Cellular and Molecular Biology

Jabeen *et al. Cell. Mol. Biol.*2016, 62 (7): 110-117
ISSN: 1165-158X
doi: 10.14715/cmb/2016.62.7.19

Review

How sesquiterpenes modulate signaling cascades in cancers

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Abstract: Data obtained from high-throughput technologies has started to shed light on the interplay between signal transduction cascades and chromatin modifications thus adding another layer of complexity to the already complex regulation of the protein network. Based on the insights gleaned from almost a decade of research, it has now been convincingly revealed that sesquiterpenes effectively modulated different intracellular signaling cascades in different cancers. In this review we summarize how sesquiterpenes mediated Wnt, Shh, Notch and TRAIL induced signaling cascades.

Key words: Sesquiterpene, Apoptosis, Signaling, Cancer, TRAIL, Wnt, SHH, Notch.

Introduction

Increasingly it is being realized that resistance mechanisms to 'classical' chemotherapeutic drugs and to targeted therapies have many features in common, such as genomic instability, tumor heterogeneity, ineffective induction of cell death and activation of pro-survival signaling cascades (1,2,3). With the increasing arsenal of naturally derived and synthetic agents, improved preclinical models of tumor bearing mice and arrival of high-throughput methodologies for screening, there are now opportunities to develop a better and comprehensive knowledge related to strategies to overcome resistance against therapeutics by clinically evaluating rationally designed drug combinations and the use of predictive biomarkers to enable stratification of patients (4,5,6).

With the growing list of natural products from a variety of sources, many fundamental questions remain. Is the phytochemical safe with significantly higher bioavailability, how it targets oncogenic network in cancer cells, how it activates frequently inactive tumor suppressor genes in cancer cells. Upcoming section provides an overview of most recently reported sesquiterpenes who have shown efficacy in overcoming resistance against TRAIL based therapeutics.

TRAIL mediated apoptosis: Rebalancing of pro- and anti-apoptotic proteins to overcome resistance against TRAIL based Therapeutics

Loss of apoptosis is a hallmark feature of cancer and decades of research has revealed different signaling cascades which contribute to induce apoptosis (7,8,9). TNF-related apoptosis-inducing ligand (TRAIL) has attracted considerable attention because of its ability to selectively kill cancer cells while leaving normal cells intact. TRAIL induced apoptosis in cancer cells through death receptors (DR4, DR5). TRAIL induced assembly of different proteins at death receptor which included FADD and pros-caspase-8 (10,11). This multi-protein machinery is noted to be necessary for activation of caspase-8. Caspase-8 activated its downstream effector caspase-3. Intrinsically controlled apoptosis is triggered through translocation of truncated Bid into mitochondrion. Entry of tBid induces release of cytochrome c from mitochondrion. Interaction of Cytochrome c, APAF and pro-caspaspase-9 leads to the assembly of a signaling platform, the apoptosome, which activates the initiator caspase-9 (12,13,14). (Shown in figure 1). It has been extensively reported that expression levels of death receptors are frequently downregulated on surface of cancer cells. Different natural products have been tested to improve cell surface expression of death receptors. In the upcoming section we discuss different sesquiterpenes which have been shown to either enhance cell surface expression of death receptors or rebalance pro- and anti-apoptotic proteins to induce apoptosis in TRAIL resistant cancer cells.

Parthenolide, a sesquiterpene lactone, significantly enhanced DR5 expression on surface of treated cancer cells. (Shown in figure 1). Additionally, Parthenolide induced tumor growth inhibition in xenografted mice (15,16). 100 ng/mL of TRAIL and 50 µg/mL aplysin

