miR-129

miR-129 mediated targeting of Bcl-2 was blocked by a long non-coding RNA, NEAT1 in nasopharyngeal cancer cells. Intratumorally injected miR-129 substantially potentiated the tumor-suppressive effects of HDAC inhibitor (SAHA) in mice xenografted with C666-1R cells (36).

Resistance to gefitinib (tyrosine kinase inhibitor) has become a major stumbling block in improving the clinical outcome of patients with advanced-stage and metastatic esophageal squamous cell carcinoma. PART1, an oncogenic lncRNA induced by STAT1 sponged away miR-129 and potentiated the expression of Bcl-2 (37).

Piceatannol stimulated miR-129 in colorectal cancer (HCT116, HT29) cells (38). miR-129 directly targeted BCL-2 and induced apoptosis in colorectal cancer cells.

miR-181a

Piceatannol induced miR-181a expression in melanoma (WM266-4, A2058) cells (39). BCL-2 was also found to be directly targeted by miR-181a (39).

Piceatannol mediated inhibition of miR-21

PTEN (Phosphatase and tensin homolog) is a tumor suppressor molecule and negatively regulates PI3K/AKT signaling. PTEN is directly targeted by miR-21 in osteosarcoma cells. Piceatannol inhibited miR-21 mediated targeting of PTEN (40).

Xenografted mice-based Studies

Preclinical modeling has been compounded over the past few years by the existing bottlenecks that tumors are not as simple as was previously surmised. There is now growing evidence of highly intricate intra- and inter-tumor heterogeneity which exists within and between human cancer samples and for a central role of the tumor microenvironment in driving carcinogenesis, drug resistance and loss of apoptosis.

Mouse models comprise xenograft, spontaneous or genetically modified models. Importantly, xenografted mice are most widely utilized models in the drug discovery pipeline for evaluation of drug efficacy, pharmacodynamic and pharmacokinetic features.

Piceatannol and trimethoxy-resveratrol reduced and delayed tumor growth in mice xenografted with LNCaP prostate cancer cells (41). As piceatannol carried an additional hydroxyl group, therefore it had a shorter plasma half-life (4.23 hr). Intravenously administered piceatannol was rapidly glucoronidated in rats [42]. Piceatannol had high volume of distribution values which provided evidence of greater distribution of piceatannol in tissues (42).

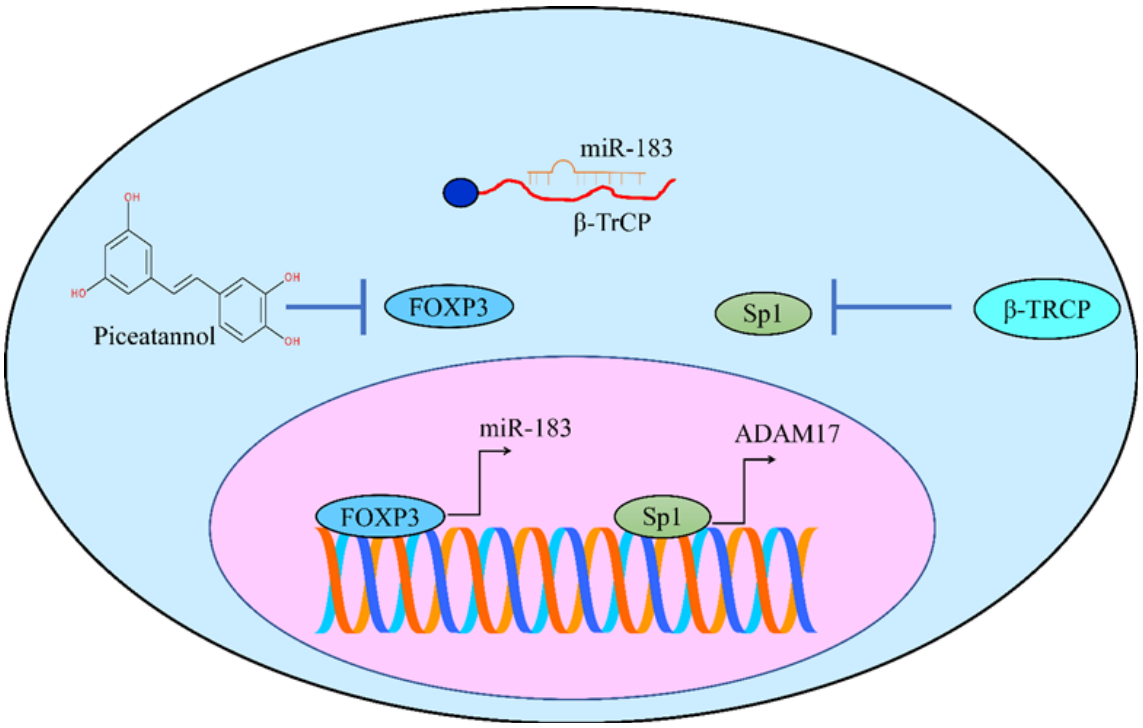

Figure 1. Piceatannol mediated inhibition of FOXP3/miR-183 signaling axis. FOXP3 transcriptionally upregulated miR-183. Consequentially, miR-183 directly targeted β-TrCP and potentiated the expression of Sp1. Sp1induced upregulation of ADAM17 and promoted cancer.

Failure of most of the drugs in later phases of clinical trials is challenging. Comprehensive analysis of bioactive molecules and detailed analysis of multiple dimensions of pharmacological aspects will help in

bridging the translational gaps and development of clinically effective drugs (43-46). Validation of drug candidates in disease-based animal models (47-50) that are integrated with translationally relevant end point analysis will be useful in reduction of the costly clinical-stage attrition in drug discovery and eventually guide to therapies having minimum off-target effects.

Concluding remarks

Translation of therapeutically effective products to a clinically effective drug needs cutting-edge research. Firstly, different products are screened for possible pharmacological characteristics. Therefore, based on the encouraging scientific results obtained through cell culture-based studies, scientists evaluate the biological and therapeutic efficacy of potential drug in animal models. Technically, animal models are characterized into different categories. An introspective appraisal of current preclinical models is warranted to improve future translational modeling and maximize the possibility of entry of therapeutically relevant natural products into various phases of clinical trials.

Natural product research has always remained at the forefront to provide novel lead compounds having premium pharmacological properties and ability to target oncogenic cell signaling pathways in wide variety of cancers. Piceatannol has been shown to modulate different transduction cascades however, it seems clear that we still have to go a long way to realistically reap full benefits of piceatannol as an effective anticancer agent. There are visible knowledge gaps in our understanding related to regulatory role of piceatannol in different cancers. As is often the case in molecular oncology, as ground-breaking discoveries bring answers to specific questions but simultaneously, they also pose new ones. For example, it remains to be defined how piceatannol modulated TGF/SMAD, SHH/Gli and Notch pathways in different cancers.

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