Received June 16, 2016; **Accepted** June 25, 2016; **Published** June 30, 2016

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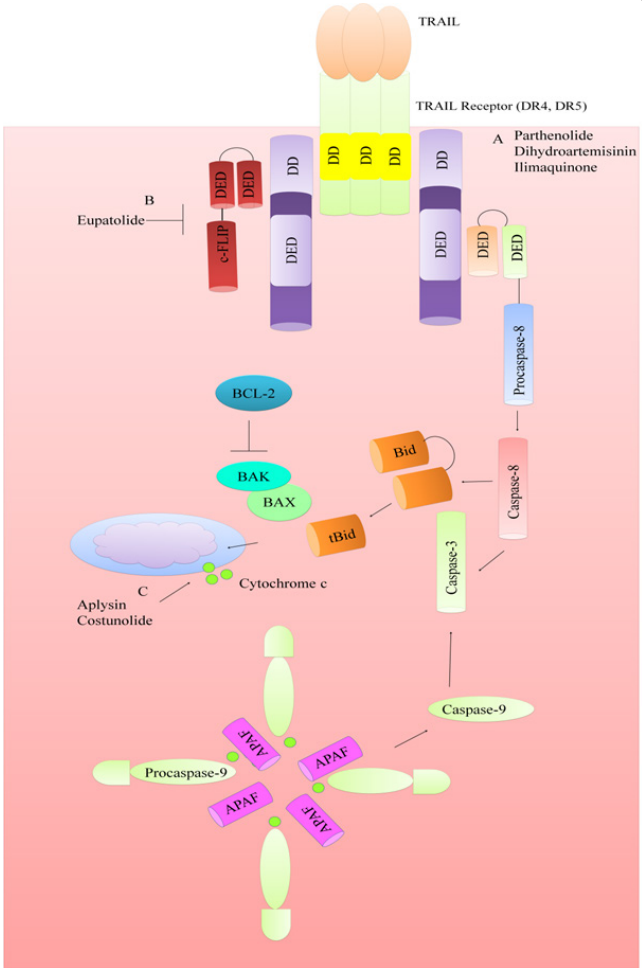

Figure 1. TRAIL mediated signaling. (A) shows chemicals mediated upregulation of DR5. (B) shows Eupatolide mediated inhibition of cFLIP (a negative regulator of apoptosis). (C) shows sesquiterpenes mediated increase of cytochrome c in cytoplasm.

combinatorially inhibited survival of different tested cancer cell lines by 70%–90%. Aplysin facilitated cytosolic accumulation of cytochrome C and notably reduced survivin levels in treated cancer cells (17).

Bcl2 and Bcl-xL are negative regulators of TRAIL induced apoptosis and effectively inhibited by Ilimaquinone (18). Ilimaquinone strongly up-regulated expression levels of DR4 and DR5 in treated cancer cells. DR4 and DR5 were induced by ilimaquinone through upregulation of CCAAT/enhancer-binding protein homologous protein (CHOP). CHOP, DR4 and DR5 were upregulated through activation of p38 mitogen-activated protein kinase (MAPK) and extracellular-signal regulated kinase (ERK) signal transduction cascades (18). Another important piece of information was added that highlighted role of an additional protein for upregulation of CHOP and DR5. Eukaryotic translation initiation factor-2α (eIF2α) is noted to be involved in upregulation of CHOP (19). Transfection assay indicated that CHOP mediated upregulation of DR5 was considerably reduced in mutant-eIF2α expressing cancer cells. Verrucarin A has been shown to increase phosphorylated levels of eIF2α (19).

Guaianolides and Eudesmane type sesquiterpenoid obtained from *Kandelia candel* dramatically sensitized resistant gastric adenocarcinoma cells to TRAIL (20).

Costunolide, an active sesquiterpene lactone is reportedly involved in promoting cytosolic accumulation of cytochrome c. Costunolide also notably reduced Bcl-2/Bax ratio to induce apoptosis in osteosarcoma U2OS cells (21). Dihydroartemisinin considerably increased cell surface expression of DR5 by enhancing ROS levels in treated cancer cells (22). Mode of action of different sesquiterpenes from different sources has been shown in table 1 and 2.

Eupatolide considerably inhibited expression levels of c-FLIP in MCF-7 cells. Moreover, Eupatolide mediated effects were non-significant in cancer cells reconstituted with c-FLIP. Euaptolide dose- and time-dependently reduced phosphorylated levels of AKT (23).

Wnt signaling

Wnt induced intracellular signaling biology has undergone substantial broadening over the years. It is now known that in the absence of signals, a multi-protein destruction complex consisting of GSK3β, adenomatous polyposis coli (APC) and Axin post-translatio-

Table 1. Targeting of different proteins by Sesquiterpenes.

Compounds/Source	Targets	Cancer Cell Lines	Reference
Alpinisin A (*Alpinia officinarum Hance*)		SGC-7901, MCF-7, Caski	61
Dihydro-β-agarofuran sesquiterpene polyesters (*Tripterygium regelii*)		Taxol-resistant A549T	62
1β-O-p-methoxy-E-cinnamoyl-5α-keto-11α-enol-albicanol, isomer 1β-O-p-methoxy-E-cinnamoyl-5α-keto-11β-enol-albicanol, 1β-O-p-methoxy-E-cinnamoyl-isodrimeninol (*Drimys brasiliensis Miers*)		K562, Nalm6	63
Alantolactone	CDKN1B (p21) Bax, Caspase-3 ↑ Bcl-2 ↓	SW480, SW1116 colorectal cancer cells	64
Costunolide	P53, P21, Bax ↑ Bcl-2 ↓	Esophageal cancer Eca-109 cells	65
Zerumbone (*Zingiber zerumbet Smith*)		Hep-2	66
Chaetopenoids A-F, dendryphiellin A1, 6-methyl-(2E, 4E, 6S) octadienoic acid (Hawaiian endophytic fungus Chaetoconis sp)		A2780	67
Furanodiene	AMPK	Doxorubicin-resistant MCF-7 (MCF-7/DOX(R)) cells	21
Deoxyelephantopin (*Elephantopus scaber*)	Cyclin D1, A2, B1, E2, CDK4, CDK2 ↓	HCT116	68

Table 2. Targeting of different proteins by Sesquiterpenes.

Products/Sources	Targets	Cancer cell lines	Reference
5'-methoxy-armillasin (1), 5-hydroxyl-armillarivin (*Armillaria mellea*)		HepG2 cells ↑	69
Gaillardin	Bax, p53 ↑	MCF-7, MDA-MB-468 ↓	70
α-Bisabolol	KISS1R	Pancreatic cancer cells	71
β-Bisabolene Essential Oil Extract of Opoponax (*Commiphora guidottii*)		MCF-7, MDA-MB-231, SKBR3, BT474 ↑	72
Antrocin (*Antrodia cinnamomea*)	MMP-2, ERK, c-Fos ↓ Bax, Fas, and DR5 ↑	Bladder cancer ↓	73
Neoambrosin, Damsin (*Ambrosia maritima*)	STAT5, AKT	HCT116 $p53^{+/+}$ and HCT116 $p53^{-/-}$	74
Leptocarpin (*Leptocarpha rivularis*)	Cytochrome c, Caspase-3 ↑ NF-κB ↓	HT-29 cells , PC-3, DU-145, MDA-MB-231, MCF7, CCD 841 CoN	75
Aitchisonolide, desoxyjanerin, rhaserolide (*Cousinia aitchisonii*)	JNK		76
11α,13-ihydroxanthinin, 11α,13 dihydroxanthuminol (*Xanthium strumarium*)	DR4, DR5, p53, CHOP, Bax, cleaved caspase-3, cleaved caspase-8, cleaved caspase-9 ↑	DU145, HeLa, MCF7	77
AT-101, (-)-enantiomer of gossypol	DR4, DR5 ↑	MCF-7 and MDA-MB-231	78
Artesunate	NF-κB, Akt, survivin, XIAP and Bcl-XL ↓	HeLa cells	79
Parthenolide	STAT3 ↓ Caspase-8, 3 ↑	Hepatocellular carcinoma cells	80
β-2-himachalen-6-ol		B16F-10, Caco-2, MB-MDA-231, A549 and SF-268	81
α-Bisabolol	Autophagy, apoptosis ↑	CML-T1, Jurkat and HeLa	82
β-caryophyllene, β-caryophyllene oxide (CAO), α-humulene (HUM), trans-nerolidol (NER), Valencene (Myrica rubra leaves)	Drug accumulation in cancer cells	CaCo-2 cancer cells	83
Zerumbone	GRP-78, CHOP/GADD153 ↑ Mcl-1, Cdc25C ↓	Prostate cancer cells	84
Neurolenin B (*Neurolaena lobata*)	NPM/ALK, JunB, PDGF-Rβ ↓	NPM/ALK^{+} ALCL	85
Widdrol	VEGFR2, AKT, FAK, eNOS ↓	HUVECs	86

nally modulate β catenin (24, 25, 26). Moreover, TCF/LEF transcription factor family has also been found to be associated with transcriptional repressors. Binding of WNT to frizzled (FZD) and co-receptors (LRP5 or LRP6) transduced signals intracellularly that resulted in the activation of the Dishevelled (Dvl) protein. Functionally active Dvl exerted inhibitory effects on formation of destruction complex and chaperoned β-catenin from degradation. Consequently, there are increasing levels of nuclear β-catenin, facilitate TCF/LEF-mediated transcriptional activation of target genes (24, 25, 26).

Dimeric sesquiterpenes have shown great potential to target protein network in cancer cells. Shizukaol D (dimeric sesquiterpene) obtained from *Chloranthus serratus* is noted to be an efficient natural agent. β-catenin/Tcf4 reporter activity was notably reduced in shizukaol D treated liver SMMC-7721 cancer cells. Dishevelled 2 (Dvl2) and Axin2 were consistently downregulated upon treatment with Shizukaol D. Furthermore, the phosphorylated levels of co-receptor LRP6 were also reduced (27).

Dihydroartemisinin (DHA) substantially suppressed growth of A431 cells by targeting Wnt/β-catenin signaling cascade (28). Total β-catenin levels and its targets (c-myc and cyclin D1) were significantly reduced in cancer cells treated with Dihydroartemisinin. DHA increased GSK3β activity via suppression of phosphorylated levels of GSK3β at serine 9 (29).

Dehydrocostus lactone (DCL) and costunolide obtained from root of *Saussurea lappa* remarkably inhibited nuclear accumulation of β-catenin. It was further investigated to see if some proteins were involved in facilitating the transportation of β-catenin from nucleus to cytoplasm (30). Results revealed that Galectin-3, was associated with β-catenin and translocated synchronously into nucleus to increase the expression of target genes (30). Shown in figure 2. Because of promising anticancer effects, transferrin conjugates of artemisinin dimer and monomeric artemisinin have been designed and noted to be effective against Wnt signaling in different cancer cell lines (31).

Ethylsmenoquinone and Ilimaquinone induced degradation of β-catenin in multiple myeloma cells (32). Different molecules including Tangeritin, Limonin, Ganoderic Acid A, Ganoderic Acid, 6-Gingerol and Zerumbone notably inhibited β-catenin and Wnt5α/β and enhanced the phosphorylation of GSK3β at 9^{th} serine residue in IOMM-Lee and CH157MN cells (33).

Nanomolar concentrations of salinomycin markedly reduced Wnt-mediated phosphorylation of LRP6 at serine 1490. LRP6 protein was noted to be degraded in cancer cells treated with salinomycin (34). Shown in figure 2.

Notch Signaling

Notch signaling is triggered by interaction between Notch-expressing cell and ligand-expressing cell.

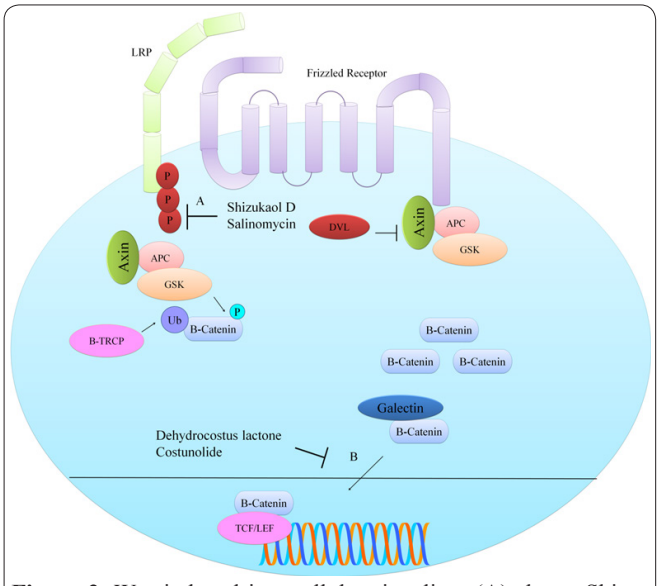

Figure 2. Wnt induced intracellular signaling. (A) shows Shizukaol D and Salinomycin mediated inhibition of phosphorylation of LRP6. (B) Dehydrocostus lactone (DCL) and costunolide induced inhibition of nuclear accumulation of Catenin.

Ligand receptor interaction induced proteolytic processing of Notch to form Notch intracellular domain (NICD). NICD directed loading of proteins including co-activators, mastermind-like 1 (MAML1) and others, to convert CSL-repressor complex into a transcriptionally active complex to trigger expression of the target genes (35, 36, 37).

Musashi-1 (MSI1), an RNA-binding protein translationally repressed Numb mRNA. Gossypol exerted inhibitory effects on MSI1 via binding to its RNA binding domain (38). Shown in figure 3. Numb expression was noted to be considerably enhanced in HCT-116 cells treated with 10 mM gossypol (38).

Levels of proteolytically processed Notch4 and Notch1 were reduced upon treatment with zerumbone in cancer cells. However levels of processed Notch2 were noted to be increased (39). Zerumbone also significantly reduced Jagged1 and Jagged2 levels in MCF-7 and MDA-MB-231 breast cancer cells. Contrarily, Zerumbone markedly enhanced levels of Presenilin-1 in treated cancer cells. Zerumbone induced apoptosis was notable in Notch 2 silenced breast cancer cells (39).

Atractylenolide I (AT-I), a sesquiterpenoid lactone obtained from *Rhizoma Atractylodis Macrocephalae* was noted to effectively downregulate Jagged1, Notch1 and its downstream Hes1/ Hey1 levels in treated cancer cells (40). Shown in figure 3.

Attempts to identify and design Notch signaling inhibitors have shown encouraging results. There are different classes of drugs which are noted to be effective against Notch induced intracellular signaling and efficiently inhibit different steps of signaling cascade. However, successful transition of drugs from preclinical studies to clinical trials will depend largely on biodistribution, pharmacogenomics and pharmacokinetics. Atractylenolide has been tested as a major component in a traditional Chinese medical formula and reported to efficiently inhibit tumor growth in mice transplanted with hepatocellular carcinoma cells (52). It has also been reported to be effective with minimal toxicity when administered in mice xenografted with bladder cancer cells (53). Zerumbone is also being tested by improving its delivery by nanotechnological approaches. Spleen tissues of mice treated with Nanostructured lipid carriers loaded with Zerumbone demonstrated significantly reduced leukemic cell population (54).

Sonic Hedge Hog Signaling

In the absence of SHH induced signaling, smoothened (SMO) is inhibited by patched (PTCH1) that allows protein kinase A directed phosphorylation and truncation of GLI2 and GLI3. There was a nuclear accumulation of GLI2rep and GLI3rep to transcriptionally inhibit target genes (41, 42). However interaction of with PTCH1 relieved inhibition of SMO. Functionally active SMO protected GLI proteins from PKA-induced phosphorylation and activated them. GLI1act–GLI3act moved into the nucleus to upregulate expression of target genes (43). It has lately been persuasively shown that Shh peptides inhibited ectopic WOX1-mediated radio-sensitizing effects. Zerumbone (Shh signaling inhibitor) sensitized glioblastoma cells that ectopically and parentally expressed WOX1. It was concluded that Shh signaling counteracted radio-sensitizing effects of WOX1 overexpression (44). Zerumbone has also been reported to downregulate Gli-1 in renal cell carcinoma cells (45).

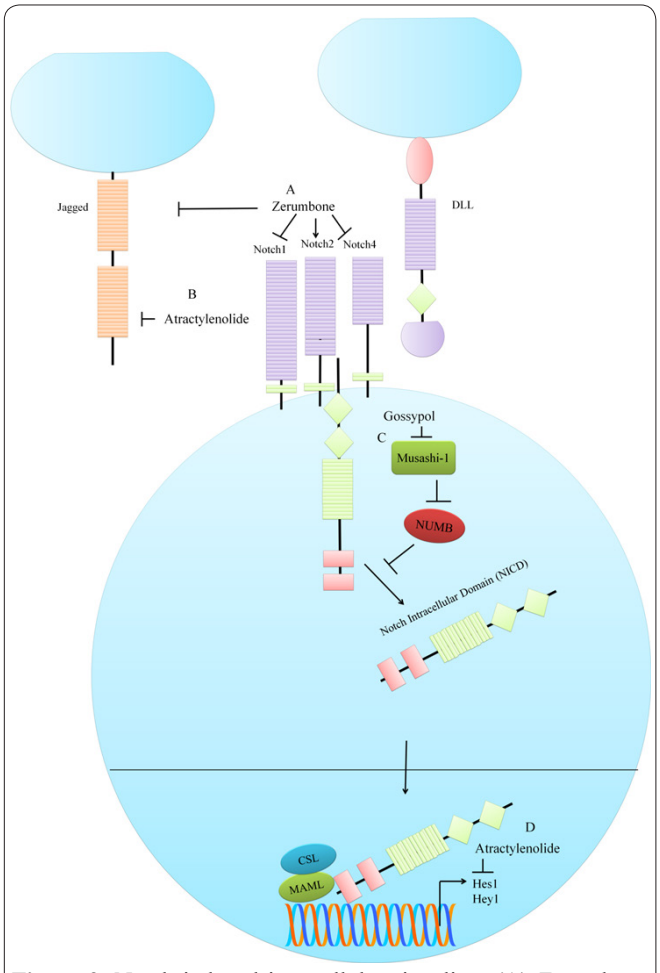

Figure 2. Notch induced intracellular signaling. (A) Zerumbone differentially modulated different Notch isoforms. (B) Atractylenolide inhibited Jagged. (C) Gossypol induced inhibition of Musashi-1 that consequently restored Numb levels. (D) Atractylenolide inhibited expression levels of Hes1 and Hey1.

How Sesquiterpenes modulate different proteins in cancer cells

Thioredoxin reductase (TrxR), an oxidoreductase is frequently overexpressed in different cancers. Structural studies have revealed that TrxR contained conserved sequence, -Gly-Cys-Sec-Gly-COOH which contained an active selenocysteine. Transfer of electrons from NADPH to the N-terminal active site of TrxR is an early step of catalysis from where they are delivered to the C-terminal redox-active sites (Sec498 and Cys497) (46). EM23, sesquiterpene lactone obtained from *Elephantopus mollis* dose-dependently inhibited TrxR. EM23 significantly impaired activity of TrxR by binding to selenocysteine site. EM23 mediated apoptosis was considerably reduced in TrxR silenced cancer cells (46).

Dynamin-related protein 1 (Drp1) has been shown to modulate mitochondrial division in mammalian cells. Drp1-dependent mitochondrial fission is reportedly involved in promoting hypoxia-induced cellular migration and improved sensitivity of cancer cells to different chemotherapeutic drugs (47). Micheliolide (MCL), a guaianolide sesquiterpene lactone considerably upregulated Drp1 and induced fragmentation of mitochondria. Micheliolide was noted to be more effective against Drp1 overexpressing breast cancer cells (47).

Functionally active levels of c-Jun N-terminal kinase (JNK) were notably enhanced in osteosarcoma U2OS cells treated with Costunolide (48).

MyD88 is frequently overexpressed in prognostically poor ovarian cancer patients. Myeloid differentiation protein-2 (MD-2), an accessory protein, is required for TLR4 signaling complex. TLR4/MD-2 complex has been shown to trigger MyD88-dependent NF-κB pathway (49). Atractylenolide I, a naturally occurring sesquiterpene lactone obtained from Atractylodes macrocephala Koidz significantly inhibited expression levels of TLR4/MD-2 complex in ovarian cancer cells. Atractylenolide also effectively inhibited functional activation of Akt and NF-KB in treated ovarian cancer cells (49).

In vivo studies

It is encouraging to note that different sesquiterpene lactones are being modified semi-organically with notable efficacy. DETD-35 is a recently reported example. DETD-35, a modified version of deoxyelephantopin (DET), combinatorially with vemurafenib considerably reduced phosphorylated levels of MEK, ERK, Akt and STAT3 (50). Furthermore, DETD-35 efficiently inhibited tumor growth in mice inoculated either with intrinsically resistant melanoma cells or cells having acquired resistance against vemurafenib (50). Dehydroleucodine remarkably reduced tumor volumes in C57/BL6 mice subcutaneously injected with B16F0 cells (51). Mulberry-like dual-drug complicated nanocarriers (MLDC NCs) are high-payload delivery vehicles (55). Doxorubicin hyaluronic acid nanoparticles and apogossypolone amphiphilic starch micelles were prepared. MLDC NCs efficiently encapsulated ApoG2 and DOX (55). ApoG2 release was very slow as levels were low even after 80 h and release rate of doxorubicin was less than 30% even after 72 h. Intravenously injected MLDC NCs efficiently targeted and accumulated at the tumor site and levels were maintained for 96 h in mice (55). $1/5^{th}$ normal dose of the 2 drugs in MLDC NCs revealed considerably reduced tumor size thus showing that the mulberry-like dual-drug platform are potential anticancer agents (55). Artemisinin has recently been tested to be effectively delivered by pH-responsive Fe3O4@MnSiO3-FA nanospheres. The nanotechnologically delivered Artemisinin was injected intravenously into tail veins of mice every 3 days and markedly reduced tumor growth (56). TNP-470, a synthetically designed analog of fumagillin has also been shown to be delivered through calcium-phosphate ceramic microspheres (CPMs). NP-470-loaded CPMs were injected 3 times/week for 8 weeks into nude mice inoculated with FU-MMT-3. There was a significant reduction in tumor growth with minimal off target effects (57). β-Caryophyllene strongly induced tumor regression and inhibited metastasis of lymph nodes of melanoma cells in high fat diet induced obese C57BL/6N mice (58). Different approaches are currently being used to maximize the delivery of Dihydroartemisinin. In accordance with this notion, novel nanodrug (DHA-GO-Tf) was constructed based on Graphene oxide (GO) dual-dressed with Transferrin (Tf) and Dihydroartemisinin. After internalization, Ferric ion (Fe(III)) was released from the Transferrin, triggered by low lysosomal pH in cancer cell. Reduction of Fe (III) into Fe (II) enhanced interaction with Dihydroartemisinin to increase its cancer killing activity (59). It is evident that Sesquiterpenes have emerged as promising anticancer agents, and recent wealth of information has helped us to fully understand the molecular mechanisms of these chemicals (60). Stumbling blocks in the delivery and bioavailability of these chemicals are being overcome using various nanotechnological approaches.

Conclusion

Although tremendous breakthroughs have been made in demystifying underlying causes of cancer, we still incompletely understand intricate relationships which exist between cancer genotype and phenotype.

These limitations can be overcome by functionally testing live patient tumor cells through exposure to different therapeutics. Sesquiterpenes have gained substantial appreciation because of their ability to modulate protein machinery in cancer cells. Different sesquiterpenes also effectively inhibited tumor growth in xenografted mice. Sesquiterpenes have shown immense potential in significant modulation of intracellular signaling networks in cancer cells. Efficient regulation of Wnt, Notch and TRAIL mediated signaling advocates transition of Sesquiterpenes from preclinical stages into clinical trials. SHH signaling however is insufficiently studied and it needs to be seen how various Sesquiterpenes target modulators and effectors of SHH signaling in detail. Epigenetic inactivation and degradation of death receptors are important aspects which need to be studied in detail. It needs to be seen how Sesquiterpenes modulate post-translational modifications of death receptors. Moreover, which steps of death receptor degradation or loss of expression can be regulated by Sesquiterpenes ranging from internalization of death receptors

to impairment of sorting towards cell surface? There is recently emerging evidence of miRNA regulation of death receptors, therefore it will be exciting to investigate if Sesquiterpenes also regulated different miRNAs involved in regulation of death receptors. Currently, different 'next-generation' functional diagnostic techniques are being used which include novel methods for tumor manipulation, device-based in situ approaches and molecularly precise assays of tumor responses. These promising new technologies will be helpful in integration of functional testing with next-generation sequencing (NGS) and efficient immuno-profiling to accurately match combinatorially designed therapeutics to individual cancer patients.

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